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## **New drugs under development for COPD**

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## **Abstract**

**Introduction:** Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by chronic bronchitis, emphysema, and remodelling. Its prevalence is increasing worldwide, however there are few effective therapies, and none of the treatments currently available prevent the progression of the disease or target all of the hallmark features. The development and progression of COPD is heterogeneous, which has hampered the development of new therapies.

**Areas covered:** In this review, we cover the emergence of the improvement of existing classes of drugs including glucocorticoids,  $\beta$ 2-adrenoceptor agonists, phosphodiesterase inhibitors, PDE4 selective inhibitors, PDE3/PDE4 inhibitors, protease inhibitors, recombinant  $\alpha$ 1-antitrypsin and neutrophil elastase inhibitors. We also highlight new compounds that target recently identified mechanisms of COPD, new dual-action muscarinic antagonists and  $\beta$ 2-agonists, kinase inhibitors, cytokine modifiers, chemokines modifiers, NF- $\kappa$ B inhibitors, senolytics, antioxidants, inhaled antiviral agents, anti-fibrotic compounds and compounds stimulating lung regeneration.

**Expert opinion:** Given the myriad of potential therapeutic avenues that can be pursued, careful consideration of the phenotypes/endotypes of COPD patients will be important for personalised treatment options in the future, and a full understanding of disease mechanisms in patient subsets will ensure these emerging therapies are targeted appropriately.

**Keywords:** COPD, exacerbation, pathogenesis, new drugs, therapy

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic and progressive lung disease that has increasing prevalence worldwide, and there are few effective therapies and no cures. None of the current treatments that are available prevent the progression of the disease. COPD is associated with active inflammatory processes that can result in progressive obstruction of small airways, destruction of lung parenchyma and decline in lung function. Whilst some mechanisms of COPD have been identified, an increased understanding of what drives COPD pathogenesis will identify novel targets for future therapy [1].

The search for new therapies is multifaceted, including 1) improvement of existing classes of drugs, 2) development of novel therapies through better understanding of the disease processes and 3) identification of novel genetic targets. 'Omics-based approaches are increasingly used to identify abnormal modifications of genes (molecular genomics), RNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) from human samples and the application of in silico algorithms and artificial intelligence approaches to resolve the interactome of signalling pathways is nascent.

New promising drugs/compounds that we have reviewed are summarised in the table 1.

## 2. Improved existing classes of drugs

### 2.1 *New inhaled glucocorticoids*

The development of new inhaled glucocorticoids [inhaled corticosteroids (ICS)], is directed to obtain (1) potent anti-inflammatory effect upon topical administration; (2) long persistence of the anti-inflammatory effects in the lower airways but without significant accumulation of the compound in the lung tissues; (3) minimal systemic exposure; (4) high clearance and formation of inactive metabolites; and (5) compatibility with inhalers [2]. Currently, few new inhaled glucocorticoids are under early clinical development.

Valsecorat (AZD7594) is a non-steroidal, inhaled, selective, glucocorticoid receptor modulator, currently in early clinical development. It is a once-daily

administered compound, which has low solubility enabling prolonged lung retention, with a potentially prolonged anti-inflammatory effect in the airways, and slow absorption into the systemic circulation [3], potentially minimising unwanted systemic side effects.

A small phase 1 randomised placebo-controlled, dose escalation clinical trial (NCT02645253) in healthy subjects (n=27, mean age 34 years, all males, no other clinical data are available) to evaluate the safety, pharmacokinetics and pharmacodynamics of a single inhaled dose of AZD7594 was completed in 2018. The effect of multiple daily doses (200 µg and 400 µg) via a multiple-dose dry powder inhaler (DPI) and metered dose inhaler (MDI) for 12 days was also assessed. AZD7594 was well tolerated at all dosages with a significant 24 hours plasma cortisol suppression of ~25% only seen at the highest dose [4].

Furthermore, two 12-week randomized, open-label cross-over, phase 1 clinical trials in healthy volunteers have also been completed. These studies investigated the effects of particle size on pharmacokinetics of AZD7594 following a once daily single inhaled dose *via* DPI (NCT02928354, n=12) and the association of AZD7594 with abediterol (detailed below) which was administered in both a once daily fixed dose combination or administered in 2 separate DPIs to each subject (NCT02967159, n=14). However, no published results are currently available from these studies.

## **2.2 New inhaled $\beta$ 2-receptor agonists**

Current long acting/ultra-long acting inhaled  $\beta$ 2-adrenoceptor agonists ( $\beta$ 2-agonist, LABAs/ULABAs) are effective and well tolerated in their long-term use in stable COPD patients. However, there is continued interest in developing new inhalable  $\beta$ 2-agonists with core structures different from existing drugs in this class to improve selectivity [5].

Abediterol is a novel and selective long acting  $\beta$ 2-agonist with the potential for once daily treatment of COPD. This drug *in vitro* and *in vivo* exhibits superior bronchodilatory efficacy, and similar or superior selectivity for  $\beta$ 2-receptors over  $\beta$ 1-receptors compared to current LABAs (formoterol and indacaterol) [6].

Importantly, the duration of abediterol is similar or superior to other LABA compounds, with a reduced effect on heart rate [6].

Two phase 1 clinical trials in healthy subjects (n=14 and n=25 respectively) were completed in April 2017 (NCT02967159) and May 2020 (NCT04199598) to evaluate pharmacokinetics and safety of a once daily DPI dose of abediterol, and the bioavailability of two different abediterol nebulised formulations compared with DPIs in the second study. No published results are available.

Abediterol has been assessed in a randomised, double-blind, cross-over, placebo controlled phase 2 clinical trial (NCT01425814) to evaluate the pharmacodynamics of a DPI single dose in COPD patients [n=70, 26 females, mean age 61 years, mean forced expiratory volume in 1 sec (FEV<sub>1</sub>) 58%, 29 former smokers, mean pack-years (p-y) 49, n=49 GOLD stage II, n=21 GOLD stage III]. randomised to abediterol 0.625 µg, 2.5 µg, 5 µg, 10 µg, indacaterol 150 µg or placebo. All doses of abediterol significantly increased FEV<sub>1</sub> from baseline compared with placebo, and the higher doses of abediterol (2.5 µg, 5 µg, 10 µg) also had significantly improved FEV<sub>1</sub> compared with indacaterol [7]. Abediterol is still under phase 2 development (<https://www.astrazeneca.com/our-science/pipeline.html>).

## **2.3 New phosphodiesterase inhibitors**

### **2.3.1 Inhaled PDE4 selective inhibitors**

Phosphodiesterase (PDE) inhibitors, that target different isoforms of PDE, are classes of drugs with emerging roles in treating lung diseases. CHF6001 is an phosphodiesterase (PDE) 4 inhibitor that administrated *in vivo* by DPI in a murine model of LPS-induced lung inflammation, significantly decreased the number of total leukocytes and neutrophils and interleukin (IL)-1β, tumor necrosis factor (TNF) α, CCL5, and granulocyte colony-stimulating factor (G-CSF) levels in bronchoalveolar lavage (BAL) [8]. Subsequently, inhaled (DPI) CHF6001 has been shown to have a good safety profile in healthy subjects in two different randomised, double-blind, placebo-controlled clinical trials [NCT01703052 (completed in 2012) and NCT02386761 (completed in 2016)] (n=74 and n=48 respectively) [9].

