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REVIEW

Emerging inhaled bronchodilators: an update

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ABSTRACT: Bronchodilators remain central to the symptomatic management of chronic obstructive pulmonary disease and asthma, and, for this reason and also because the patent protection of many bronchodilators has expired, several companies have reinitiated research into the field.

The only limits set for the development of a long-lasting bronchodilator with a new product profile are medical needs and marketing opportunities. The incorporation of once-daily dose administration is an important strategy for improving adherence and is a regimen preferred by most patients.

A variety of β_2-agonists and antimuscarinic agents with longer half-lives and inhalers containing a combination of several classes of long-acting bronchodilator are currently under development.

The present article reviews all of the most important compounds under development, describing what has been done and discussing their genuine advantage.

KEYWORDS: Bronchodilators, combination therapy, long-acting antimuscarinic agents, ultra-long-acting β_2-agonists

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The central position of bronchodilators in the treatment of airways disorders (inhaled bronchodilators are the mainstay of the current management of chronic obstructive pulmonary disease (COPD) [1, 2] and are critical in the symptomatic management of asthma [3, 4]), as well as the fact that the patent protection of many bronchodilators has expired, have influenced several companies to reinitiate research into the field [5–7]. Obviously, overtaking such important and widely used drugs as the current bronchodilators requires a new approach that might produce truly innovative agents or, at least, take into account the needs of patients.

Inadequate adherence to inhaled therapy is a major cause of poor clinical outcomes in the treatment of COPD and asthma. In general, adherence to treatment with inhalants is poor because of the complex procedures required to use them, as well as the tedious frequent dosing [8]. An important step in simplifying COPD and asthma management and improving adherence to prescribed therapy is reducing the dose frequency to the minimum necessary to maintain disease control [9]. Consequently, the incorporation of once-daily dosing is an important strategy in improving compliance, and is a regimen preferred by most patients [10].

The interest within the pharmaceutical industry in developing novel inhaled bronchodilators with an improved duration of action compared to drugs currently on the market is intense because there is a well-established belief that the only limits set for the development of a long-lasting bronchodilator with a new product profile are medical needs and marketing opportunities.

Since it has proven difficult to discover novel classes of bronchodilatory agents, the logical approach has been to improve the existing bronchodilators [11]. The present article reviews the most important compounds under development, describing what has been done and discussing the genuine advantage, if any, of these compounds.

NOVEL ULTRA-LONG-ACTING β_2-AGONISTS

A variety of β_2-agonists with longer half-lives are currently undergoing development, with the hope of achieving once-daily dosing (table 1) [5–7].

Indacaterol

Indacaterol (QAB-149) is a once-daily long-acting β_2-agonist (LABA) in development by Novartis (Basle, Switzerland). It will probably be the first new bronchodilator to enter the market. Indeed, its development is very advanced and, although

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information on results of long-term trials have not yet been provided, it is likely that this drug will be launched by the end of 2009/beginning of 2010 because of its strong efficacy in both asthma and COPD and safety at high doses.

Preclinical studies documented that indacaterol is a fast-acting compound with a longer duration of action than salmeterol and formoterol [12, 13]. Moreover, indacaterol behaves as a nearly full β_2-agonist [14].

Considering this excellent pharmacological profile, several trials have evaluated the efficacy and safety of indacaterol in patients with asthma and COPD.

Asthma

An initial investigation reported that, in patients with intermittent or mild-to-moderate persistent asthma, single 200- and 400-μg doses of indacaterol provided effective and sustained 24-h bronchodilatory control, with a rapid onset of action (<5 min) and a good tolerability and safety profile [15]. Patients with persistent asthma (n=25) received a randomised sequence of single doses of 400 μg indacaterol *via* a single-dose dry-powder inhaler (SDDPI), 200 μg indacaterol *via* a multiple-dose dry-powder inhaler (MDDPI) and placebo [16]. The adjusted mean forced expiratory volume in 1 s (FEV_1) was significantly higher for both indacaterol doses *versus* placebo at most time-points. The first time-points at which significant treatment differences in FEV_1 were observed for indacaterol and placebo were 5 min after dosing for 400 μg indacaterol (SDDPI; 0.17 L) and 10 min for 200 μg indacaterol (MDDPI; 0.21 L) (both $p<0.001$ *versus* placebo). Differences relative to placebo at the final time-point, 24 h after dosing, were 0.29 and 0.15 L for 400 and 200 μg indacaterol, respectively (both $p \leqslant 0.003$ *versus* placebo). Overall, the FEV_1 was significantly higher for the 400-μg dose compared with the 200-μg dose from 15 min to 2 h after dosing ($p \leqslant 0.013$) and from 5 h onwards ($p \leqslant 0.022$). Indacaterol was associated with good tolerability and safety. In a third dose-finding trial, the 24-h bronchodilatory efficacy and safety of a single morning dose of 150, 300 or 600 μg indacaterol *via* an SDDPI, 12 μg formoterol morning and evening *via* an Aerolizer® (Novartis), or placebo were assessed in 42 patients with persistent asthma [17]. The trough FEV_1 at 24 h following the dose (the primary end-point) was significantly higher with all doses of indacaterol and formoterol, compared with placebo, but, for the two highest doses of indacaterol, the trough FEV_1 was higher than with formoterol. The most frequent adverse events (AEs) were transient cough and throat clearing, which were observed in 15% of subjects with the 300- and 600-μg doses of indacaterol. Measurements of serum potassium and corrected Q–T interval on ECG revealed no abnormalities.

