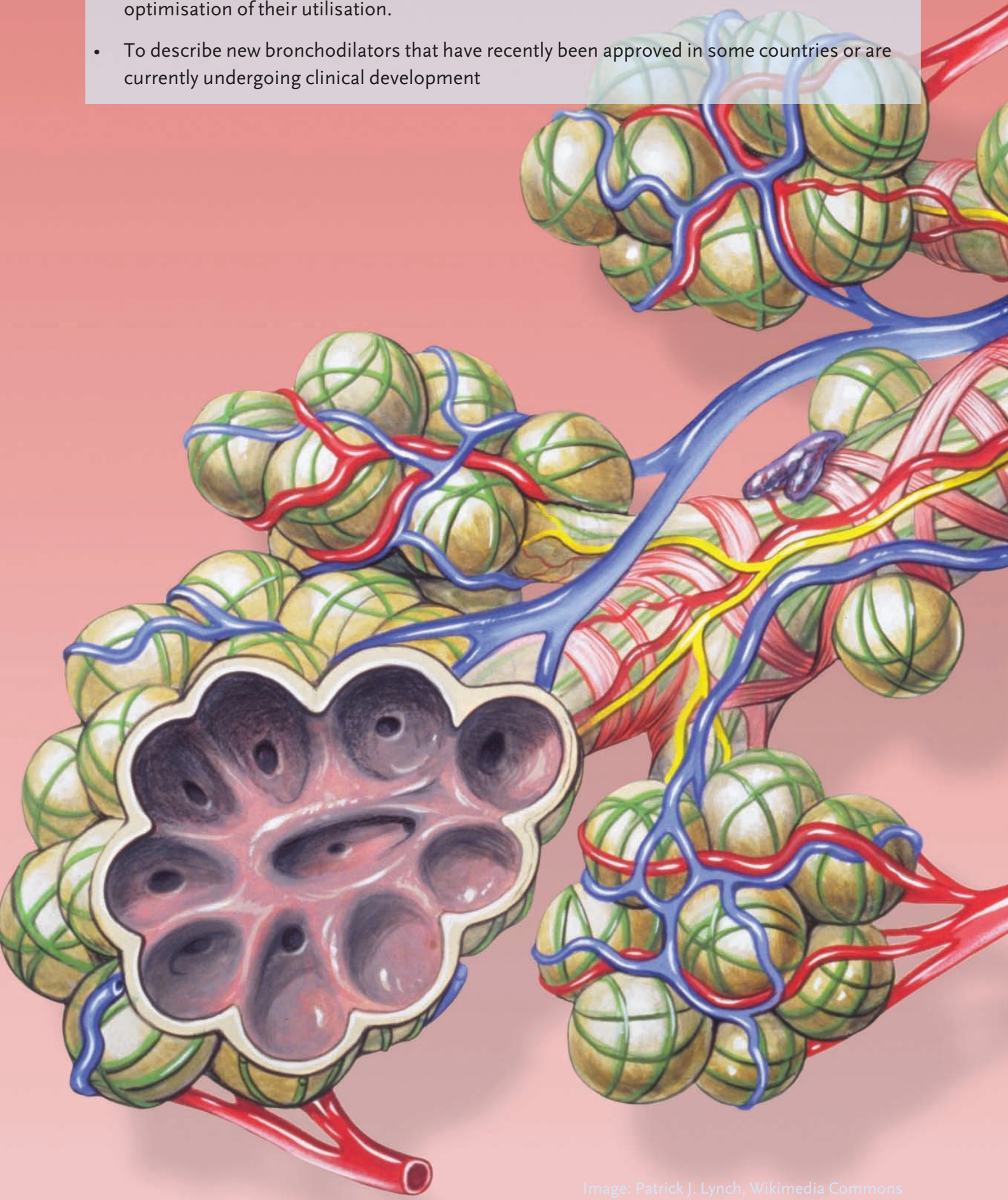
Educational aims

- To discuss fundamental questions relating to the use of bronchodilators that can lead to an optimisation of their utilisation.
- To describe new bronchodilators that have recently been approved in some countries or are currently undergoing clinical development



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Long-acting bronchodilators in COPD: where are we now and where are we going?

Summary

Bronchodilators are central to the treatment of chronic obstructive pulmonary disease (COPD) because they alleviate bronchial obstruction and airflow limitation, reduce hyperinflation, and improve emptying of the lung and exercise performance. For this reason, all guidelines highlight that inhaled bronchodilators are the mainstay of the current management of all stages of COPD.

However, there are still fundamental questions regarding their use that require clarification to optimise utilisation of these drugs. It is crucial to address the following questions. Is it appropriate to treat all COPD patients with long-acting bronchodilators? Is it better to start treatment with a β_2-agonist or with an anti-muscarinic agent in patients with stable mild/moderate COPD? Is it useful to use a bronchodilator with rapid onset of action? Is it preferable to administer a bronchodilator on a once- or twice-daily basis? Can a second bronchodilator be introduced for patients with stable COPD (''dual'' bronchodilator therapy), and if so when? Are inhaled corticosteroids (ICSs) really useful in COPD patients without chronic bronchitis, since long-lasting bronchodilators may prevent exacerbations even in the absence of an ICS in frequent exacerbators? Finally, is combined therapy really useful in non-frequent exacerbators?

Due to the the central role of bronchodilators in the treatment of COPD, there is still considerable interest in finding novel classes of bronchodilator drugs. However, new classes of bronchodilators have proved difficult to develop because either new emerging targets are not really important and/or it is difficult to find substances capable of interacting with them. As a consequence, many research groups have sought to improve the existing classes of bronchodilators.