Furthermore, a phase 2 placebo-controlled clinical trial (NCT03004417, completed in 2019) of DPI CHF6001 administered twice daily to stable moderate-to-severe COPD patients (n=61, 18 females, 27 former smokers, mean p-y not available,

mean FEV<sub>1</sub> 50%, all maintaining regular therapy with twice daily inhaled budesonide/glycopyrronium/formoterol) demonstrated significant reduction of key inflammatory mediators, TNF- $\alpha$ , leukotriene B<sub>4</sub> (LTB<sub>4</sub>), CXCL8, and matrix metalloproteinase (MMP)-9 sputum levels, and serum surfactant protein D (SP-D) [10]. CHF6001 is still under clinical development (<https://www.chiesi.com/ricerca-e-sviluppo/pipeline/>).

### 2.3.2 Dual PDE3/PDE4 inhibitors

Ensifentrine (RPL554) is a dual PDE3/PDE4 [PDE3 affinity is >3440 higher than PDE4] inhibitor [11]. PDE3 is an isoenzyme expressed in airway smooth muscle [12]. The inhibition of PDE3 leads to airway smooth muscle relaxation, whereas the PDE4 isoenzyme is dominant in many inflammatory cells in COPD pathogenesis and its inhibition suppresses airway inflammation [13, 14]. Compounds that inhibit both PDE3 and PDE4 should increase airway caliber by relaxing the smooth muscle and suppress the airway inflammatory responses [15]. The mechanisms that underpin this apparent synergistic effect of dual PDE3/4 inhibition have not yet been clarified.

Inhaled nebulised ensifentrine twice daily at different dosages (0.75 mg, 1.5 mg, 3 mg and 6 mg), in a 4 week randomised, double blind, placebo-controlled, parallel group, dose-ranging study (NCT03443414, completed on June 2019) in stable moderate COPD patients (n=405, 160 females, mean age 63 years, average FEV<sub>1</sub> 56%, 183 former smokers, mean p-y 42, not under regular bronchodilator therapy), significantly improved peak FEV<sub>1</sub> response (on week 4 of treatment) and symptoms scores [16].

In addition, a separate phase 2 randomised, double-blind, clinical trial (NCT04091360) is ongoing (estimated completion date on August 31, 2020) to assess the safety and pharmacodynamics of single and repeat doses of ensifentrine (0.1 mg, 0.3 mg, 1 mg, 3 mg, 6 mg) administered by MDI in stable COPD patients (n=40). The primary outcome is the change from baseline in peak FEV<sub>1</sub>.

## **2.4 New protease inhibitors**

### **2.4.1 Improved intravenous recombinant human $\alpha$ 1-antitrypsin**

$\alpha$ 1-antitrypsin deficiency has been associated with COPD. Intravenous INBRX-101 is a 160kDa recombinant human  $\alpha$ 1-antitrypsin (AAT) Fc fusion protein, designed to address some of the limitations of plasma derived AAT replacement therapy. Human AAT Fc fusion protein is a plasma-derived AAT fused to an IgG Fc-domain (Fc fusion protein), which increases its circulation half-life by allowing it to be recycled [17,18]. Human AAT Fc fusion protein has some anti-inflammatory properties including decreasing TNF $\alpha$ -induced IL-6 release from human blood mononuclear cells [19] and reducing bronchoalveolar lavage (BAL) neutrophil numbers and TNF $\alpha$  levels in a mouse model of LPS-induced inflammation [20].

Intravenous INBRX-101 (80 mg/kg and 120 mg/kg weekly) is currently in an open-label, two-part, dose-escalating phase 1 clinical trial (NCT03815396) with an estimated completion date in December 2021). The study will evaluate its safety in COPD patients with AAT deficiency (n=30, any allelic combination with exception of the ZZ genotype, FEV<sub>1</sub>≤40%, who quit smoking for at least 6 months prior to the entry into the study) as the primary outcome and the results are awaiting.

Human  $\alpha$ 1-antitrypsin Modified Process ( $\alpha$ 1-MP) is a new human-derived protein made with a specialised manufacturing process, including additional ion-exchange chromatography to increase the AAT purity, and enhanced the capacity to inactivate and/or remove viral contamination. Thus, the preparation is stable, sterile and lyophilised [21].

Weekly intravenous administration of 60 mg/kg of AAT-MP for 8 weeks has been evaluated in a multicenter, open-label, phase 1 and 2 clinical trial (Study GTI1401, NCT02870309, completed in 2017) in patients with AAT deficiency (n=4, age >20 years) demonstrating good tolerability [22]. The GTI1401-OLE study is an ongoing extension of the study (NCT02870348) with an estimated completion date of January 20, 2023. It will assess the effect of intravenous administration (60 mg/kg weekly) of AAT-MP in the same population with safety (determined by adverse events, discontinuations due to adverse events and COPD exacerbations) as the primary outcome.

SPARTA is a currently recruiting phase 3 multi-centre, randomised, placebo-controlled, double-blind clinical trial (NCT01983241, estimated completion date in November 2023). It will assess the efficacy and safety of two separate dose regimens (60 and 120 mg/kg weekly) of AAT-MP compared with placebo for 156 weeks. Lungs computed tomography (CT) to evaluate lung density will be used as the main measure of efficacy in patients with emphysema due to congenital AAT deficiency (n=339, age 18-70 years, ZZ, SZ, Z(null), (null)(null), S(null) genotype or "at-risk" alleles).

#### *2.4.2 Inhaled recombinant $\alpha$ 1-antitrypsin*

Only 2–3% of intravenous AAT reaches the lung, therefore inhaled approaches are currently being explored as a different route of administration. However, these come with some limitations, including the delivery of AAT to the alveoli using conventional nebulizers can take up to 100 min, and may be less effective in patients with low FEV<sub>1</sub> and the amount of AAT needed in the interstitium to prevent disease is unclear [23]. However, inhaled “Kamada-AAT” is a promising drug, with plasma-derived high purity solution for inhalation.

Inhaled “Kamada-AAT” (80 mg twice-daily) has been tested in a 50-week multicentre, double-blind, randomised parallel group, placebo-controlled, phase 2/3 clinical trial (NCT01217671). COPD patients with AAT deficiency (ZZ or other rare genotypes with AAT serum level <11 $\mu$ M) were recruited from 12 sites between 2010 and 2014 (n=168, 68 females, mean age 55 years, mean FEV<sub>1</sub> 39%, mean p-y not available) to assess safety but it showed no effect on time until first exacerbation [24]. Furthermore, a phase 2, double-blind, placebo-controlled clinical trial (NCT02001688) of inhaled “Kamada-AAT” was completed in January 2020 in patients with AAT deficiency (ZZ or Z null) (n=36, age between 18 and 65 years, FEV<sub>1</sub>  $\geq$  50%) and it was found to be safe and well tolerated with no adverse events, both at 80 mg and 160 mg dosages. Currently, inhaled “Kamada-AAT” 80 mg once daily is in a large European prospective phase 3 multi-centre, placebo controlled, double-blind clinical trial (NCT04204252, estimated completion date in March 2023). This study evaluated efficacy as the change from baseline in post bronchodilator FEV<sub>1</sub> at the end of the treatment period (104

weeks), and safety in patients with AAT deficiency and airflow obstruction [ $n=220$ ,  $50\% \leq FEV_1 \leq 80\%$ ,  $FEV_1/\text{forced vital capacity (FVC)} \leq 70\%$ ].