KANNIESS *et al.* [18] randomised 115 patients in a double-blind incomplete-block crossover design to sequences of four 7-day periods (separated by 7-day washouts) of treatment with 100, 200, 300, 400 or 600 μg indacaterol or placebo, once daily, *via* an SDDPI. After the fourth washout, patients received 1 day of open-label formoterol, 12 μg twice daily. For standardised FEV_1, the area under the curve between 22 and 24 h ($AUC_{22–24\ h}$) on day 1, indacaterol doses of $\geqslant$200 μg were superior to placebo ($p<0.05$) and similar or superior to 12 μg formoterol

TABLE 1 Ultra-long-acting β-agonists undergoing development

Drug	Advantages	Latest developments	Company working on this strategy
Indacaterol	It behaves as a nearly full β_2-agonist. It offers a quick onset of action and true 24-h control in both asthma and COPD. It has a broad therapeutic window, with cough being the most frequently reported adverse event.	Phase III	Novartis, Basle, Switzerland
Carmoterol	It binds very firmly to the β_2-adrenoceptor. It displays a fast onset and long duration of activity in both asthma and COPD at very low dosage (2–4 μg).	Phase III	Chiesi Farmaceutici, Parma, Italy
Milveterol	It shows comparable bronchodilatory activity to 50 μg salmeterol twice daily in asthma.	Phase IIb	GlaxoSmithKline, London, UK/ Theravance, South San Francisco, CA, USA
GSK-642444	It displays a long duration of activity in both asthma and COPD. It is safe and well tolerated, with the most frequently reported adverse event being headache. Apparently, GSK-642444 possesses a potentially greater therapeutic index than milveterol.	Phase IIb	GlaxoSmithKline, London, UK/ Theravance, South San Francisco, CA, USA
BI-1744-CL	It seems to be equivalent to formoterol for speed of onset, but with a longer duration of action. It displays a long duration of activity in both asthma and COPD.	Phase IIb	Boehringer Ingelheim, Ingelheim, Germany
LAS-100977	It displays a longer duration of activity than 50 μg salmeterol in asthma patients.	Phase IIa	Almirall Prodesfarma, Barcelona, Spain
Saligenin- or indole-containing and adamantyl-derived β_2-agonists	UK-503590 displays greater potency/duration of action and a superior therapeutic index to salmeterol. Compound X *in vitro* has a duration of action that is significantly longer than that of formoterol but shorter than that of salmeterol; *in vivo* it shows equivalent potency and a superior duration of action/therapeutic index to salmeterol.	Preclinical phase/ phase I	Pfizer, New York, NY, USA

COPD: chronic obstructive pulmonary disease.

twice daily. By day 7, mean differences from placebo in standardised FEV1 ($AUC_{22–24\ h}$) were 0.08, 0.16, 0.15, 0.11 and 0.16 L for 100, 200, 300, 400 and 600 μg indacaterol, respectively (all $p<0.05$ *versus* placebo). The mean FEV1 for indacaterol doses of ⩾200 μg on day 7 was higher than that for placebo before the dose and at all post-dose time-points ($p<0.05$). AEs were generally mild in severity; no serious AEs occurred.

In another trial, 436 patients with persistent asthma on a stable regimen of inhaled corticosteroids (ICSs) were randomised to treatment for 7 days with 50, 100, 200 or 400 μg indacaterol once daily *via* an MDDPI (Certihaler®; SkyePharma, Saint-Quentin-Fallavier, France/Novartis), 400 μg indacaterol *via* an SDDPI or placebo [19]. All doses of indacaterol provided rapid-onset sustained 24-h bronchodilatory efficacy using once-daily dosing from day 1, with no loss of efficacy after 7 days of treatment, although 200 μg indacaterol appeared to be the optimum dose, offering the best efficacy/safety balance. A randomised open-label crossover study in adult subjects with asthma (FEV1 of ⩾60% of the predicted value) confirmed that 200 μg indacaterol provides effective 24-h bronchodilation, with a longer duration than 50 μg salmeterol and a good overall safety profile [20].

The safety and tolerability of indacaterol were assessed in 156 asthma patients in a multicentric randomised double-blind placebo-controlled study [21]. Patients received 200, 400 or 600 μg indacaterol or placebo once daily for 28 days. The results of this study suggested that indacaterol has a wide therapeutic index; it is well tolerated and is associated with neither adverse cardiac effects nor clinically significant changes in β_2-mediated systemic effects. This may be because the doses used were simply not high enough to have an impact on these safety variables despite all indacaterol doses achieving clinically relevant differences in FEV1 of >200 mL *versus* placebo at most post-dose time-points. In a subsequent study, higher doses (800 μg) of indacaterol demonstrated effects on serum potassium and blood glucose levels; however, these changes were considered not to be clinically meaningful [22]. At a higher single dose of 1,000 μg, indacaterol had a good safety profile and was not associated with sustained systemic adverse effects; mean cardiac frequency and corrected Q–T interval remained within normal ranges following administration [18].

COPD

Indacaterol has also been investigated in COPD patients, in whom it demonstrated 24-h bronchodilatory efficacy, with a clinically meaningful bronchodilatory effect within 1 h following the dose and no evidence of tachyphylaxis [23]. A randomised double-blind placebo-controlled crossover trial assessed the 24-h bronchodilatory efficacy and safety of single-dose indacaterol in patients with moderate-to-severe COPD [24]. On separate study days with ⩾6-day washout periods, patients inhaled a single morning dose of 150, 300 or 600 μg indacaterol, placebo or formoterol (12 μg *b.i.d.*). The study population comprised 51 subjects. The trough FEV1 24 h following the dose (the primary end-point) was significantly higher with all doses of indacaterol compared with placebo, with clinically relevant differences of ⩾140 mL. The 24-h trough FEV1 with formoterol was greater than with placebo (by 130 mL), and greater with 300 and 600 μg indacaterol *versus* formoterol. All indacaterol doses and formoterol significantly increased the FEV1 and forced vital capacity (FVC) *versus* placebo at all post-dose assessment time-points ($p<0.001$). The most frequent AE was transient cough (3.9–6.4%) and, in general, AEs were mild.

In the study of RENNARD *et al*. [25], 635 patients with moderate-to-severe COPD received 50, 100, 200 or 400 μg indacaterol once daily *via* an MDDPI, 400 μg indacaterol once daily *via* an SDDPI or placebo. All doses of indacaterol were associated with significant dose-dependent improvements in FEV1 compared with placebo, starting from 5 min after the first dose on day 1 of the 7-day treatment period. Dose-dependent FEV1 increases were seen for indacaterol by the first time-point (5 min) and at all time-points on days 1 and 7 ($p<0.05$ *versus* placebo, at all doses). The treatment effect persisted throughout the 24-h dosing interval, and increases in trough FEV1 with the 200- and 400-μg·day^{-1} dosages were classified as clinically relevant. FVC and forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25\sim75}$) were also significantly improved by indacaterol *versus* placebo, and rescue medication use was reduced. During an open-label extension period involving 263 patients, the effects of indacaterol on FEV1 were similar to those of tiotropium bromide. This is a particularly intriguing finding that warrants further investigation.