Statement of Interest

Mario Cazzola has received honoraria for speaking and consulting and/or financial support for attending meetings from Abbott, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Dey, GlaxoSmithKline, Guidotti, Lallemand, Malesci, Menarini Farmaceutici, Mundipharma, Novartis, Pfizer, Sanovel, Sigma Tau, Takeda and Valeas. Clive Page has received speaker fees from Novartis and Almirall. He is a co-founder and has equity in Verona Pharma who are developing RPL 554 as a novel bronchodilator.

Introduction

Bronchodilators are central to the treatment of chronic obstructive pulmonary disease (COPD), notwithstanding that there is often limited reversibility of airflow obstruction [1, 2]. The existing drug classes (β_2-agonists and muscarinic receptor antagonists) work by relaxing airway smooth muscle tone, leading to reduced respiratory muscle activity and

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improvements in ventilatory mechanics, making it easier for patients to breathe. Bronchodilation aims at alleviating bronchial obstruction and airflow limitation, reducing hyperinflation, and improving emptying of the lung and exercise performance [1, 2].

The importance of bronchodilation explains why all guidelines highlight that inhaled bronchodilators are the mainstay of the current management of COPD at all stages of the disease [3–5]. However, the recent American College of Physicians (ACP)/American College of Chest Physicians (ACCP)/American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines conclude that no sufficient evidence exists to support bronchodilator treatment in asymptomatic COPD patients [5].

Where are we now?

Although bronchodilators are important in the management of patients with COPD, there are still fundamental questions regarding their use that require clarification to optimise utilisation of these drugs (table 1).

Is it appropriate to treat all COPD patients with long-acting bronchodilators?

Both the TORCH (Toward a Revolution in COPD Health) [6] and UPLIFT (Understanding Potential Long-Term Impacts on Funtion with Tiotropium) [7] studies have documented that regular treatment with long-acting bronchodilators does not reduce the accelerated decline in lung function in some patients with COPD. This finding should not be considered unexpected as it is well known that COPD is not invariably progressive. Individual rates of decline in forced expiratory volume in 1 s (FEV_1) have been found to vary considerably across participants with COPD in both observational cohorts and intervention trials, ranging from decreases as rapid as 150–200 mL per year to increases of up to ~150 mL per year [8]. A trial that disregards this fundamental aspect includes all COPD patients regardless of whether or not they are undergoing FEV_1 decline, but it is likely that bronchodilators are only effective in those who lose pulmonary function.

Data collected in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) observational study found that the rate of decline in FEV_1 over a 3-year period was highly variable, with an increase in the magnitude of the decline among current smokers, patients with bronchodilator reversibility, frequent exacerbators and patients with emphysema [9]. However, the mean rate of decline appeared to be inversely related to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [9]. Intriguingly, both the TORCH [10] and UPLIFT [11] studies have suggested that long-acting bronchodilators reduce the rate of decline of post-bronchodilator FEV_1 in patients with GOLD stage II COPD. Since it is impossible to identify fast decliners, it seems appropriate to treat all COPD patients with bronchodilators, particularly those in the early stages of the disease, current smokers, those with emphysema or bronchodilator reversibility, and frequent exacerbators. It is noteworthy that a consensus initiative for optimising therapeutic appropriateness among Italian specialists concluded that regular therapy with long-acting bronchodilators should be started in obstructed patients in both the presence and absence of symptoms [12].

Table 1 *General questions to be addressed to optimise use of bronchodilators in COPD*

- **Is it appropriate to treat all COPD patients with long-acting bronchodilators?**
- **Is it better to start with a β_2-agonist or with an anti-muscarinic agent?**
- **Is it useful to use a bronchodilator with a rapid onset of action?**
- **Is once- or twice-daily dosing preferable?**
- **When can we add a second bronchodilator with a different mechanism of action?**
- **When must we add an ICS?**

Is it better to start with a β_2-agonist or with an anti-muscarinic agent?

In almost all guidelines no distinction is made as to which class of bronchodilators should be considered first, but they only recommend the use of long-acting bronchodilator agents [3–5]. The National Institute for Health and Clinical Excellence (NICE), in its 2010 update of COPD treatment guidelines, reviewed all studies that compared long-acting β-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), and concluded that there was no evidence to favour one treatment

over another [4]. Whereas the GOLD guidelines [3] affirm that the choice depends on the availability of drugs and the patient's response in terms of symptom relief and side-effects. However, data from efficacy trials suggest that twice-daily LABAs (salmeterol and formoterol) are preferable to short-acting anti-muscarinic agents (ipratropium) [13, 14], whereas once-daily tiotropium, a LAMA [15, 16], and indacaterol, an ultra-LABA [17], are superior to twice-daily LABAs.

Unfortunately, there is no head-to-head randomised controlled trial (RCT) that evaluates all the different monotherapies available, and it is unlikely that such a trial will ever be performed (given the increasing number of options available) [18]. In any case, it is likely that the lack of indication of the class of bronchodilators that must be used as first choice is due to the fact that the superiority of one class over another, which has been documented by some RCTs, can be correlated to a specific outcome or be obtained by a specific method of research. Thus, LABAs are more effective than LAMAs if we consider symptoms or health-related quality of life (HRQoL) as the primary outcome [19], although LAMAs also impact favourably on both outcomes [18]. By contrast, LAMAs appear to be more effective than LABAs if exacerbations are the expected primary outcome, and this is regardless of whether LABAs are administered on a twice-daily [16] or once-daily basis [20]. Therefore, the choice of bronchodilator to start treatment with in a patient with COPD mainly depends on the outcome of interest. In the symptomatic patient, there is no substantial difference between LABAs or LAMAs, whereas in frequent exacerbators, it seems preferable to use a LAMA.