#### 2.4.3 New inhibitors of neutrophil elastase

Neutrophils are important in the development and progression of COPD and neutrophil elastase (NE) released from neutrophils has been shown to breakdown lung tissue.

Alvelestat (MPH-996), is selective and reversible oral daily NE inhibitor, currently in two 12 week multi-centre, double-blind, randomised, placebo-controlled, phase 2 clinical trials, the ASTRAEUS study (NCT03636347, to be completed on 2020) and the ATALANTa ("Alvelestat for the Treatment of ALpha-1 ANTitrypsin", NCT03679598, to be completed in 2021). Both studies are currently recruiting and aim to reduce lung damage and slow the progression of lung disease in patients with AAT deficiency ( $n=165$  and  $n=66$  respectively), with primary endpoint as the change from baseline of the desmosine/isodesmosine which are both biomarkers of NE activity.

BAY 85-8501 (Bayer) is a novel dihydropyrimidinone-based neutrophil elastase inhibitor that prevents the development of lung injury and subsequent inflammation *in vivo* in a mouse model of lung injury induced by intratracheal instillation of NE. Prophylactic administration 1 h prior to the NE instillation reduced BAL neutrophilia [25]. Oral BAY 85-8501 has been investigated in a safety and efficacy trial in patients with non-cystic fibrosis bronchiectasis (NCT01818544, completed in 2014), however its safety and efficacy has not yet been assessed in COPD patients or other lung diseases [26].

### 3. New classes of drugs in development for COPD

#### 3.1 New classes of bronchodilators

##### 3.1.1 Inhaled dual-action muscarinic antagonists and $\beta_2$ -agonists

A number of new dual-action compounds that are both muscarinic antagonists and  $\beta_2$ -agonists (MABAs) are in development for the treatment of stable COPD patients [5]. In a double-blind, phase 2, randomised, clinical trial (NCT02573870, completed in 2017) stable COPD patients ( $n=62$ , 36 females, mean age 62 years, 25 former smokers, mean p-y 46, mean  $FEV_1$  57%) were treated with inhaled once daily batefenterol

(GSK961081) 300 µg/fluticasone furoate 100 µg for 6 weeks and safety was similar to placebo [27].

A phase 2 international multi-centre, randomised, placebo-controlled, double-blind, parallel group study (NCT02570165) was conducted in stable COPD patients (n=325). The study was designed to assess the dose response, efficacy and safety of five dose regimens administered *via* DPI once-daily for 42 days. The study was completed in July 2019 and preliminary data suggest a positive effect on the primary outcome. However, batefenterol has not yet entered phase 3 clinical development.

Navafenterol (LAS191351 or AZD8871) is a MABA that has prolonged competitive occupation at M<sub>3</sub> receptors and has been shown to prevent acetylcholine-induced bronchoconstriction for 24 hours in guinea pigs and dogs [28]. Many phases 1 and 2 clinical trials using navafenterol in healthy subjects and COPD patients were completed between 2016 and 2017 (NCT02971293, NCT03159442, NCT02573155 and NCT02814656), and even if preliminary data for some of these suggest positive effects on the primary outcome, most of the results have not been published. Inhaled navafenterol (600 µg once daily DPI) has also been completed in phase 2 randomised, multi-centre, double-blind, placebo-controlled, crossover study (NCT03645434) to check its safety and tolerability in moderate to severe COPD patients (n=73) but results are also not available at this stage.

LAS190792 (AZD8999) is another MABA able to induce the relaxation in dogs and in electrically stimulated isolated human bronchi, with a similar efficacy to batefenterol, but with a longer duration of action [29]. LAS190792 has been assessed in a pharmacokinetic and pharmacodynamic phase 1 study, primarily designed to assess the safety and tolerability of single dose administered by DPI once daily in stable COPD patients (NCT02059434). In a separate phase I study, LAS190792 both as a monotherapy and combined with fluticasone propionate, was assessed in COPD patients (n=22, 6 females, mean age 65 years, mean FEV<sub>1</sub> 52% predicted, mean p-y 34) and healthy never-smokers subjects (n=17, 4 females, mean age 67 years, mean FEV<sub>1</sub> 99%) (NCT02573870) and it significantly inhibited inflammatory cytokine release (IL-1β, IL-8, MMP-9) induced by 6 h LPS stimulation, in blood neutrophils from both healthy and COPD patients [30].

The first human study of another MABA, CHF6366, was a randomised, double-blind, placebo-controlled phase 2 clinical trial (NCT03378648) completed in 2019. It primarily assessed safety, tolerability, pharmacokinetics and pharmacodynamics (change in FEV<sub>1</sub>) of a once daily single ascending and multiple ascending inhaled doses in COPD patients (n=118). No results have been published.

### **3.2 New anti-inflammatory compounds**

#### **3.2.1 Janus-kinase inhibitors**

Janus-kinases (JAKs)-signal transducers and activators of transcription (STATs) signalling pathways may be involved in the pathogenesis of COPD [31]. A pan-JAK inhibitor (PF-06263276) suitable for inhaled administration in COPD patients has passed the preclinical phase [32] showing a dose-related inhibition of IL-6-induced increases of pSTAT3 in murine lung *in vivo* following intratracheal administration. A phase 1 clinical trial using topical administration of PF-06263276 was completed in 2014 in healthy subjects (NCT01981681) but no results are published.

Pyridone 34 is an inhaled potent pan-JAK inhibitor with a dose-dependent inhibition of BAL neutrophils and IL-6 levels in an LPS-induced mouse model of airway inflammation. It is well retained in the lung when administered as a nano-suspension ( $t_{1/2}$ =16.3 hours) by intratracheal instillation showing promise for inhaled administration and low oral bioavailability, as very low levels of compound were found in plasma after oral administration [33]. However, no clinical trials have been started with this compound but studies are warranted.

#### **3.2.2 Mitogen-activated protein kinase inhibitors**

Currently, mitogen-activated protein kinase (MAPK) inhibitors evaluated for the treatment of COPD target p38 MAPK. CHF6297 is a new p38 $\alpha$  MAPK inhibitor, which has been assessed in a recent randomised, double-blind, crossover, placebo-controlled phase 2 clinical trial (NCT02815488) to evaluate safety, tolerability and pharmacokinetics of DPI single and repeated doses in healthy subjects, and anti-inflammatory effects in COPD patients (n=118), but the results have not yet been published. Other compounds such as LASSBio-1824 [34] and LASSBio-1828 [35] are

N-acylhydrazone derivatives that are also inhibitors of p38 $\alpha$  MAPK. These drugs have significantly reduced the expression of MAPK-driven inflammatory mediators such as TNF $\alpha$  and IL-1 $\beta$  *in vivo* in a mouse carrageenan-induced subcutaneous air pouch model and in a mouse model of formalin-induced acute inflammation, respectively.