The safety and tolerability of once-daily administration of two doses (400 and 800 μg) of indacaterol, over a 28-day period, has been compared with that of placebo in patients with moderate COPD [26]. Once-daily indacaterol was well tolerated at doses up to 800 μg with a good overall safety profile. There was no difference at any dose between the safety of indacaterol and placebo. Since 800 μg represents two to four times the therapeutic dose suggested by earlier studies, these results imply that the therapeutic window for indacaterol may be wide.

Carmoterol

Carmoterol (CHF 4226; TA 2005), a noncatechol β_2-adrenoceptor agonist with a *p*-methoxyphenyl group on the amino side chain and a 8-hydroxyl group on the carbostyril aromatic ring [27], possessing structural elements from both formoterol and procaterol, binds very firmly to the β_2-adrenoceptor [28]. Carmoterol displays a fast onset and long duration of activity under both *in vitro* and *in vivo* experimental conditions [27–29]. Carmoterol is in development by Chiesi Farmaceutici (Parma, Italy), under license from Tanabe Seiyaku Co. (Saitama, Japan). Unfortunately, although carmoterol is the oldest of the ultra-LABAs under investigation, its development is greatly delayed.

Asthma

The results obtained in healthy volunteers and asthmatic patients provided evidence that the pharmacokinetics of carmoterol are proportional to the dose, and nonlinear accumulation of the drug following repeated dosing treatments is negligible [30]. Interestingly, using Modulite™ (Chiesi Farmaceutici) technology, which utilises a hydrofluoroalkane propellant, lung deposition of carmoterol as high as 41% of the nominal dose can be reached [31]. Owing to the small particle size of the hydrofluoroalkane pressurised metered-dose inhaler aerosol (0.8 μm), no significant differences in lung deposition of carmoterol between healthy

subjects, patients with asthma and patients with COPD have been documented [31]. This finding justifies the effectiveness and safety profile of carmoterol.

A randomised double-blind parallel-group trial in 124 patient with persistent asthma documented that 2 μg carmoterol administered once daily was as effective as 12 μg formoterol twice daily [32]. The study, conducted over an 8-day treatment period, showed that both carmoterol and formoterol provided significant improvements in lung function. The trough FEV_1 on the morning of day 8 were clinically and significantly greater in both active treatment groups, compared with placebo, and the effect of carmoterol on trough FEV_1 was comparable to that of formoterol. Safety and tolerability results were similar between carmoterol and formoterol [33].

COPD

A dose-finding study explored the efficacy of three different doses (1, 2 and 4 μg) of carmoterol for 2 weeks in 278 patients with COPD [34, 35]. On day 1, a single 4-μg, but not 1- or 2-μg, dose of carmoterol had an effect on 24-h trough FEV_1 that was better than that of two 50-μg doses of salmeterol given 12 h apart, suggesting that carmoterol may be useful as a once-daily bronchodilator in patients with COPD. On day 14, once-daily doses of 2 and 4 μg carmoterol resulted in placebo-adjusted improvements compared to baseline in trough FEV_1 of 94 and 112 mL, respectively, whereas 50 μg salmeterol *b.i.d.* resulted in an increase of 78 mL. Similarly, doses of 2 and 4 μg carmoterol resulted in placebo-adjusted improvements compared to baseline in trough FVC of 133 and 123 mL, respectively. The subgroup FEV_1 $AUC_{0–24\ h}$ showed a dose–response relationship. All doses of carmoterol were safe and well tolerated [36]. Carmoterol (4 μg) was associated with more nervous system AEs (one patient reported headache and two tremor) than lower doses. Lower doses of carmoterol were associated with cough (n=3) and one case of dyspnoea (in the 2-μg patients). There were no significant changes in ECG results, blood pressure, or serum potassium or glucose levels compared with salmeterol or placebo. It is important to highlight the fact that no tolerance to the bronchodilatory effects of carmoterol or salmeterol was observed over the 2 weeks of treatment, as evidenced by the unchanged mean FEV_1 and unchanged peak FEV_1 [37]. A small but insignificant reduction in the acute bronchodilation seen after dosing on day 14 was considered to be due to a significant increase in pre-dose trough FEV_1 rather than to the development of tolerance.

Milveterol

Milveterol (GSK-159797; TD-3327) is a once-daily LABA in development by GlaxoSmithKline (GSK, London, UK) and Theravance (South San Francisco, CA, USA).

Milveterol achieved the target increase in FEV_1 throughout the 25-h evaluation period in a study of 38 patients with mild asthma following single-dose inhalation. It was well tolerated, with no increase in cardiac frequency [5]. A placebo-controlled crossover study tested the bronchodilatory effect, safety and tolerability of multiple dose levels of milveterol administered *via* a dry-powder inhaler in 20 patients with mild asthma [6]. Doses in the anticipated clinical range produced clinically significant increases in FEV_1 over 24 h, with little change in cardiac frequency. At 24 h, 10- and 20-μg doses of milveterol produced adjusted mean changes from baseline FEV_1 of 460 and 540 mL, respectively, compared to a change of 130 mL for placebo. The placebo-corrected mean maximum cardiac frequency increase over the 26-h period of measurement was 1.0 beats·min^{-1} for the 10-μg dose and 2.7 beats·min^{-1} for the 20-μg dose. In patients with asthma who were controlled using ICSs, all studied doses of milveterol (10, 15 and 20 μg), dosed once daily, showed comparable bronchodilatory activity to 50 μg salmeterol, dosed twice daily, at trough on the fourteenth day of treatment [38]. The lowest dose also produced a placebo-adjusted weighted mean cardiac frequency change over the first 4 h after dosing on day 14 that was similar to that of salmeterol.

Despite this interesting profile, it is likely that GSK and Theravance will continue to explore an optimised dose range for milveterol only as a back-up because of the greater therapeutic index of GSK-642444, another ultra-LABA in development by the two companies.

GSK-642444

GSK-642444 is another ultra-LABA compound that GSK and Theravance have put into a pool for potential development for clinical use.

Asthma

All doses (25, 100 and 400 μg) of GSK-642444 studied, dosed once daily over 14 days in patients with asthma, showed greater bronchodilatory activity than salmeterol dosed twice daily, and produced placebo-adjusted dose-dependent mean changes from baseline FEV_1 of >200 mL at trough on the fourteenth day of treatment. The two lower doses also produced smaller changes than salmeterol in placebo-adjusted weighted mean cardiac frequency over the first 4 h after dosing on day 14 [38]. Apparently, GSK-642444 exhibits a potentially greater therapeutic index than does milveterol [38].