Is it useful to use a bronchodilator with rapid onset of action?

It is not yet clear if the differences in bronchodilator onset of action (fast-onset action *versus* slow-onset action) have any clinical role in COPD. In COPD patients, symptoms vary over the day, with morning considered the time when symptoms are more severe [21]. It might be hypothesised that fast-acting agents could be more effective on these symptoms than those with a relatively slow onset of action by providing a rapid relief of symptoms after morning dosing [22]. In addition, adherence is lower for medications that do not have an immediate effect on symptoms [23]. Prompt symptom relief will give reassurance of effectiveness and could be a key factor in patient compliance. Obviously, among LABAs, agents with a rapid onset of action could be more effective on morning symptoms than those with a relatively slow onset of action. This means that in the symptomatic patient formoterol and indacaterol should be preferred to salmeterol, and glycopyrronium or aclidinium to tiotropium.

Is once- or twice-daily dosing preferable?

An important question that has been highlighted in recent years is whether it is preferable to administer a bronchodilator on a once- or twice-daily basis. Apparently, the duration of bronchodilation appears to determine the clinical efficacy of a bronchodilator at least in COPD. It has been suggested that, with an extended duration of bronchodilation, the net area under the time/airflow curve increases and persistent bronchorelaxant effects of once daily bronchodilators lead to increased morning FEV_1 following the last inhalation (''trough'' FEV_1) [24]. This could result, on average, in less dyspnoea and facilitated lung emptying during tidal breathing at rest over 24 h [24]. Recently, however, a population pharmacodynamic model of the longitudinal FEV_1 response to an inhaled LAMA in COPD patients has suggested that with the same total daily dose of a new muscarinic receptor antagonist, aclidinium, a twice-daily regimen provides higher bronchodilation at trough than a once-daily regimen [25]. In any case, since there is a progressive attempt to shift attention towards controlling nocturnal symptoms and those present on awakening, which epidemiological studies indicate to be the most troublesome for COPD patients [21], the twice-daily dosing of bronchodilators should be considered a useful approach at least for the symptomatic treatment of COPD. Unfortunately, we cannot yet determine, even indirectly, whether twice-daily administration may be preferred to the once-daily dosing of bronchodilators, particularly when the drug is administered in the evening or early in the morning, due to a lack of evidence from appropriate large trials [26]. Nonetheless, a recent small short-term study (6 weeks of treatment) showed that aclidinium, a twice-daily LAMA, provided improvements in

early-morning and night-time symptoms that were consistently numerically greater than those observed with tiotropium, which is a once-daily LAMA [27].

When can we add a second bronchodilator with a different mechanism of action?

Since there is no solid guidance on when to combine two bronchodilators with different mechanisms of action, an answer to this question, whether and when a second bronchodilator can be added (''dual'' bronchodilator therapy) in patients with stable COPD, is imperative. Most specialists believe that patients not controlled by a single bronchodilator should be given two bronchodilators with different mechanisms of action [12]. Certainly this seems to be a good choice because using multiple drugs in combination may lower doses of individual agents, decrease adverse effects, simplify medication regimens, and improve compliance [2]. In effect, the revised 2014 GOLD recommendations indicate that the combined use of short-acting β-agonists or LABAs and LAMAs may be considered if symptoms are not improved with single agents [3]. Studies of LABA/LAMA combinations, to date, indicate that combining different classes of bronchodilator results in significantly greater improvements in lung function and other meaningful outcomes such as inspiratory capacity, dyspnoea, symptom scores, rescue medication use, and health status in comparison with individual drugs [28]. Nonetheless, according to the NICE guidelines [4], treatment with LAMAs plus LABAs is recommended in people with COPD who remain symptomatic on treatment with a LABA alone, whereas the LABA/LAMA combination is not recommended in those already taking a LAMA as sole maintenance therapy. However, this recommendation is certainly surpassed by recent evidence documenting that the regular addition of a LABA to a LAMA not only induces a larger bronchodilation than that obtained with only the LAMA [29], but also significantly improves many patient-reported outcomes [30].

When must we add an ICS?

The last big question that still awaits a definitive answer is whether and when to add an inhaled corticosteroid (ICS) (''combined'' therapy). This is a crucial question because ICSs are still overprescribed, by both general practitioners [31] and pulmonologists [32], and there is now growing concern that this drug class may increase the risk of pneumonia in some patients with COPD. Moreover, although monotherapy with ICSs is not approved for the treatment of COPD, even specialists in respiratory medicine sometimes prescribe ICS monotherapy to COPD patients [32]. The magnitude of the drawbacks of ICSs in COPD when compared with the benefits [33] explain why all national and international COPD guidelines recommend ICSs only for patients with severe impairment and high risk of exacerbations. NICE guidelines encourage the use of ICS with bronchodilators if patients have moderate or severe COPD and are still symptomatic, or are experiencing two or more exacerbations requiring treatment per year [4]. The GOLD strategy recommends ICSs in combination with LABAs or, alternatively, with LAMAs for those patients who have few symptoms but are at a high risk of exacerbations (group C patients) and also for those patients who have many symptoms and a high risk of exacerbations (group D patients) [3]. The very recent Spanish COPD guidelines [34], which recognise the clinical heterogeneity of COPD and suggest a specific therapeutic approach directed by the so-called clinical phenotypes of the disease, recommend that ICSs can be used in the mixed COPD phenotype characterised by airflow obstruction that is not completely reversible and accompanied by symptoms or signs of an increased reversibility of the obstruction. Moreover, ICSs may be tried in patients at severity level II (moderate COPD) who persist with exacerbations despite treatment with one or two long-acting bronchodilators. In patients at severity level III (severe COPD) who do not present a level of control of symptoms or exacerbations with two drugs (two long-acting bronchodilators or one long-acting bronchodilator plus an ICS), triple therapy (LAMA+LABA+ICS) can be used.