The anti-inflammatory effect of AZD7624, a selective competitive inhibitor against p38 MAPK  $\alpha/\beta$  optimised for inhaled delivery, was compared with that of budesonide in stable COPD patients (n=32, 8 females, median age 64 years, median p-y 44), frequent exacerbating COPD patients (>2 of exacerbations/year for the last year) or COPD patients with infrequent exacerbations (no exacerbations for the last year), and smokers with normal lung function (n=8, 4 females, median age 54 years, median p-y 29, median FEV<sub>1</sub> 77%). The results demonstrated that the suppression of IL-6 expression in bronchial epithelial cells from all COPD patients was significantly greater with AZD7624 compared with budesonide [36].

The anti-inflammatory effect of other p38 MAPK inhibitors such as VX745 (Tocris) and SCIO469 have been assessed in BAL macrophages obtained from stable COPD patients (n=16, 2 females, median age 68 years, median p-y 59 $\pm$ 8, median FEV<sub>1</sub> 64 $\pm$ 3%), stage GOLD II and III, compared with current or former smokers with normal lung function (n=12, 2 females, median age 58 years, median p-y 10 $\pm$ 4, median FEV<sub>1</sub> 109 $\pm$ 6%). The levels of TNF $\alpha$  and IL-6 in BAL macrophages from COPD patients were significantly reduced [37]. However, no clinical trials have been performed.

RV568 is a p38 MAPK  $\alpha,\gamma$  inhibitor that has shown significant anti-inflammatory effects in *in vitro* and *in vivo* preclinical studies. These include inhibition of IL-6 and CXCL8 in primary bronchial epithelial cells and inhibition of BAL neutrophils in a murine model of COPD (inhaled LPS-induced pulmonary inflammation) [38]. Despite this preclinical data and an improvement in FEV<sub>1</sub> in COPD patients in a phase 2 clinical trial (NCT01475292, completed in 2012), development of RV568 has been abandoned.

BIRB796, a p38 MAPK  $\alpha,\gamma,\delta$  inhibitor, and SB203580, a p38MAPK  $\alpha, \beta$  inhibitor, both significantly decreased TNF $\alpha$ - and LPS-induced IL-8 expression in human airway smooth muscle cells obtained from COPD patients (n=5, 2 females, median age 70 $\pm$ 2 years, 4 current smokers, median p-y 51 $\pm$ 9, median FEV<sub>1</sub> 64 $\pm$ 5%). The combination of BIRB796/fluticasone and SB203580/fluticasone significantly reduced LPS-induced IL-8,

but BIRB796/fluticasone also reduced TNF $\alpha$ -induced IL-8 compared with single treatment [39]. Currently, no clinical trials have been conducted in COPD patients.

### 3.2.3 Phosphoinositide-3-kinase inhibitors

Phosphoinositide-3-kinase (PI3K)  $\delta$  responses are increased in peripheral lung tissue of patients with COPD and this is linked with reduced steroid sensitivity. Histone deacetylase 2 (HDAC2) responses normally enhance the anti-inflammatory effects of glucocorticoid, however, increased PI3K $\delta$  responses in patients with COPD leads to its hyperphosphorylation and ubiquitination and this results in impairment of glucocorticoid-induced, HDAC2-mediated repression of pro-inflammatory gene expression [40]. Non-selective PI3K inhibitor (LY294002) has also shown beneficial effects in murine models of experimental COPD with influenza A virus-induced exacerbations [41]. For these reasons, PI3K $\delta$  is a new target in the treatment of COPD.

Inhaled GSK045, a selective PI3K $\delta$  inhibitor, and ZSTK474, a pan PI3K inhibitor have both been assessed in COPD patients both during stable phase (n=11, 4 females, median age 67 years, 5 current smokers, median p-y 40, median FEV<sub>1</sub> 66 $\pm$ 13%) and during COPD exacerbations (n=15, 4 females, median age 66 years, 6 current smokers, median p-y 40, median FEV<sub>1</sub> 45 $\pm$ 11%). GSK045 significantly reduced MMP-9 secretion from blood neutrophils of stable COPD patients, and both GSK045 and ZSTK474 significantly reduced MMP-9 secretion from blood neutrophils of COPD patients during exacerbation. Both GSK045 and ZSTK474 significantly reduced the intracellular and extracellular oxidants released from blood neutrophils in all COPD patients. Moreover, GSK045 and ZSTK474 also significantly reduced neutrophils in sputum from stable COPD patients [42].

Nemiralisib (GSK2269557), highly selective PI3K $\delta$  inhibitor, has been administered in single and repeated doses using a DPI and it was well tolerated in healthy subjects (n=22) in a single centre, randomised, phase 1 clinical study (NCT02691325) [43]. In addition, a larger international phase 2a, multi-centre, randomised, stratified, double-blind, placebo controlled parallel-group study (NCT03345407) nemiralisib was administered to COPD patients (n=943, age between 40 and 80 years, current or former cigarette smoker with a history of cigarette smoking

of  $\geq 10$  p-y) with history of exacerbations, was discontinued in February 2020 due to an unfavourable risk-benefit.

CHF6523 is a PI3K inhibitor currently in a phase 1 study (NCT04032535, estimated to be completed on December 30, 2020). The study is designed to investigate the safety, tolerability and pharmacokinetics of DPI of single and multiple ascending doses in healthy male subjects first and then in COPD patients (n=102).

### **3.3 Cytokine modifiers**

Numerous compounds targeting specific pro-inflammatory cytokines have been under investigation for COPD, and these include monoclonal antibodies and/or other blockers directed against IL-1 $\beta$  (canakinumab) or IL-1R1 (MEDI8968), IL-5 (mepolizumab) or IL-5R (benralizumab), IL-8 (ABX-IL8), IL-18 (MEDI2338), IL-33 (MEDI3506) and thymic stromal lymphopoietin (TSLP) (tezepelumab). Clinical trials with selective cytokine modifiers in COPD patients have been either suspended or not shown any clinical benefit. The only targets currently in clinical trials in COPD are IL-5, IL-33, and TSLP.

IL-5 is associated with Th2-driven inflammation, but there is evidence of increased IL-5 levels in COPD patients during exacerbations. In a pilot study of mepolizumab over 6 months in patients with COPD and increased sputum eosinophils (NCT01463644, completed in 2015), there was no improvement in symptoms, lung function or exacerbations rate despite a marked reduction in sputum eosinophils. However, the study was underpowered to show such clinical effects [44].

In a large phase 3 multi-centre, randomised, placebo-controlled, double-blind, clinical trial (NCT02105948, completed in August 2018) involving administration of 100 mg of mepolizumab every 4 weeks, there was a 20% reduction in COPD exacerbations in patients treated with ICS, LABA and LAMA, who had a history of exacerbations. A similar reduction in exacerbations was observed in a phase 3 parallel multi-centre, randomised, placebo-controlled, double-blind, parallel group (NCT02105961, completed in August 2018) that used 100 mg and 300 mg monthly doses of mepolizumab. A greater effect on exacerbations was found in patients who had higher baseline blood eosinophil counts, indicating that eosinophilia may contribute to exacerbations in these

patients [45]. Currently, mepolizumab is still under phase 3 development (<https://www.gsk.com/en-gb/research-and-development/our-pipeline/>).