A study was designed to evaluate the efficacy of five doses (3, 6.25, 12.5, 25 and 50 μg) of GSK-642444 administered once daily for 4 weeks *via* a novel inhaler in 607 patients with moderate-to-severe asthma [39]. The primary end-point for assessing efficacy was change in trough (23–24 h) FEV_1 from baseline after 28 days. The secondary end-points included serial 24-h FEV_1 on days 1 and 28, morning and evening peak expiratory flow averaged over the 28-day treatment period, and the percentage of symptom-free and rescue-free 24-h periods. GSK-642444 induced dose-dependent improvements in lung function. All but the two lowest doses of GSK-642444 produced significant improvements in FEV_1 measured 23–24 h after the last dose in a large study population of asthmatics already being treated with ICSs and short-acting β_2-agonist rescue medication as needed ($p<0.05$). Efficacy was observed in a number of secondary end-points, including improvements in peak expiratory flow in both the morning and evening, and the percentage of symptom-free days and rescue-free days. Use of rescue medication was significantly lower in patients receiving the three highest doses of GSK-642444 than in patients on placebo. The onset of action was dose-dependent, with the bronchodilatory effect being sustained over 24 h. Furthermore, improvements in lung function 24 h after the first dose were maintained throughout the 28-day treatment period. Throughout the 4-week study period, GSK-642444 was

well tolerated at all doses and the frequency of AEs was comparable to that with placebo. Headache was the most commonly observed AE in all arms, and its frequency was comparable to that with placebo. The highest dose (50 μg) produced a small change in cardiac frequency (a known effect of β_2-agonists) that did not exceed the predefined clinically relevant threshold. There were no serious AEs reported in the study.

COPD

A trial, which evaluated the dose-response, efficacy and safety of five doses (3, 6.25, 12.5, 25 and 50 μg) of GSK-642444 administered once daily for 4 weeks in 605 patients with moderate-to-severe COPD, met its primary end-point [40]. The results showed a dose-dependent increase in lung function, with 25 and 50 μg exceeding a predefined threshold of a 130 mL increase in FEV1 at trough. Favourable trends were also seen in morning and evening improvements in peak expiratory flow and reduced use of rescue medication. The drug was safe and well tolerated, with the most frequently reported AE being headache. There was no effect on mean cardiac frequency at any dose compared to placebo.

BI-1744-CL

BI-1744-CL is under development by Boehringer Ingelheim (Ingelheim, Germany) as a potential inhaled β_2-agonist treatment for COPD and asthma. Its preclinical development showed equivalency to formoterol for speed of onset and a longer duration of action [41, 42].

Asthma

The bronchoprotective effects of single doses (2, 5, 10 and 20 μg) of BI-1744-CL and placebo, administered using the Respimat® soft mist inhaler (Boehringer Ingelheim), against methacholine provocation were examined in 31 patients with intermittent asthma on separate days [43]. Methacholine challenges were performed at 30 min and 4, 8, 24 and 32 h following each single dose of medication. For 20 μg BI-1744-CL, the provocative concentration of methacholine causing a 20% fall in FEV1 geometric mean ratios at various post-dose time-points were also significantly increased compared with placebo (18.6 $mg \cdot mL^{-1}$ at 30 min, 18.5 $mg \cdot mL^{-1}$ at 4 h, 18.6 $mg \cdot mL^{-1}$ at 8 h and 6.3 $mg \cdot mL^{-1}$ at 32 h). Similar time profiles were observed for all other doses.

COPD

The efficacy of BI-1744-CL has been examined in a double-blind placebo-controlled five-way crossover phase II trial in 36 patients with stable COPD [41, 44]. After a 2-week run-in, subjects were randomised to either placebo or 2, 5, 10 or 20 μg BI-1744-CL. At that time, COPD exacerbations had caused two patients to drop out, and 34 subjects completed the trial. No serious AEs were reported and only four minor AEs, with no changes detected in cardiovascular measurements or serum potassium levels. The maximum effect was produced by 20 μg, but was not noticeably different from that of 10 μg. FEV1 was found to improve by 170 mL and FVC by ~200 mL, an effect that waned and reached a nadir by 15 h. There was a slight recovery by 23 h, but only to within the baseline. BI-1744-CL increased FEV1 and FVC more than did placebo at all time-points, and the plateau with slight rise in lung function seen with BI-1744-CL was replicated with placebo. Further work examining a dose of 40 μg is ongoing.

LAS-100977

Almirall Prodesfarma (Barcelona, Spain) is developing LAS-100977, a once-daily LABA. Asthma patients (n=25) were treated once daily with placebo, 50 μg salmeterol or one of several doses of LAS-100977 [45]. The primary end-point was change from pre-dose trough FEV1. A significant increase in FEV1 was seen in patients receiving all doses of LAS-100977 compared with those treated with either placebo or salmeterol. The drug was well tolerated, with tachycardia and tremor seen at the higher doses. A 24-h duration of action was confirmed.

Saligenin- or indole-containing and adamantyl-derived β_2-agonists

Pfizer (New York, NY, USA) is investigating a series of β_2-agonists for the potential treatment of respiratory disorders. The design and profile of a series of saligenin-containing LABAs has been described [46]. They have significantly longer durations of action than salmeterol and have the potential for a once-daily profile in humans. In addition, the design and profile of a series of indole-containing LABAs has been described [47]. Evaluation of these analogues demonstrates that they have a salmeterol-like duration of action with the potential for long duration of action in humans. The discovery of adamantyl-derived inhaled LABAs that would exhibit low oral bioavailability compared to salmeterol in order to reduce systemic effects through the swallowed fraction after inhalation has also been discussed [48]. An amide derivative showed twice the duration of action of salmeterol at coefficient-of-variation-tolerated doses and exhibited comparable lung absorption rates, with high clearance, a short half-life (1.6 h) and low oral bioavailability.

UK-503590 is another β_2-agonists with greater potency/duration of action and a superior therapeutic index to salmeterol [49, 50].

Compound X is a LABA that is being developed by Pfizer [51]. *In vitro*, it has a duration of action that is significantly longer than that of formoterol but shorter than of salmeterol [52]. *In vivo*, it shows equivalent potency and a superior duration of action/therapeutic index to salmeterol in anaesthetised dogs [53].