ICSs are more effective in frequent exacerbators with chronic bronchitis predominance and in those with overlap between COPD and asthma [35]. Therefore, there is room for the use of ICSs in COPD, or at least in some subtypes of COPD [36]. The right question now becomes not whether they should not be used at all, unless patients

have concomitant asthma [37], but, instead, which patients with COPD can benefit from therapy with ICSs. Consequently, we must decide if ICSs are really useful in COPD patients without chronic bronchitis, whether long-lasting bronchodilators may prevent exacerbations even in the absence of an ICS in frequent exacerbators and the utility of combined therapy in nonfrequent exacerbators [38]. Moreover, it is essential to establish whether LAMA/LABA combination therapy is preferred over LAMA plus LABA/ICS, and whether addition of an ICS to the LAMA/LABA combination provides additional clinical value because data are still too scarce and studies too short to generate a strong recommendation. The answer to these questions would allow us to optimise the use of ICSs in COPD [33].

Where are we going?

Because of the central role of bronchodilators in the treatment of COPD, there is still considerable interest in finding novel classes of bronchodilator drugs. Unfortunately, new classes of bronchodilators have proved difficult to develop. However, since 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 [39], many research groups have sought to improve the existing classes of bronchodilators (table 2) [1, 40, 41].

New examples of existing bronchodilator classes

LABAs

Several once-daily LABAs, olodaterol, vilanterol and abediterol, have recently been approved in some countries or are currently undergoing late stage clinical development [42]. These agents are single enantiomers of the (R)-configuration and have an essentially full-agonist profile at human β_2-adrenoreceptors. They all produce a dose-dependent rapid bronchodilation, which is maintained over 24 h, with a safety and tolerability profile similar to that of placebo.

LAMAs

Several new LAMAs are also in clinical development [43]. Umeclidinium bromide is being developed as a once-daily treatment of COPD. *In vitro*, it shows a longer duration of action than tiotropium bromide. Treatment with 62.5 and 125 µg inhaled umeclidinium once-daily is well tolerated and provides significant improvement in lung function, dyspnoea and health status [44]. Glycopyrronium bromide, already on the market as a once-daily LAMA (NVA237), is in clinical development in several different formulations by several pharmaceutical companies. SUN-101, formerly EP-101, is an inhalation solution formulation of glycopyrronium bromide optimised for administration *via* the investigational eFlow Nebulizer System (PARI Pharma GmbH, Munich, Germany). Once-daily treatment with SUN-101 doses ranging from 25 µg to 200 µg was well tolerated overall and produced no significant effects on cardiovascular assessments with a safety profile similar to placebo, tiotropium and ipratropium in patients with COPD [45]. CHF-5259 is another inhaled formulation of glycopyrronium bromide that is delivered using a pressurised metered-dose inhaler (MDI) [43]. PT001 is also delivered *via* a novel pressurised MDI that uses a porous particle-based suspension technology, which allows better targeting of drugs to the airways and enables the development of products

Table 2 *Bronchodilators that have recently been approved in some countries or are currently undergoing clinical development*

- **LABAs**
  Olodaterol, vilanterol, abediterol
- **LAMAs**
  Aclidinium, glycopyrronium, umeclidinium
- **LAMA/LABA combinations**
  Glycopyrronium/indacaterol (QVA149), umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/formoterol, glycopyrronium bromide/formoterol (PT001)
- **MABAs**
  GSK-961081, AZD2115
- **LABA/ICS combination**
  Fluticasone furoate/vilanterol, mometasone/indacaterol (QMF149)
- **LAMA/LABA/ICS "triple combination inhalers"**
  Ciclesonide/tiotropium/formoterol, beclomethasone/formoterol/glycopyrronium, QMF149/glycopyrronium, umeclidinium/vilanterol/fluticasone furoate, GSK961081/fluticasone

with improved physical stability and uniformity of dose content. Glycopyrrolate MDI 36 μg twice daily provided statistically significant improvements in lung function ($p<0.0001$ *versus* placebo), which were comparable with tiotropium bromide [46]. CHF-5259 and PT001 are likely being developed as twice-daily bronchodilators [2].