A decrease in soluble IL-5Ra is associated with the resolution of viral-driven COPD exacerbation. In a 48-week trial, treatment of patients with COPD and increased sputum eosinophils with benralizumab, an anti-IL-5Ra monoclonal antibody, did not reduce overall acute exacerbations compared with placebo, although exacerbations and symptoms were reduced, albeit not significantly, in patients with baseline blood eosinophils of  $\geq 300/\mu\text{L}$  [46]. Two multi-centre, randomised, double-blind, 56-week, placebo-controlled, phase 3 clinical trials (GALATHEA, NCT02138916, completed in June 2019 and TERRANOVA, completed in June 2019) have evaluated the efficacy and safety of benralizumab in patients with moderate to severe COPD with a history of frequent exacerbations. The results showed that benralizumab may be efficacious in a subpopulation of COPD patients with elevated blood eosinophil counts [47]. Currently, moderate to severe COPD patients with a history of frequent exacerbations are being recruited for a multicenter, randomised, double-blind, parallel-group, placebo-controlled phase 3 study of benralizumab (RESOLUTE, NCT04053634). The study will evaluate the efficacy and safety of benralizumab. A smaller phase 2 randomised, double-masked, clinical trial (NCT04098718) to compare benralizumab with prednisone in the treatment of COPD exacerbations is also currently recruiting subjects.

IL-33 expression is shown increased in airway epithelial cells and circulating T cells from COPD patients [48] and IL-33 blocking antibodies are now in early clinical development. AMG-282 is in a phase 2 single-centre, double-blind, placebo-controlled, parallel group, randomised clinical trial (NCT03615040, still ongoing) to assess its efficacy and safety in moderate to very severe COPD patients. MEDI3506 has completed a phase 1 clinical trial (NCT03096795) and it is currently under phase 2 development (<https://www.astrazeneca.com/our-science/pipeline.html>). The results for these studies are unknown.

TSLP is overexpressed in the bronchial epithelium of COPD patients and many triggers, such as respiratory viruses, cigarette smoke, and pro-inflammatory cytokines can stimulate the production of TSLP in COPD patients [49]. Tezepelumab (MEDI9929 and AMG157) is a human monoclonal antibody targeting TSLP that is being

investigated in an ongoing multicentre, randomised, double-blind, placebo-controlled, phase 2 clinical trial (NCT04039113). The study will examine the efficacy and safety of the drug in moderate to very severe COPD patients.

TRAIL is another cytokine recently identified to be important in experimental COPD and could be inhibited therapeutically [50]. IL-22 is another recently implicated cytokine that could be targeted, although it is important in protecting against infection [51].

Preclinical studies in representative mouse models of COPD are critical to assessing the efficacy of new cytokine treatments [52], and clinical trials that encompassed patient stratification according to their phenotypes/endotypes will be important for assessing the efficacy of cytokine treatments in COPD [53].

### **3.4 Chemokines modifiers**

Many studies have described increased/decreased expression of chemokines and/or chemokine receptors in different compartments of the lower airways in COPD patients during both a stable phase and/or during COPD exacerbations [54].

One potential limitation of targeting chemokines in COPD is the redundancy in the chemokine network. Most chemokine receptors bind several ligands, and small molecules that block the binding site for one specific chemokine may be unable to inhibit binding of other ligands. As a result, inhibition of a single chemokine receptor may not be sufficient to block the inflammatory response to a specific chemokine [55].

#### *Conventional chemokines and chemokine receptor antagonists*

Several chemokine receptor and mediator blockers have been tested in preclinical studies or in clinical trials in the past years but most studies have been halted (Table 2). CXCR1 and CXCR2 antagonists are the only class of compounds that are still under clinical development.

Danirixin (GSK1325756) is an orally twice-daily selective CXCR2 antagonist. Data obtained from healthy subjects has shown its safety [56] and data from a 52-week randomised, placebo-controlled, phase 2 study (NCT02130193, completed in 2016) conducted in Germany and USA has shown that 75 mg oral twice-daily of danirixin in

stable COPD patients (n=45, mean age 62 years, n=34 current smokers, mean FEV<sub>1</sub> 67%) has significantly improved the symptoms (breathlessness, cough and sputum) and also decreased the number of days free from COPD exacerbation compared with placebo [57]. A 52-week randomised, double-blind, pilot study on 35 mg orally twice-daily danirixin (NCT03170232) evaluated the effects on lung function and quality of life in mild to moderate COPD patients (n=54, age 40-76 years, FEV<sub>1</sub>% ≥40%, smoking history of ≥10 p-y), but the study was terminated based on the lack of efficacy in participants taking danirixin in a dose ranging study. In addition, a 14 day randomised, double-blind, phase 2, clinical trial (NCT03250689, completed in October 2018) has evaluated the effect 35 mg orally twice daily danirixin on neutrophil extracellular traps (NETs) formation in stable COPD patients (n=19, age 50-75 years, FEV<sub>1</sub>% ≥40%, smoking history of ≥10 p-y), but the study was terminated as a result of a change in the benefit-risk profile.

Although some of these studies with danirixin demonstrated a trend for improved respiratory symptoms and health status in patients with COPD, a recent 26-week, randomised, double-blind, placebo-controlled phase IIb study enrolled symptomatic patients with mild to moderate COPD at risk for exacerbations, and failed to show any benefit on the incidence and severity of respiratory symptoms. Indeed, contrary to expectations, the incidence of exacerbations and the numbers of pneumonias was elevated with danirixin [58].

#### *Atypical chemokines and atypical chemokine receptor antagonists*

New compounds against atypical chemokines and their receptor are less promising. Many of these compounds have been tested in preclinical studies or clinical trials in different inflammatory conditions, but not in COPD patients. The few studies in COPD patients have been halted (Table 2).

### **3.5 NF-κB inhibitors**

Nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) plays an important role in the orchestration of chronic inflammation in COPD, regulating many inflammatory genes [59]. NF-κB is naturally inhibited by the inhibitory protein IκB, which is degraded

after activation by specific kinases. Small molecule inhibitors of the I $\kappa$ B kinase (IKK2 or IKK $\beta$ ) are in early clinical development [31].

The recognition of feedback activation of IL-1 $\beta$  and neutrophilia in animal models during direct genetic and pharmacological targeting of IKK2 highlighted the complexity of NF- $\kappa$ B biology [60] resulting in the development of drugs that either act directly or indirectly on NF- $\kappa$ B such as those acting on the proteasome [61].

The IKK2 inhibitor IMD-1041 has been investigated in a proof of concept study in COPD (NCT00883584) completed in 2009 although no results have been published. In contrast, the oral NF- $\kappa$ B p50 inhibitor edasalonexent (CAT-1004) has progressed to phase 3 studies for Duchenne Muscular Dystrophy on the back of a successful phase 2 study (NCT02439216).

17-oxo-acid docosahexaenoic acid (DHA) is an endogenous bioactive electrophilic  $\alpha$ ,  $\beta$ -unsaturated keto-derivative of the omega-3 fatty DHA, which is synthesized in activated macrophages by cyclooxygenase-2 and dehydrogenase. 17-oxo-DHA has anti-inflammatory and cytoprotective actions, by inducing the Nrf2-dependent anti-oxidant response and suppressing NF- $\kappa$ B-dependent inflammatory reactions [62]. Exposure of LPS-stimulated blood mononuclear cells from stable COPD patients (n=10, mean FEV<sub>1</sub> 57 $\pm$ 14, mean FEV<sub>1</sub>/FCV 63 $\pm$ 6, mean 47 $\pm$ 19 p-y) to 17-oxo-DHA significantly inhibited TNF $\alpha$  and IL-1 $\beta$  expression compared with never smokers with normal lung function (n=11, mean FEV<sub>1</sub> 113 $\pm$ 13, mean FEV<sub>1</sub>/FCV 108 $\pm$ 6) [63]. This data suggests a possible therapeutic efficacy of this compound although no clinical trials have been conducted.