NOVEL LONG-ACTING ANTIMUSCARINIC AGENTS

Some new long-acting muscarinic antagonists (LAMAs) are also undergoing development (table 2). Both good selectivity for and slow dissociation from the M_3 muscarinic receptor is deemed important for new antimuscarinic drugs efficacious by inhalation *via* once daily administration.

Aclidinium bromide

Aclidinium is a quinuclidine carbamate derivative undergoing development by Almirall Prodesfarma. Preclinical studies documented that aclidinium exhibits M_3/M_2 kinetic selectivity [54]. Moreover, they showed equivalency to ipratropium for speed of onset and a longer duration of action, but faster onset and shorter duration of action than tiotropium [55]. Intriguingly, aclidinium is rapidly hydrolysed in human plasma to inactive metabolites [54].

TABLE 2 Novel long-acting antimuscarinic agents undergoing development

Drug	Advantages	Latest developments	Company working on this strategy
Aclidinium bromide	Apparently, it displays a faster onset but shorter duration of activity than does tiotropium. The rapid hydrolysis of aclidinium bromide in human plasma to inactive metabolites is an advantage over tiotropium as its degradation is negligible, and may account for a favourable cardiovascular safety profile. The partially disappointing efficacy results of the ACCLAIM/COPD trials question the possibility that aclidinium is at least as effective as tiotropium.	Phase III	Almirall Prodesfarma, Barcelona, Spain
Glycopyrronium bromide	It shows low systemic absorption. It exhibits a rapid onset of action. Overall, improvements in lung function with glycopyrronium bromide appear comparable with those of tiotropium.	Phase III	Novartis, Basle, Switzerland
GSK-573719	Its long duration of action when administered *via* inhalation in animal models supports the potential for use as a once-daily bronchodilator for COPD. Clinical data have not been disclosed.	Phase II	GlaxoSmithKline, London, UK
QAT-370	It displays a short plasma half-life but long duration of action similar to that of tiotropium.	Preclinical phase	Novartis, Basle, Switzerland
CHF 5407	It is an antagonist as potent and long-acting as tiotropium on human M_3 muscarinic receptors, but significantly short-acting on M_2 receptors. Its duration of action is similar to that of tiotropium.	Phase I/II	Chiesi Farmaceutici, Parma, Italy
Darotropium bromide	Its long duration of action when administered *via* inhalation in animal models supports the potential for use as a once-daily bronchodilator for COPD, but no data have yet been presented.	Phase II	GlaxoSmithKline, London, UK
TD-4208	It shows the potential for 24-h bronchodilation in COPD patients.	Phase I/II	Theravance, South San Francisco, CA, USA
Dexpirronium	It seems to be similar to formoterol in reducing acetylcholine-induced bronchospasm, at least in animals.	Phase I	Meda Pharma, Bad Homburg, Germany

ACCLAIM/COPD: AClidinium CLinical Trial Assessing Efficacy and Safety In Moderate to Severe COPD Patients; COPD: chronic obstructive pulmonary disease.

Clinical development

Single doses (100, 300 and 900 g) of inhaled aclidinium produced a significant bronchodilatory response in 17 patients with COPD [56]. Mean FEV1 and FVC were significantly increased with all studied doses of aclidinium over a 24-h time period, as compared to placebo. The onset of significant bronchodilation was observed as early as 15 min after aclidinium treatment, and this effect was sustained for $\geqslant$24 h.

The efficacy and safety of aclidinium (25, 50, 100, 200 or 400 μg) was investigated in 464 patients with moderate-to-severe stable COPD, who were randomised to double-blind once-daily treatment with aclidinium, placebo or open-label tiotropium (18 μg) for 4 weeks, in order to establish the optimal dose for phase III studies [57]. Aclidinium produced sustained bronchodilation over 24 h. Aclidinium (200 and 400 μg) showed similar bronchodilatory effects to open-label tiotropium. Aclidinium (all doses) was well tolerated. Based on these data, 200 μg aclidinium was selected as the investigational dose for future clinical trials in COPD.

In addition, a 7-day exploratory crossover study evaluating morning or evening administration of aclidinium *versus* placebo treatment was recently completed [58]. At day 7, a significant difference in aclidinium *versus* placebo normalised FEV1 $AUC_{0–24\ h}$ was observed, but not in trough FEV1 for both aclidinium dosing groups. No differences in FEV1 $AUC_{0–24\ h}$ or trough FEV1 were found between the morning or evening aclidinium administrations.

A total of 1,647 patients with moderate-to-severe COPD received 200 μg aclidinium or placebo for 1 yr in two phase III studies (AClidinium CLinical Trial Assessing Efficacy and Safety In Moderate to Severe COPD Patients (ACCLAIM/COPD) I and II) [59]. The mean FEV1 at baseline were 1.406 and 1.199 L in ACCLAIM/COPD I and ACCLAIM/COPD II, respectively. Both studies met their primary end-points of improved trough FEV1 at weeks 12 and 28 compared with placebo. The improvement compared with placebo was in the range 60–70 mL and was maintained over 1 yr. The change from baseline ranged 154–177 mL, with a median time to peak of 2 h. In ACCLAIM/COPD I, aclidinium significantly improved the percentage of patients showing a clinically relevant improvement ($\geqslant$4 points) in health-related quality of life compared with placebo, as measured by the St George's Respiratory Questionnaire (SGRQ) at week 52 ($p=0.025$). ACCLAIM/COPD II showed improved quality of life ($p<0.001$) at all time-points up to, but not including, week 52 ($p=0.074$). Pooled analysis of both studies showed a significantly higher percentage of patients improving by $\geqslant$4 points in the SGRQ score at week 52 ($p=0.04$). ACCLAIM/COPD II met the secondary end-point of delaying time to first moderate-to-severe disease exacerbation ($p=0.01$); the results were nonsignificant in ACCLAIM/COPD I. In the pooled

analysis of both studies, there was a positive trend in delaying the time to first moderate or severe exacerbation ($p=0.054$).

Apparently, aclidinium is a safe drug, although the relative scarcity of available data should be highlighted. In any case, it is intriguing that GARCIA GIL *et al.* [60] were unable to identify the maximum tolerated dose despite using single high doses of aclidinium (600–6,000 μg) in 16 healthy subjects because there were no limiting AEs in ⩾50% of subjects at any dose and no serious AEs.