LAMA/LABA combinations

Since an increasing body of evidence suggests that the LAMA/LABA combination appears to play an important role in maximising bronchodilation, there is a strong interest in developing new once-daily LABA/LAMA fixed-dose combinations. Glycopyrronium/indacaterol (QVA149) has just been approved by the European Commission and the Japanese Ministry of Health Labour and Welfare as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The pivotal phase III IGNITE programme, which explored the effects of QVA149, comprised 11 studies in total with more than 10 000 patients across 52 countries, has documented a significant improvement in lung function and patient-reported outcomes including breathlessness and rescue medication use compared with current standard of care, reduced rates of COPD exacerbations, and improved HRQoL compared to open-label tiotropium 18 μg and glycopyrronium 50 μg [47–50]. Umeclidinium/vilanterol, which has been developed using two different dose combinations that contain 25 μg of vilanterol with either 62.5 or 125 μg umeclidinium bromide and are delivered using the new Ellipta inhaler (GlaxoSmithKline, Brentford, UK) [51], has been approved by the US Food and Drug Administration (FDA) New Drug Application to be used for maintenance treatment of airflow obstruction in patients with COPD at a dose of 62.5 μg of umeclidinium and 25 μg of vilanterol once daily [52]. It has subsequently been approved for use in the same indication in Canada, with submissions for regulatory approval in patients with COPD under review elsewhere, including in Europe and Japan [52]. Pivotal RCTs have shown that both doses elicited significant improvements with respect to lung function, dyspnoea and HRQoL relative to placebo and either monotherapy [53–55]. Tiotropium/olodaterol, another once-daily LAMA/LABA inhaled fixed-dose formulation, is being developed in two dose combinations: 2.5 or 5 μg tiotropium plus 5 μg olodaterol using the Respimat inhaler (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany). To date, no clinical results with the combination have been published, but preliminary results presented as abstracts at European Respiratory Society congresses have shown significant improvements in peak FEV_1 with tiotropium/olodaterol 5/2.5 μg, 5/5 μg, and 5/10 μg, and in trough FEV_1 with tiotropium/olodaterol 5/10 μg *versus* tiotropium monotherapy [56], and with all doses of tiotropium (1.25, 2.5, and 5 μg) in combination with olodaterol either 5 μg or 10 μg *versus* olodaterol monotherapy, with evidence of dose ordering [57].

We have already mentioned that there is a progressive shift towards controlling nocturnal symptoms and those present on awakening, for this reason the twice-daily dosing of bronchodilators is still considered a useful approach at least for the symptomatic treatment of COPD. Therefore, it is not surprising that two twice-daily LABA/LAMA fixed-dose combinations, aclidinium/formoterol and glycopyrronium bromide/formoterol, are under clinical development. Aclidinium/formoterol is being developed exploring the effects of two dose combinations (400/12 μg and 400/6 μg) given twice daily. The few clinical data at our disposal show that the addition of formoterol fumarate to aclidinium bromide results in greater bronchodilation and improvements in dyspnoea and HRQoL than formoterol fumarate or aclidinium bromide alone [58]. PT003 (GFF-MDI) is an inhaled combination of PT001 (glycopyrronium bromide) and formoterol fumarate, delivered *via* the eFlow Nebulizer System (PARI Pharma GmbH). Significant improvements in lung function have been reported with PT003 (36/9.6 and 72/9.6 μg) *versus* monotherapy with glycopyrronium, formoterol, or tiotropium [59, 60], and in inspiratory capacity *versus* tiotropium monotherapy [59]. Another study showed PT003 to be superior to either a Handihaler (Boehringer Ingelheim) formulation of tiotropium or an Aerolizer (Novartis Pharma AG, Basel, Switzerland) formulation of formoterol [61]. Low doses (1.2–18 μg glycopyrronium plus 9.6 μg formoterol) of PT003 provide superior bronchodilation compared with the individual components (18 μg glycopyrronium MDI and 9.6 μg formoterol MDI) and to 18 μg tiotropium Handihaler [62].

Muscarinic β_2-agonists

Bi-functional (or dual pharmacophore) muscarinic β_2-agonists (MABA) agents are a novel approach to "dual" bronchodilator therapy that combine muscarinic antagonism and β_2 agonism in a single molecule [63, 64]. This approach may offer several advantages over combination therapy with two separate drug entities [1]. They include the benefit of delivering a fixed ratio into every region of the lung reducing the complexity of combination inhalers, a single pharmacokinetic profile, a uniform ratio of activities at the cellular level and a simplified clinical development programme. However, one limitation of MABA molecules is that the ratio of muscarinic antagonism and β_2 agonism activities cannot be adjusted as needed and this may limit dosing flexibility [64]. The attractiveness of the MABA concept has led to research into several candidates, but only two (GSK-961081 and AZD2115) have progressed to advanced clinical development and, in any case, few clinical data have been reported to date. Consequently, it remains to be established if their use would offer any clinical benefits relative to LAMA/LABA combinations [65]. It has been suggested that their significance is more likely to stem from their use in combination with an ICS where only two drugs need to be co-formulated, rather than three [65].

LABA/ICS combination

Since the efficacy of combination therapy with a LABA plus a low dose of ICS in patients with COPD has been well documented, there is a strong interest in developing new LABAS/ICS combinations, mainly on a once-daily basis, in an attempt to simplify treatment, but also to overcome the loss of patent protection [41].

The US FDA has approved fluticasone furoate/vilanterol dry powder inhaler for the long-term, once-daily, maintenance treatment of airflow obstruction in COPD patients, including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbations because addition of fluticasone furoate to vilanterol is associated with a decreased rate of moderate and severe exacerbations of COPD in patients with a history of exacerbation [66]. However, it should be noted that benefits over a twice-daily ICS/LABA comparator were not shown [67]. In view of the fact that mometasone is effective when it is administered once daily, a fixed dose combination of mometasone and indacaterol (QMF149) administered *via* the Breezhaler device (Novartis) is being evaluated in patients with COPD, but no clinical data have yet been published [41].