### **3.6 Senolytics**

Considerable progress has been made in understanding the molecular mechanisms involved in accelerated ageing in COPD pathogenesis. Although it is challenging to reverse the normal ageing process, it may be possible to reduce the mechanisms that accelerate senescence [64]. Senolytics are drugs that exert their effects by inducing apoptosis in senescent cells and have little or no effect on proliferating cells [64].

Senolytics target senescent cells and the networks that sustain them, not a single molecule, biochemical pathway, or receptor. Several potential senescent cell

antiapoptotic pathways (SCAPs) have been identified, such as ephrins/dependence receptors, of PI3K-mammalian target of rapamycin (PI3K/mTOR) pathway, Bcl-2/B-cell lymphoma-extra-large (Bcl-xl)/Bcl-w, p53/FOXO4a/p21/serpine, HIF-1a and HSP-90 pathways [65].

The cytotoxic agent navitoclax (ABT263) inhibits Bcl2 proteins, and its combination with quercetin is protective against bleomycin-induced pulmonary fibrosis in mice, reducing senescence associated with lung irradiation by selectively eliminating senescent type 2 pneumocytes [64]. However no clinical trials have been performed in patients with COPD or any other lung diseases, except for a phase 2 clinical trial in patients with lung cancer (NCT00445198), completed in June 2018, whose results have not yet been published.

Quercetin and dasatinib are other senolytics targeting Bcl-xl, that have been identified as being more effective in combination than as monotherapies. The combination has been tested in a pilot, open-label, clinical trial (NCT02874989, completed in May 2020) in patients with idiopathic pulmonary fibrosis (n=14), followed by a phase 2b randomised, placebo-controlled, double-blind, clinical trial that completed in June 2019 (NCT02874989). No clinical trials have been already performed in COPD patients.

Drugs such as rapamycin and metformin, target the PI3K/mTOR pathway. *In vitro*, rapamycin has reduced the number of senescence-associated  $\beta$ -galactosidase (SA- $\beta$ Gal) positive (senescent) cells from COPD patients, with a reduction in senescence-associated secretory profile (SASP) mediators [66] but rapamycin and its analogues rapalogs (everolimus, temsirolimus) have several adverse effects, including mouth ulceration, anaemia, pneumonitis and delayed wound healing, making it unsuitable for long-term use [64]. No clinical trials have been already performed in COPD patients.

### **3.7 Antioxidants**

Oxidative stress is an important mechanism leading to accelerated ageing in lung disease, suggesting that antioxidants may be an effective strategy. Existing antioxidants

are poorly effective as they are thiol derivatives that become inactivated by oxidative stress [64].

The nuclear factor erythroid 2–related factor 2 (Nrf2) expression and activity are decreased in the airway of stable COPD patients. Novel antioxidants include various Nrf2 activators [64] including sulforaphane.

Sulforaphane 3-(Pyr-idin-3-Ylsulfonyl)-5-(Trifluoromethyl)-2H-Chromen-2-One (PSTC), is a selective small molecule activator of Nrf2, that denitrosylates HDAC2, restores glucocorticoid sensitivity, and enhances the expression of downstream genes in bronchial brushings of COPD patients and in mouse models of COPD [67]. However, 4.4 mg or 26 mg oral once daily of sulforaphane in a randomised, double blind, placebo-controlled, phase 2, clinical trial (NCT01335971, completed in 2015) resulted in no changes in Nrf2 gene expression in alveolar macrophages obtained from COPD patients (n=89, 35 females, mean age 58 years, 35 former smokers, mean FEV<sub>1</sub> 61%, mean p-y not available) [68]. Studies on this compound have been interrupted (Table 2).

NBMI ((N1,N3-bis(2-mercaptoethyl) isophthalamide), also known as emeramide or Irminix, is an oral once-daily antioxidant and metal chelator agent, that has been investigated in a 14 days pilot randomised, two-arm, double-blind, placebo-controlled, cross-over, phase 2 clinical trial (NCT03123692, completed in June 2018) in COPD patients (n=12, age 45-75 years, former smokers with a smoking history of at least 10 p-y, FEV<sub>1</sub> >30%). The aim was to evaluate its safety as a primary outcome, and the symptoms change from baseline as secondary outcomes, but as yet no the results have been presented.

### **3.8 New inhaled antiviral agents**

Respiratory viruses are a major cause of COPD exacerbations. Early administration of antiviral agents at the onset of a respiratory viral infection may have the potential to reduce the severity or even prevent COPD exacerbations. Oral ribavirin is a broad-spectrum nucleoside antiviral agent that is approved for the treatment of chronic hepatitis C virus. It is also an active agent against the key respiratory viruses that can cause COPD exacerbations, including human rhinovirus (HRV), respiratory syncytial virus (RSV), and influenza virus [69]. Inhaled ribavirin (CCI15106, GlaxoSmithKline) has

been developed in two different formulation, capsules for inhalation, called ribavirin-PRINT-CFI, and powder for inhalation called ribavirin-PRINT-IP [70], and it has been tested in two different studies (NCT03243760, completed in 2016, and NCT03235726, completed in 2018).

Inhaled ribavirin (7.5 mg, ribavirin-PRINT-CFI) has been tested in healthy volunteers and in moderate COPD patients (n=60, mean age 37 years, 6 females, mean FEV<sub>1</sub> and mean p-y not provided) in a randomised, double-blind, placebo-controlled, single and repeat escalating dose phase 1 study. It was well tolerated after a single dose in healthy subjects. In addition, the powder inhalation (ribavirin-PRINT-IP) at the same dose (7.5 mg) was well tolerated both after single and multiple doses in healthy volunteers and in COPD patients [70]. Further investigation is required to demonstrate the efficacy of inhaled powder ribavirin to reduce COPD exacerbation.

### **3.9 New anti-fibrotic compounds**

Despite the key role of small airway fibrosis in COPD progression, there are few studies in COPD patients. It is possible that signals that activate fibroblasts may include miRNAs released in extracellular vesicles that are taken up by local fibroblasts, including miRNA-34a and -570 that promote cellular senescence [64].

Antagomirs of these miRNAs might be effective in the peripheral lung of COPD patients, especially if they can be delivered by inhalation. Using the inhaled approach, it may be possible to focus these treatments in small airways and to inhibit small airway epithelial cells and fibroblasts [64]. siRNA-targeting therapies may also be of benefit for targeting airway fibrosis. Using a highly representative murine model of COPD, siRNA targeting fibulin-1c has been shown reduce small airway collagen, emphysema-like alveolar enlargement and improves lung function [71]. Serelaxin is a peptide hormone with emerging evidence supporting its role as an anti-fibrotic agent in lung diseases and improving the efficacy of current therapies including glucocorticoids and  $\beta$ 2-adrenoceptor agonists [72, 73]. However, despite promising pre-clinical studies, no clinical trials with these compounds have been performed in COPD patients.