Glycopyrronium bromide

Glycopyrronium bromide (NVA-237; AD-237) is a once-daily long-acting inhaled LAMA undergoing development by Novartis.

In an experimental setting, at doses showing similar efficacy, glycopyrronium bromide demonstrated a significantly lower effect on cardiovascular parameters than tiotropium, which may indicate a potential clinical benefit in humans [61]. In effect, inhaled glycopyrronium bromide shows low systemic absorption, and, therefore, should not be expected to be associated with typical systemic antimuscarinic AEs. This is supported by the observed lack of dry mouth (a classic antimuscarinic AE) with inhaled glycopyrronium bromide, and suggests a favourable safety profile for this once-daily antimuscarinic bronchodilator [62]. A single 480-μg dose of glycopyrronium bromide demonstrated bronchodilatory efficacy up to 32 h after the dose in patients with reversible obstructive airways disease, supporting the potential for once-daily dosing, and exhibited a rapid onset of action [63]. In particular, single doses of NVA237 provided a similar degree of bronchodilation to the short-acting β_2-agonist salbutamol over the first 40 min following the dose [64].

A dose-ranging study evaluated the efficacy and safety of four doses (12.5, 25, 50 or 100 μg) of glycopyrronium bromide *via* SDDPI in moderate-to-severe COPD patients. The estimated treatment differences (95% confidence interval) *versus* placebo for trough FEV_1 on day 7 for 12.5, 25, 50 and 100 μg glycopyrronium bromide and tiotropium were 75 (23–127), 90 (37–143), 131 (78–185), 142 (89–195) and 127 (85–169) mL, respectively ($p \leqslant 0.002$ for all). Glycopyrronium bromide (25, 50 and 100 μg) demonstrated significant FEV_1 improvements *versus* tiotropium at 5, 15 and 30 min and 1 h after the dose on day 1 ($p<0.05$). All glycopyrronium bromide doses and tiotropium were well tolerated [65].

The results of a large phase III study showed that this bronchodilator exhibits rapid onset of effect (by 5 min following the dose) [66]. Comparisons with baseline values showed that all doses of glycopyrronium bromide were associated with sustained increases in trough FEV_1 on days 2, 7, 14 and 28, which was the primary end-point. Compared with placebo, however, only peak FEV_1 improved significantly with all doses of glycopyrronium bromide at most time-points ($p<0.05$); in contrast, trough FEV_1 was better than with placebo on day 28 with only the 120-μg dose ($p=0.0048$). Overall, improvements in lung function with glycopyrronium bromide appeared comparable with those of tiotropium.

Another study evaluated the safety and tolerability of 28 days' treatment with glycopyrronium bromide (100 or 200 μg once daily) *via* SDDPI in 281 moderate-to-severe COPD patients [67]. Both glycopyrronium bromide doses were well tolerated. The most common AEs were COPD exacerbations and dry mouth. On day 28, treatment–placebo differences in trough FEV_1 for 100 and 200 μg glycopyrronium bromide were 161 and 151 mL, respectively ($p<0.05$). Peak FEV_1 and FEV_1 $AUC_{5\ min–5\ h}$ were also significantly superior for 100 and 200 μg glycopyrronium bromide *versus* placebo on days 1, 14 and 28 ($p<0.05$).

GSK-573719

GSK-573719 is another high-affinity specific muscarinic receptor antagonist. It is being developed for once-daily treatment of COPD by GSK. The long duration of action of GSK-573719 when administered *via* inhalation in animal models supports its potential for use as a once-daily bronchodilator in COPD, but data are unfortunately still lacking in the literature. In any case, several trials have been conducted that lead to the belief that this is an interesting compound. A first trial investigated whether GSK-573719 at different doses (100, 500 and 1,000 μg) was safe and tolerated in healthy volunteers [68]. A second trial evaluated the safety, tolerability, pharmacodynamics and pharmacokinetics of GSK-573719 administered as single doses (750 and 1,000 μg) and repeat doses over 14 days (250–1,000 μg once daily) of GSK-573719 in healthy male and female subjects [69]. A randomised double blind placebo-controlled double-dummy four-way crossover dose-ascending study was carried out to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK-573719 (three escalating microgram doses) and tiotropium bromide (18 μg) *via* dry-powder inhaler in COPD patients [70]. These studies have looked at GSK-573719 with an inactive substance called cellobiose octaacetate. A new study is in progress looking at the safety and tolerability of GSK-573719 with magnesium stearate for once-daily treatment of COPD [71]. Magnesium stearate itself is not a medicine but is approved as a food ingredient and has also has been approved to be used in a number of marketed medical inhalers.

QAT-370

Novartis is also developing QAT-370, the lead in a series of LAMAs containing bicyclic amine moieties. In rats, its plasma half-life is 77.8 min, but inhalation at the median effective dose produces effects that last for 72 h. In the rhesus monkey, it demonstrated a similar duration of action to tiotropium, but with 5–10-fold higher median effective doses [72].

CHF 5407

CHF 5407, under development by Chiesi Farmaceutici, is an antagonist as potent and long-acting as tiotropium at human M_3 receptors, but significantly short-acting at M_2 receptors [73]. In an animal model, it was ~2–3 times more potent than tiotropium and ipratropium at reducing acetylcholine-induced bronchospasm [73], and showed a duration of action similar to that of tiotropium [74]. Phase I/II trials of inhaled CHF 5407 are currently in progress [75].

Darotropium bromide

Darotropium bromide (GSK-233705) is undergoing development by GSK. Its long duration of action when administered *via* inhalation in animal models supports its potential for use as

a once-daily bronchodilator in COPD, but no data have yet been presented [76].

TD-4208

TD-4208 is an inhaled LAMA discovered by Theravance through the application of multivalent drug design. In a phase I study designed to assess its safety, tolerability and pharmacokinetics in 20 healthy volunteers, TD-4208 was generally well tolerated at all doses tested, with a similar incidence of AEs to placebo, with no significant increase in cardiac frequency or evidence of dry mouth. Abnormal taste was reported at the higher doses [77]. In addition, TD-4208 showed the potential for 24-h bronchodilation in COPD patients [77].

TD-4208 was licensed to GSK in 2004 (GSK-1160724) under the terms of the companies' Strategic Alliance Agreement. However, GSK recently informed Theravance that it intends to return the LAMA programme to Theravance because the current formulation of TD-4208 is incompatible with GSK's proprietary inhaler device [77].