LAMA/LABA/ICS "triple combination inhalers"

There is limited documented clinical evidence for the use of triple therapy in COPD, but studies published to date indicate that LABA/ICS in combination with tiotropium bromide improves lung function, COPD symptoms and health status, and reduces the risk of hospitalisations compared with tiotropium bromide alone in patients with moderate-to-severe COPD [68]. The first triple inhaler, containing 200 µg ciclesonide, 9 µg tiotropium and 6 µg formoterol fumarate, to be taken once daily is already available in India. This formulation is a suspension-based product. A new combination of beclomethasone/formoterol 100/6 µg plus glycopyrronium (at dosage of 25 or 50 µg) taken twice daily is under clinical evaluation. It is likely that triple combinations with QMF149 plus glycopyrronium and umeclidinium/vilanterol plus fluticasone furoate will be developed on a once daily basis. A combination of GSK961081 and fluticasone furoate is in an early phase of clinical development.

Novel classes of bronchodilators

Novel classes of bronchodilators have proved difficult to develop, but there is still a continued interest in generating new bronchodilators that act *via* emerging targets, particularly given the concerns over the long-term safety of β_2-agonists [69]. Progress to date has been limited, this is likely to be because these new targets are not really important and/or it is difficult to find substances capable of interacting with them.

Potassium channel openers, vasoactive intestinal peptide analogs, rho kinase inhibitors, brain natriuretic peptide and analogs, nitric oxide donors, E-prostanoid receptor 4 agonists, and bitter taste receptor agonists are considered potential new classes of bronchodilators (table 3) [1]. They influence alternative targets that seem important for inducing bronchodilation. Unfortunately, the

Table 3 *Potential novel classes of bronchodilators*

- **Selective phosphodiesterase inhibitors**
- **Potassium channel openers**
- **Vasoactive intestinal peptide analogues**
- **Rho kinase inhibitors**
- **Brain natriuretic peptide and analogues**
- **Nitric oxide donors**
- **E-prostanoid receptor 4 agonists**
- **Bitter taste receptor agonists**

development of many of them is delayed or blocked because of limited efficacy and/or safety problems [1].

An alternative approach is to develop molecules designed to have two distinct primary pharmacological actions based on distinct pharmacophores, *i.e.* bifunctional drugs, which might be able to deliver complementary pharmacological activities for the treatment of patients with asthma or COPD. Currently, the first bifunctional bronchodilator/anti-inflammatory drugs (phosphodiesterase (PDE)3/PDE4 inhibitors) are in clinical development [1].

There is documentation that the PDE3 isoenzyme predominates in airway smooth muscle and inhibition of this enzyme, rather than PDE4, leads to airway smooth muscle relaxation, whereas the PDE4 isoenzyme is the predominant isoenzyme in the majority of inflammatory cells, including neutrophils [70]. Consequently, dual PDE3/PDE4 inhibitors can combine bronchodilation with anti-inflammatory activity, representing a potential new class of drugs for the treatment of patients with asthma or COPD [70]. Recently, a dual PDE3/PDE4 inhibitor RPL554 has been developed. It produces a rapid, significant and sustained bronchodilator effect in patients with mild-to-moderate COPD and also in patients with asthma when administered by the inhaled route and appears to be at least as effective as salbutamol as a bronchodilator [71]. At the same dose that elicits bronchodilation, RPL554 also exhibits highly significant anti-inflammatory effects in humans, as it is able to reduce the ability of lipopolysaccharide to induce recruitment of inflammatory cells into the airways, particularly the absolute numbers of neutrophils, eosinophils, lymphocytes and macrophages [71].

Key points

- Bronchodilators, which aim to alleviate bronchial obstruction and airflow limitation, reduce hyperinflation, and improve emptying of the lung and exercise performance, are central to the treatment of COPD, notwithstanding that there is often limited reversibility of airflow obstruction.
- Although bronchodilator drugs are important in the management of patients with COPD, there are still fundamental questions regarding their use that require clarification to optimise the use of these drugs.
- There is still considerable interest in finding novel classes of bronchodilator drugs, but new classes of bronchodilators have proved difficult to develop, this is likely to be because new emerging targets are not really important and/or it is difficult to find substances capable of interacting with them.
- Since 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, many research groups have sought to improve the existing classes of bronchodilators.

References

1. Cazzola M, Page CP, Calzetta L, *et al.* Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev* 2012; 64: 450–504.
2. Cazzola M, Matera MG. Bronchodilators: current and future. *Clin Chest Med* 2014; 35: 191–201.
3. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD 2014. www.goldcopd.org
4. National Clinical Guideline Centre. Chronic Obstructive Pulmonary Disease: Management of

Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care. National Clinical Guideline Centre, London, 2010. http://guidance.nice.org.uk/CG101/Guidance/pdf/English
5. Qaseem A, Wilt TJ, Weinberger SE, *et al.* Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011; 155: 179–191.
6. Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178: 332–338.
7. Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
8. Tashkin DP. Variations in FEV_1 decline over time in chronic obstructive pulmonary disease and its implications. *Curr Opin Pulm Med* 2013; 19: 116–124.
9. Vestbo J, Edwards LD, Scanlon PD, *et al.* Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365: 1184–1192.
10. Jenkins CR, Jones PW, Calverley PMA, *et al.* Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009; 10: 59.
11. Decramer M, Celli B, Kesten S, *et al.* Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; 374: 1171–1178.
12. Cazzola M, Brusasco V, Centanni S, *et al.* Project PriMo: sharing principles and practices of bronchodilator therapy monitoring in COPD: a consensus initiative for optimizing therapeutic appropriateness among Italian specialists. *Pulm Pharmacol Ther* 2013; 26: 218–228.
13. Rennard SI, Anderson W, ZuWallack R, *et al.* Use of a long-acting inhaled β_2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1087–1092.
14. Dahl R, Greefhorst LA, Nowak D, *et al.* Inhaled formoterol dry powder *versus* ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 778–784.
15. Donohue JF, van Noord JA, Bateman ED, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122: 47–55.
16. Vogelmeier C, Hederer B, Glaab T, *et al.* Tiotropium *versus* salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011; 364: 1093–1103.
17. Vogelmeier C, Magnussen H, LaForce C, *et al.* Profiling the bronchodilator effects of the novel ultra-long-acting β_2-agonist indacaterol against established treatments in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2011; 5: 345–357.
18. Cope S, Donohue JF, Jansen JP, *et al.* Comparative efficacy of long-acting bronchodilators for COPD – a network meta-analysis. *Respir Res* 2013; 14: 100.
19. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β-agonists for stable COPD: a systematic review. *Chest* 2012; 142: 1104–1110.
20. Decramer ML, Chapman KR, Dahl R, *et al.* Once-daily indacaterol *versus* tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med* 2013; 1: 524–533.
21. Kessler R, Partridge MR, Miravitlles M, *et al.* Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J* 2011; 37: 264–272.
22. Roche N, Chavannes NH, Miravitlles M. COPD symptoms in the morning: impact, evaluation and management. *Respir Res* 2013; 14: 112.
23. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008; 63: 831–838.
24. Beeh KM, Beier J. The short, the long and the "ultra-long": why duration of bronchodilator action matters in chronic obstructive pulmonary disease. *Adv Ther* 2010; 27: 150–159.
25. Wu K, Looby M, Pillai G, *et al.* Population pharmacodynamic model of the longitudinal FEV_1 response to an inhaled long-acting anti-muscarinic in COPD patients. *J Pharmacokinet Pharmacodyn* 2011; 38: 105–119.
26. Cazzola M, Rogliani P, Matera MG. Aclidinium bromide/formoterol fumarate fixed-dose combination for the treatment of chronic obstructive pulmonary disease. *Expert Opin Pharmacother* 2013; 14: 775–781.
27. Beier J, Kirsten AM, Mróz R, *et al.* Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD* 2013; 10: 511–522.
28. van der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. *Prim Care Respir J* 2012; 21: 101–108.
29. Mahler DA, D'Urzo A, Bateman ED, *et al.* Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 2012; 67: 781–788.
30. Mahler DA, Buhl R, Lawrence D, *et al.* Efficacy and safety of indacaterol and tiotropium in COPD patients according to dyspnoea severity. *Pulm Pharmacol Ther* 2013; 26: 348–355.
31. Cazzola M, Segreti A, Bettoncelli G, *et al.* Change in asthma and COPD prescribing by Italian general practitioners between 2006 and 2008. *Prim Care Respir J* 2011; 20: 291–298.
32. Corrado A, Rossi A. How far is real life from COPD therapy guidelines? An Italian observational study. *Respir Med* 2012; 106: 989–997.
33. Cazzola M, Rogliani P, Novelli L, *et al.* Inhaled corticosteroids for chronic obstructive pulmonary disease. *Expert Opin Pharmacother* 2013; 14: 2489–2499.
34. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* Spanish COPD Guidelines (GesEPOC): pharmacological treatment of stable COPD. *Arch Bronconeumol* 2012; 48: 247–257.
35. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J* 2013; 41: 1252–1256.
36. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* A new approach to grading and treating COPD based on clinical phenotypes: summary of the Spanish COPD guidelines (GesEPOC). *Prim Care Respir J* 2013; 22: 117–121.
37. Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J* 2009; 34: 13–16.
38. Cazzola M, Segreti A, Rogliani P. Comparative effectiveness of drugs for chronic obstructive pulmonary disease. *Drugs Today (Barc)* 2012; 48: 785–794.

39. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. *Eur Respir J* 2009; 34: 757–769.
40. Matera MG, Page CP, Cazzola M. Novel bronchodilators for the treatment of chronic obstructive pulmonary disease. *Trends Pharmacol Sci* 2011; 32: 495–506.
41. Cazzola M, Rogliani P, Segreti A, *et al.* An update on bronchodilators in Phase I and II clinical trials. *Expert Opin Investig Drugs* 2012; 21: 1489–1501.
42. Cazzola M, Page CP, Rogliani P, *et al.* β_2-agonist therapy in lung disease. *Am J Respir Crit Care Med* 2013; 187: 690–696.
43. Cazzola M, Page C, Matera MG. Long-acting muscarinic receptor antagonists for the treatment of respiratory disease. *Pulm Pharmacol Ther* 2013; 26: 307–317.
44. Trivedi R, Richard N, Mehta R, *et al.* Umeclidinium in patients with COPD: a randomised, placebo-controlled study. *Eur Respir J* 2014; 43: 72–81.
45. Kerwin EM, Fogarty C, Dunn K, *et al.* Cardiovascular safety of nebulized glycopyrrolate (SUN-101) compared with tiotropium, ipratropium and placebo in patients with COPD. *Am J Respir Crit Care Med* 2013; 187: A1483.
46. Orevillo C, St Rose E, Strom S, *et al.* Glycopyrrolate MDI demonstrates comparable efficacy and safety to tiotropium DPI in a randomised, double-blind, placebo-controlled phase 2b study in patients with COPD. *Eur Respir J* 2011; 38: Suppl. 55, 724s.
47. Wedzicha JA, Decramer M, Ficker JH, *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; 1: 199–209.
48. Vogelmeier CF, Bateman ED, Pallante J, *et al.* Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol–fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med* 2013; 1: 51–60.
49. Bateman ED, Ferguson GT, Barnes N, *et al.* Dual bronchodilation with QVA149 *versus* single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013; 42: 1484–1494.
50. Dahl R, Chapman KR, Rudolf M, *et al.* Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir Med* 2013; 107: 1558–1567.
51. Cazzola M, Segreti A, Matera MG. New developments in the combination treatment of COPD: focus on umeclidinium/vilanterol. *Drug Des Devel Ther* 2013; 7: 1201–1208.
52. Scott LJ, Hair P. Umeclidinium/vilanterol: first global approval. *Drugs* 2014; 74: 389–395.
53. Anzueto A, Decramer M, Kaelin T, *et al.* The efficacy and safety of umeclidinium/vilanterol compared with tiotropium or vilanterol over 24 weeks in subjects with COPD. *Am J Respir Crit Care Med* 2013; 187: A4268.
54. Celli B, Crater G, Kilbride S, *et al.* Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest* 2014 [In press DOI: 10.1378/chest.13–1579].
55. Donohue JF, Maleki-Yazdi M, Kilbride S, *et al.* Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med* 2013; 107: 1538–1546.
56. Maltais F, Beck E, Webster D, *et al.* Four weeks once daily treatment with tiotropium + olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients. *Eur Respir J* 2010; 36: Suppl. 54, 1014s.
57. Aalbers R, Maleki-Yazdi MR, Hamilton A, *et al.* Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat® inhaler in patients with COPD. *Eur Respir J* 2012; 40: Suppl. 56, 525–526s.
58. Cazzola M, Rogliani P, Matera MG. Aclidinium bromide/formoterol fumarate fixed-dose combination for the treatment of chronic obstructive pulmonary disease. *Expert Opin Pharmacother* 2013; 14: 775–781.
59. Reisner C, St Rose E, Strom S, *et al.* Fixed combination of glycopyrrolate and formoterol MDI (GFF-MDI) demonstrates superior inspiratory capacity (IC) compared to tiotropium DPI (Tio) following 7 days dosing, in a randomized, double-blind, placebo-controlled phase 2b study in patients with COPD. *Eur Respir J* 2011; 38: Suppl. 55, 150s.
60. Reisner C, Fogarty C, Spangenthal S, *et al.* Novel combination of glycopyrrolate and formoterol MDI (GFF-MDI) provides superior bronchodilation compared to its components administered alone, tiotropium DPI, and formoterol DPI in a randomized, double-blind, placebo-controlled Phase 2b study in patients with COPD. *Am J Respir Crit Care Med* 2011; 183: A6435.
61. Rennard S, Fogerty C, Fischer T, *et al.* Pearl therapeutics' combination LAMA/LABA MDI (GFF MDI, PT003) provides a significant benefit on home peak expiratory flow rate (PEFR) and reduces the need for rescue albuterol use compared to its components administered alone, Spiriva Handihaler 18 µg and Foradil Aerolizer 12 µg in a randomized, double-blind, placebo-controlled phase 2b study in patients with COPD. *Am J Respir Crit Care Med* 2012; 185: A2259.
62. Reisner C, Gotfried M, Denenberg MB, *et al.* Low doses of Pearl therapeutics' LAMA/LABA combination MDI (GFF MDI, PT003) provide superior bronchodilation compared to components and to open-label Spiriva Handihaler in a randomized, double-blind, placebo-controlled phase IIb study in patients with COPD. *Am J Respir Crit Care Med* 2013; 187: A2434.
63. Cazzola M, Lopez-Campos JL, Puente-Maestu L. The MABA approach: a new option to improve bronchodilator therapy. *Eur Respir J* 2013; 42: 885–887.
64. Hughes AD, McNamara A, Steinfeld T. Multivalent dual pharmacology muscarinic antagonist and β_2 agonist (MABA) molecules for the treatment of COPD. *Prog Med Chem* 2012; 51: 71–95.
65. Norman P. New dual-acting bronchodilator treatments for COPD, muscarinic antagonists and β_2 agonists in combination or combined into a single molecule. *Expert Opin Investig Drugs* 2013; 22: 1569–1580.
66. Dransfield MT, Bourbeau J, Jones PW, *et al.* Once-daily inhaled fluticasone furoate and vilanterol *versus* vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013; 1: 210–223.
67. Agustí A, de Teresa L, De Backer W, *et al.* A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *Eur Respir J* 2014; 43: 763–772.
68. Gaebel K, McIvor RA, Xie F, *et al.* Triple therapy for the management of COPD: a review. *COPD* 2011; 8: 206–243.
69. Kuehn BM. FDA Offers advice to reduce risks of long-acting β-agonists in asthma care. *JAMA* 2010; 303: 1353–1354.
70. Abbott-Banner KH, Page CP. Dual PDE3/4 and PDE4 inhibitors: novel treatments for COPD and other inflammatory airway diseases. *Basic Clin Pharmacol Toxicol* 2014; 114: 365–376.
71. Franciosi LG, Diamant Z, Banner KH, *et al.* Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. *Lancet Respir Med* 2013; 1: 714–727.