### **3.10 New compounds stimulating lung regeneration**

Many potential stem cell therapies already exist, but most of them are at the preclinical stages [74]. A new potential approach to regenerative medicine is laser therapy. Lasers typically generate electromagnetic radiation which is relatively uniform in wavelength, phase and polarisation, and classical medical applications of lasers are considered “high energy” because of their intensity, which ranges from about 10 to 100 W. Low level lasers (LLLs) elicit their effects through non-thermal means and may activate endogenous pulmonary stem cells and neoangiogenesis, which is optimal for stem cell growth. LLLs been proposed as regenerative photoceutical treatment for COPD. Activation of endogenous pulmonary stem cells may be one mechanism by which thermal or freezing ablation therapy acts [74].

A randomised, placebo-controlled, phase 2 clinical trial (NCT04010084, completion date in June 2020) is ongoing to evaluate the effects of LLL therapy in COPD patients (n=30). The study uses transcutaneous irradiation in the sublingual region for 30 seconds, with a total treatment time of 3 minutes, with combined wavelength (660 and 780 nm), 1J of energy per point and output power of 35 mW. The treatment is performed twice weekly for 4 consecutive weeks. The change from baseline in the six minute walking test is the primary outcome with the quantification of serum levels of cytokines (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-17, IL-10, and IFN- $\alpha$ ), the spirometric change in lung function and quality of life assessment questionnaire are the secondary outcomes. The results are still awaited.

### **3.11 Drugs against pulmonary innate immune dysfunction**

Current evidence highlights a number of metabolic pathways that may play an integral role in innate immune responses in COPD patients. Restoration of normal metabolic function by targeting critical metabolic enzymes or sensors may offer new therapeutic opportunities for innate immune dysfunction in COPD [75].

Furthermore, there is increasing evidence that metabolites may act as local ‘cytokines’ to modulate immune and inflammatory function [76]. Activation of glycolysis is an early step in the maturation, migration, differentiation and pro-inflammatory

activation of innate immune cells and is therefore an attractive therapeutic target for COPD [75].

Dimethyl fumarate was recently shown to inhibit glycolysis by inactivating glyceraldehyde 3-phosphate dehydrogenase, causing an increase in oxidative phosphorylation and M2 ('anti-inflammatory') polarisation of macrophages [77]. Furthermore, dichloroacetic acid, a drug that attenuates the activity of pyruvate dehydrogenase kinase, a negative regulator of pyruvate dehydrogenase, restricts glycolysis and enhances oxidative phosphorylation by increasing the flow of pyruvate into the mitochondrion. Truncated glycolysis due to inactivation of pyruvate kinase isoform M2 leads to channelling of upstream glycolytic intermediates towards the biosynthesis of macromolecules required for the activation of immune cells such as macrophages and mast cells. A number of pyruvate kinase isoform M2 activators are currently in preclinical development [78].

Semicarbazide-sensitive amine oxidase (SSAO) is an enzyme that has many roles in the body, including formation of advanced glycation end-products and leukocyte extravasation at inflammation sites. An inhibitor of SSAO [BI 1467335 (previously known as PXS-4728A)] has been shown in a preclinical mouse model of COPD to have beneficial effects on the hallmark features, including reducing airway inflammation (macrophages and neutrophils), small airway collagen deposition, and improving lung function [79]. Although clinical trials in patients with COPD have yet to be established.

#### **4. Expert opinion**

The prevalence of COPD is increasing worldwide. Current therapies only treat some of the symptoms, and no treatments reverse the hallmark features of disease. As our understanding of the mechanisms that drive disease increases, this has opened exciting new avenues for treatment. There have been two major approaches to improving treatment options for COPD patients: 1) improving existing classes of compounds and 2) targeting new pathways.

Improving existing classes of drugs has resulted in many new clinical trials for different classes of glucocorticoids,  $\beta$ 2-adrenoceptor agonists, phosphodiesterase

inhibitors, PDE4 selective inhibitors, PDE3/PDE4 inhibitors, protease inhibitors, recombinant  $\alpha$ 1-antitrypsin and neutrophil elastase inhibitors.

From pre-clinical studies and studies in human samples, multiple pathways involved in the development and progression of COPD have been identified, with new drugs under development for targeting these pathways. These include dual-action muscarinic antagonists and  $\beta$ 2-agonists, kinase inhibitors, cytokine modifiers, chemokines modifier, NF- $\kappa$ B inhibitors, senolytics, antioxidants, inhaled antiviral agents, anti-fibrotic compounds and compounds stimulating lung regeneration.

As with all new clinical trials in chronic lung diseases, the phenotyping/endotyping of patients prior to enrolment in clinical trials is absolutely critical, as the assessment of new classes of drugs will be most pronounced in patient cohorts who have changes/alterations in those pathways. Recent advances in 'omic' technologies have allowed for a new depth of understanding of disease but also highlighted the heterogeneity of COPD patients. Application of drug-responder, and non-responder, signatures from other therapeutic areas will also further enrich patient stratification. It is probable that combined PDE3/PDE4 drugs will soon reach the market and that re-purposing of cytokine-selective agents used in other diseases will follow. Drugs directed against TLR/inflammasome activation and mast cell proteases should become available should they be amenable to inhaled formulation.

Despite all of these promising avenues of research, there is still a need to fully understand the mechanisms that drive both the development and progression of COPD. New and updated murine models of cigarette smoke-induced COPD have been developed that replicate the hallmark features of the human disease in a short time timeframe [32-80]. Their interrogation provides invaluable insight into new mechanisms of disease and their infectious exacerbations [81, 82] and provide a platform for preclinical assessment of new treatments. This has led to the identification of a range of new therapeutic targets and potential treatments that have or are being assessed in human samples and are being progressed towards human use. These include inflammasomes [83-85], cytokine suppressors [86], mast cells and their proteases [80, 87, 88], microRNAs [89-91] and Toll-like-receptors [92-93]. Another emerging area of intense interest is the role of microbiomes and their metabolites in the gut and lung in

COPD that could be modulated with antimicrobials, dietary or pre/probiotic interventions with cause and effect delineated in animal models including germ-free mice [85, 94, 95].

Finally, both smoking and COPD are strong risk factors for severe COVID-19 [96]. COVID-19 involves the induction of specific set of immune responses that drive excessive inflammation and a cytokine storm that results in acute respiratory distress syndrome. The already exaggerated inflammatory lung environment and impaired immune response against the causative virus likely predisposes to this. Prophylactic or therapeutic treatments that suppress these events have the potential to suppress these events and these should be tested in human samples and mouse [97, 98].