Dexpirronium

Meda Pharma (Bad Homburg, Germany) is developing dexpirronium, an anticholinergic compound that an *in vivo* animal model has shown to be similar to formoterol in reducing acetylcholine-induced bronchospasm [78]. The drug was reported to be in phase I [79].

NOVEL COMBINATIONS

LABA and long-acting antimuscarinic agents undergoing development

Several recent clinical trials have shown that concomitant therapy with a LABA and tiotropium provides significant and clinically relevant improvements in bronchodilation and COPD symptoms over each individual bronchodilator [80–85] or a LABA/ICS combination [86]. Moreover, a combination of a LABA and a LAMA is more effective than treatment with either bronchodilator alone in reducing the rate of exacerbations [84]. Nonetheless, a longer-duration trial, the Canadian Optimal Management Trial, has shown that there is no clinical advantage of combining tiotropium with salmeterol [87]. Therefore, further long-term studies are required to determine whether the combination of a LABA and a LAMA shows a genuine clinically relevant effect.

Looking at the aforementioned trials, it might be argued that it is possible that the type of LABA included in combination with a LAMA might make a difference to the results (table 3) [88].

It is not surprising, therefore, that indacaterol is being developed in a fixed-dose combination with glycopyrronium bromide (QVA-149) [6, 7]. A phase II randomised double-blind placebo-controlled multicentric study has determined the effect of 7 days of treatment with QVA-149 on lung function (mean change from baseline to 24 h post-dose FEV_1 trough) in patients with COPD [89]. Another phase II 14-day study has investigated the effect of 14-day treatment with QAV-149 compared to placebo and indacaterol on cardiac frequency and cardiovascular effects in patients with moderate-to-severe COPD in order to ensure that the product is safe [90]. The results of these two trials have not yet been released, but Novartis expects to apply for regulatory approval in 2011 [91].

Boehringer Ingelheim is developing an inhaled combination of BI-1744-CL and tiotropium. A first phase II study will explore one of two once-daily doses of BI-1744-CL administered in combination with a fixed dose of 5 μg tiotropium bromide solution for inhalation, delivered *via* the Respimat® inhaler, once daily for 4 weeks in 120 COPD patients. The primary end-point will be the trough FEV_1 response [92]. A second phase II study will determine the optimum dose (2, 5 or 10 μg) of BI-1744-CL administered with 5 μg tiotropium bromide solution for inhalation, delivered *via* the Respimat® inhaler, once daily for 4 weeks in 350 patients with COPD. Again, the primary end-point will be the trough FEV_1 response [93].

An inhaled combination of aclidinium and formoterol (LAS-40464) is also undergoing development. A randomised double-blind placebo-controlled 4-week, phase II trial was initiated in patients with moderate-to-severe stable COPD (n=513) in order to determine the optimal dose of the aclidinium/formoterol combination for investigation in phase III clinical trials. The study assessed the efficacy, safety and pharmacokinetics of three doses of formoterol combined with aclidinium compared with both agents as monotherapy, all administrated once daily by inhalation, but no information has yet been released [94]. Moreover, a randomised double-blind active-controlled parallel-group multicentric 4-week phase II pilot study is in progress to assess symptoms in moderate-to-severe stable COPD patients (n=200) taking 200 μg aclidinium once daily in combination with formoterol once or twice daily *versus* formoterol twice daily [95].

Combinations of milveterol or GSK-642444 with darotropium bromide [7], carmoterol with tiotropium [96], and formoterol with dexpirronium [78] are other possible options undergoing development for the once-daily treatment of COPD.

Several companies are also adopting a different approach and have a dimer molecule in which a bifunctional mechanism of action, combining both muscarinic antagonist and β_2-agonist pharmacology, is present in a single molecule, which is known as a dual-acting muscarinic antagonist–β_2-agonist (MABA) bronchodilator [97]. MABAs have the advantage of delivering a fixed ratio into every region of the lung, reducing the complexity of combination inhalers. The company furthest advanced in the field is Theravance together with GSK. In phase I randomised double-blind placebo-controlled single- and multiple-dose studies that enrolled healthy volunteers, GSK-961081 was generally well tolerated and demonstrated evidence of bronchodilation over 24 h after a single dose and after seven consecutive daily doses, and, consequently, has entered into phase II [7]. In a phase II study, GSK-961081 dosed at both 400 and 1,200 μg once daily showed bronchoprotection at day 14 that was at least equivalent to that of 50 μg salmeterol *b.i.d.* plus 18 μg tiotropium *u.i.d.* as measured by changes in FEV_1 [98]. Both the time to peak effect and maximum bronchodilation of GSK-961081 were numerically better than salmeterol plus tiotropium, although the study was not powered to compare the results to the salmeterol plus tiotropium control. Bicyclo[2.2.1]hept-7-ylamine derivatives are other potential MABAs under development [7]. In any case, there are many patent applications from different companies [98]. Argenta Discovery (Harlow, UK) has disclosed a series of oxazole-based muscarinic antagonists [99] wherein

TABLE 3 Novel combinations of long-acting β_2-agonists and long-acting antimuscarinic agents undergoing development

Drug(s)	Advantages	Latest developments	Company working on this strategy
Indacaterol/glycopyrronium bromide (QVA-149)	No data presented yet.	Phase II/III	Novartis, Basle, Switzerland
BI-1744-CL/tiotropium	No data presented yet.	Phase II	Boehringer Ingelheim, Ingelheim, Germany
Aclidinium/formoterol (LAS-40464)	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis.	Phase II	Almirall Prodesfarma, Barcelona, Spain
Milveterol or GSK-642444/ darotropium bromide	No data presented yet.	Phase I/II	GlaxoSmithKline, London, UK
Carmoterol/tiotropium	No data presented yet.	Phase I/II	Chiesi Farmaceutici, Parma, Italy
Formoterol/dexpirronium	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis.	Phase I/II?	Meda Pharma, Bad Homburg, Germany
GSK-961081	It is both a muscarinic antagonist and a β_2-adrenoceptor agonist. It is at least equivalent to 50 μg salmeterol *b.i.d.* plus 18 μg tiotropium *u.i.d.*	Phase II	GlaxoSmithKline, London, UK/Theravance, South San Francisco, CA, USA

the two pharmacologies are linked by an alkylene, alkenylene or alkynylene chain. A range of β_2-agonist head groups are claimed.

LABA and ICS undergoing development

As combination therapy with an ICS and a LABA is now considered a therapeutic option for treating patients suffering from severe-to-very-severe COPD or asthma [1–4], there is a genuine interest in developing a once-daily combination therapy, again in an attempt to simplify the treatment, and also to overcome the loss of patent protection. The awareness that new ICSs, such as ciclesonide and mometasone, which can be used with once-daily dosing, have been developed or are in development has further supported the development of new ultra-LABAs that can be used on a once-daily basis (table 4) [7, 91].

The carmoterol/budesonide combination, which was two-fold more effective than the formoterol/budesonide combination in animal models, may represent a new fixed combination in asthma and COPD [100].

Combinations containing formoterol and the once-daily ICS mometasone (MFF258) or formoterol and ciclesonide in a single inhalation device are undergoing development [97]. A next-generation once-daily combination consisting of fluticasone furoate, a new long-acting ICS, and milveterol, was stated to be in phase II studies in asthma and COPD. Fluticasone furoate has shown evidence of greater potency and the potential for once-daily dosing, compared to existing treatments [6]. Fluticasone furoate plus GSK-642444 is also undergoing development and it is likely that it will be the fluticasone plus salmeterol successor, apparently because of the apparent better profile of GSK-642444.

Another new inhaled therapy will combine indacaterol with mometasone (QMF-149) or with QAE-397, a novel corticosteroid in phase II development for the treatment of asthma [6, 7]. In particular, two trials have investigated the safety and tolerability of QMF-149. The first was designed to evaluate the bronchodilatory efficacy of QMF-149 delivered *via* an MDDPI (Twisthaler; Schering-Plough Corporation, Kenilworth, NJ, USA) in adult patients with persistent asthma using open-label salmeterol/fluticasone (50/250 μg *b.i.d.*) as an active control [101], whereas the second one investigated the safety and tolerability of 14 days' treatment with QMF-149 (500 μg indacaterol/800 μg QAE-397) in patients with mild-to-moderate asthma [102]. The results of these trials have not yet been released.

TABLE 4 Novel combinations of long-acting β_2-agonists and inhaled corticosteroids undergoing development

Drugs	Advantages	Latest developments	Company working on this strategy
Carmoterol/budesonide	It is two-fold more effective than formoterol/budesonide in animal models.	Phase I/II	Chiesi Farmaceutici, Parma Italy
Indacaterol/mometasone (QMF-149)	It has a superior delivery profile than formoterol/budesonide owing to its once-daily dosing.	Phase III	Novartis, Basle, Switzerland/Schering-Plough Corporation, Kenilworth, NJ, USA
GSK-642444/fluticasone furoate	No data presented yet.	Phase IIb	GlaxoSmithKline, London, UK
Formoterol/mometasone (MFF258)	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis.	Phase III	Novartis, Basle, Switzerland/Schering-Plough Corporation, Kenilworth, NJ, USA
Formoterol/ciclesonide	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis.	Phase II	Nycomed, Zurich, Switzerland/Sanofi Aventis, Paris, France

LABA, LAMA and ICS or novel anti-inflammatory compounds

The development of once-daily dual-action ultra-LABA/LAMA combination products may also serve as a basis for improved triple therapy combinations through co-formulation with novel ICSs or novel anti-inflammatory compounds, such as inhaled phosphodiesterase (PDE) 4 inhibitors, that could deliver three complementary therapeutic effects in patients with asthma and, mainly, COPD [7, 88, 97]. The potential for these therapeutic strategies to be administered once daily simplifies patient treatment regimens and therefore increases the likelihood of compliance with therapy.

A combination of indacaterol, glycopyrronium bromide and mometasone seems to be a real possibility [97]. A combination of milveterol or GSK-642444 with darotropium bromide and fluticasone furoate is another valid option, whereas the combination of LAS-40369, an association of aclidinium plus an undisclosed ICS under development, with formoterol is a potential possibility that should be explored. A combination that features the inhaled PDE4 inhibitor tofimilast (phase II) with a LAMA (potentially tiotropium) in addition to, potentially, a MABA seems to be less realistic [97].

It is intriguing that a family of dual-action M_3 antagonists/PDE4 inhibitors has recently been discovered [103, 104]. The pharmacological profile of UCB-101333-3, a 4,6-diaminopyrimidine, is interesting [104]. The addition of an ultra-LABA to UCB-101333-3 should create a potent combination for treating asthma and, mainly, COPD.

CONCLUSION

Bronchodilators remain central to the symptomatic management of COPD and asthma. We believe that once-daily dosing of a bronchodilator would be a significant convenience and probably a compliance-enhancing advantage, leading to improved overall clinical outcomes in patients with asthma and COPD. The only limits set for the development of a long-lasting bronchodilator with a new product profile are medical needs and marketing opportunities. For example, the growing evidence of the importance of tiotropium in the maintenance treatment of COPD and its high brand loyalty in the COPD market are pushing pharmacological research to find new LAMAs that might be as successful as tiotropium is. Nonetheless, if this is the main reason for the introduction of new bronchodilators to the market, it is mandatory to document that they are at least as effective as tiotropium. It should also be mentioned that several companies are probably proceeding in attempts to create fixed combinations with a LAMA or novel ICSs and formoterol because the patent for formoterol has expired, whereas the first patent for salmeterol expired in August 2008 and there are other circumstances that could come up to extend the exclusivity period of salmeterol beyond 2008. These circumstances could include things such as other patents for specific salmeterol use or lawsuits.

In any case, we believe that these new drugs, although effective, should not be more expensive than those currently on the market. Indeed, in a period of containment of healthcare costs, drugs that cannot be considered genuinely to have overtaken current therapies cannot justify an increase in costs.

Our opinion is that it will be advantageous to develop inhalers containing a combination of several classes of long-acting bronchodilator in an attempt to simplify treatment regimens as much as possible. The investigational therapies for COPD and asthma discussed above have shown promising results. It is likely that the development of once-daily dual-action ultra-LABA/LAMA combination products may serve as a basis for improved triple therapy combinations through co-formulation with novel ICSs or novel anti-inflammatory compounds, such as inhaled PDE4 inhibitors, that could deliver three complementary therapeutic effects in patients with COPD and asthma. Such a therapeutic option should certainly be considered an advance because it permits greater adherence to treatment, which will ensure improved cost-effectiveness of the prescribed therapy.

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