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\*\* of considerable interest

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**Table 1. Improved existing classes and promising new drugs for COPD treatment**

|                                                                        | Phase 1<br>(completion date) | Phase 2<br>(completion date)                    | Phase 3<br>(completion date) | ClinicalTrials.gov<br>and pipelines                                                                                                      | Identifier |
|------------------------------------------------------------------------|------------------------------|-------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>Inhaled glucocorticoids</b>                                         |                              |                                                 |                              |                                                                                                                                          |            |
| Valsecorat<br>(AZD7594)                                                | 2017<br>2017<br>2018         |                                                 |                              | NCT02928354<br>NCT02967159<br>NCT02645253                                                                                                |            |
| <b>Inhaled <math>\beta_2</math>-receptor agonists</b>                  |                              |                                                 |                              |                                                                                                                                          |            |
| Abediterol                                                             | 2017<br>2020                 |                                                 |                              | NCT02967159<br>NCT04199598                                                                                                               |            |
|                                                                        |                              | 2012<br>currently under<br>clinical development |                              | NCT01425814<br><a href="https://www.astrazeneca.com/our-science/pipeline.html">https://www.astrazeneca.com/our-science/pipeline.html</a> |            |
| <b>Phosphodiesterase inhibitors</b>                                    |                              |                                                 |                              |                                                                                                                                          |            |
| <i>Inhaled PDE4 selective inhibitors</i>                               |                              |                                                 |                              |                                                                                                                                          |            |
| CHF6001                                                                | 2012<br>2016                 |                                                 |                              | NCT01703052<br>NCT0238676                                                                                                                |            |
|                                                                        |                              | 2019<br>currently under<br>clinical development |                              | NCT03004417<br><a href="https://www.chiesi.com/ricerca-e-sviluppo/pipeline/">https://www.chiesi.com/ricerca-e-sviluppo/pipeline/</a>     |            |
| <i>Dual PDE3/PDE4 inhibitors</i>                                       |                              |                                                 |                              |                                                                                                                                          |            |
| Ensifentrine<br>(RPL554)                                               |                              | 2019<br>2021                                    |                              | NCT03443414<br>NCT04091360                                                                                                               |            |
| <b>Protease inhibitors</b>                                             |                              |                                                 |                              |                                                                                                                                          |            |
| <i>Intravenous recombinant human <math>\alpha_1</math>-antitrypsin</i> |                              |                                                 |                              |                                                                                                                                          |            |
| INBRX-101                                                              | 2021                         |                                                 |                              | NCT03815396                                                                                                                              |            |
| AAT-MP                                                                 | 2017                         | 2017<br>2023                                    |                              | NCT02870309<br>NCT02870348                                                                                                               |            |
|                                                                        |                              |                                                 | 2023                         | NCT01983241                                                                                                                              |            |
| <i>Inhaled recombinant <math>\alpha_1</math>-antitrypsin</i>           |                              |                                                 |                              |                                                                                                                                          |            |
| Kamada-AAT                                                             |                              | 2019<br>2020                                    | 2019                         | NCT01217671<br>NCT02001688                                                                                                               |            |
|                                                                        |                              |                                                 | 2023                         | NCT04204252                                                                                                                              |            |
| <i>Inhibitors of neutrophil elastase</i>                               |                              |                                                 |                              |                                                                                                                                          |            |
| Alvelestat<br>(MPH-996)                                                |                              | 2020<br>2021                                    |                              | NCT03636347<br>NCT03679598                                                                                                               |            |
| <b>MABAs</b>                                                           |                              |                                                 |                              |                                                                                                                                          |            |
| Batefenterol<br>(GSK961081)                                            |                              | 2017<br>2019                                    |                              | NCT02573870<br>NCT02570165                                                                                                               |            |
| LAS190792<br>(AZD8999)                                                 | 2016                         |                                                 |                              | NCT02573870                                                                                                                              |            |
| CHF6366                                                                |                              | 2019                                            |                              | NCT03378648                                                                                                                              |            |
| <b>Inhaled antiviral agents</b>                                        |                              |                                                 |                              |                                                                                                                                          |            |
| Ribavirin<br>(CCI15106)                                                |                              | 2016<br>2018                                    |                              | NCT03243760<br>NCT03235726                                                                                                               |            |
| <b>Stimulators of lung regeneration</b>                                |                              |                                                 |                              |                                                                                                                                          |            |
| LLs                                                                    |                              | 2020                                            |                              | NCT04010084                                                                                                                              |            |

Data obtained from clinical trials.gov (<http://clinicaltrials.gov/ct2/home>) and the current pipeline in the websites of the pharmaceutical companies.

\* AAT-MP:  $\alpha$ 1-antitrypsin Modified Process; LLLs: Low level lasers MABAs: muscarinic antagonists and  $\beta$ 2-agonists.

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**Table 2. Past clinical trials of potential novel treatments in COPD patients and/or healthy volunteers that were halted**

|                                                      | Phase 1   | Phase 2                                  | Completion date | ClinicalTrials.gov Identifier |
|------------------------------------------------------|-----------|------------------------------------------|-----------------|-------------------------------|
| <b>Antioxidants</b>                                  |           |                                          |                 |                               |
| Nrf2                                                 |           | Sulforaphane                             | 2015            | NCT01335971                   |
| <b>Antimuscarinics</b>                               |           |                                          |                 |                               |
| M3 mAChR                                             | AZD9164   |                                          | 2010            | NCT01016951                   |
|                                                      |           | V0162                                    | 2012            |                               |
|                                                      |           | AZD8683                                  | 2014            | NCT01708057                   |
| <b>Chemokines and chemokine receptor antagonists</b> |           |                                          |                 |                               |
| <i>Conventional</i>                                  |           |                                          |                 |                               |
| CCL5                                                 | NI-0701   |                                          | 2010            | NCT01255501                   |
| CXCL8                                                | PA401     |                                          | 2013            | NCT01627002                   |
|                                                      |           | ABX-IL8                                  | 2005            | NCT00035828                   |
| CCR1                                                 |           | AZD4818                                  | 2008            | NCT00629239                   |
| CCR2                                                 |           | AZD2423                                  | 2011            | NCT01215279                   |
|                                                      |           |                                          |                 | NCT01153321                   |
| CXCR1                                                | ADZ8309   |                                          | 2009            | NCT00860821                   |
| CXCR2                                                | SB-656933 |                                          | 2007            | NCT00504439                   |
|                                                      |           | AZD5069                                  | 2011            | NCT01233232                   |
|                                                      |           | Navarixin (SCH 527123, MK-7123, AZD4721) | 2011            | NCT01006616                   |
| <i>Atypical</i>                                      |           |                                          |                 |                               |
| AMPs                                                 |           | Aprepitant                               | 2013            | NCT01854177                   |
| TLR4 antagonist                                      | NI-0101   |                                          |                 |                               |
| CRTH2/DP2 antagonist                                 |           | AZD1981                                  | 2008            | NCT00690482                   |
| <b>MAPK inhibitors</b>                               |           |                                          |                 |                               |
| p38 MAPK                                             |           | Losmapimod (GW856553)                    | 2011            | NCT01218126                   |
|                                                      |           |                                          | 2014            | NCT01541852                   |
|                                                      |           |                                          | 2016            | NCT02299375                   |
|                                                      |           | RV568                                    | 2012            | NCT01475292                   |

Data obtained from clinical trials.gov (<http://clinicaltrials.gov/ct2/home>) and the current pipeline in the websites of the pharmaceutical companies.

mAChR: acetylcholine receptor; AMP: antimicrobial peptides; CRTH2/DP2: prostaglandin D2 receptor 2; MAPK: mitogen-activated protein kinase; Nrf2: nuclear factor erythroid 2-related factor 2; TLR: toll-like receptor.

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