

Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



The COPD Pipeline XXXVI

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; Food and Drug Administration, **FDA**; long-acting muscarinic antagonist, **LAMA**; forced expiratory volume in 1 second, **FEV₁**; phosphodiesterase, **PDE**; epithelial sodium channel, **ENaC**; cystic fibrosis transmembrane conductance regulator, **CFTR**; acute respiratory distress syndrome, **ARDS**; acute exacerbations of COPD, **AECOPD**

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Contract Pharma

Contract Pharma is a publication that reviews, among other things, the pharmaceutical industry annually. Those of us who work in chronic obstructive pulmonary disease (COPD) take an interest in the source of the drugs we use and *Contract Pharma* brings that information to us. Each year they report the status of the top 25 pharmaceutical companies.¹ For each pharma, a report lists the newly approved drugs, those pending approval, drugs in phase 2, those in early research, drugs coming off patent, and some other less interesting data. There is usually a tussle between Pfizer and Novartis for the top. For the 2017 report (which is based on 2016 sales) Pfizer, Inc., is number 1. As I sift through the top 25 pharma companies, I look for drugs that might be the ones we will one day be prescribing for our patients with COPD.

Pfizer has no new COPD drugs anywhere in the process of development unless one includes Prevnar 13 which was just approved. Next is Novartis which has Fevipiprant, an interesting CRTh2 antagonist in phase 1. But it is for an asthma indication. Merck, at number 3, has MK-1029, also a CRTh2 antagonist, but also in trials as a potential asthma therapy. Merck has no agents in development for COPD. Nor, going down the list, has Roche. GlaxoSmithKline has Relvar Elipta (recently approved), a triple for COPD that is pending the Food and Drug Administration's (FDA's) review, and mepolizumab for COPD. Next on the list are Sanofi,

Johnson & Johnson, Gilead, and ABBVie with no COPD drugs. Then AstraZeneca with Bevespi/Aerosphere and benralizumab both in phase 2 for a COPD indication. Teva has several drugs for asthma but none for COPD.

Next on the list are Lilly, Bristol-Myers Squibb, and Bayer. Finally, Boehringer Ingelheim has worked with Hamni Pharmaceuticals on HCP1202 for COPD. It is in a Phase 2 trial. Then, moving down the list, comes a desert with no potential COPD drugs, - Novo Nordisk, Merck KGAA, Takeda, Allergan, Biogen, Shire, and Celgene. Mylan brings the list to a close with its revefenacin, a nebulized long-acting muscarinic antagonist (LAMA) in phase 3. The point here is that the third largest cause of death in most of the world needs more novel therapies. Other than the me-too's, we have just 2 '-lizumabs' in the works for COPD. Cancer, heart, and diseases of ageing are all well represented in late stage development, which is appropriate. But COPD should be up there with them. Autologous bronchial basal cells transplantation is

Autologous Bronchial Basal Cells Transplantation

a possible treatment for chronic respiratory diseases including COPD and bronchiectasis. Regend Therapeutics has the novel and interesting idea that autologous bronchial cells can be obtained by bronchoscopy, expanded *in vitro*, and reinjected directly into lesions via bronchoscopy. Progress of the treatments will be followed for 6 months (but it is not clear how the donated cells will be identified). Two phase 1/2 trials will be conducted, NCT03153800² and NCT03188627,³ and the studies will be single-centered, non-randomized, and conducted in 30 and 20 stable COPD patients, respectively. Primary outcomes will be forced expiratory volume in 1 second (FEV₁) and diffusing capacity of the lungs for carbon monoxide.

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GSK2269557 is a phosphoinositide-3 kinase delta

GSK2269557

inhibitor that is being investigated for an anti-inflammatory action in COPD. A recently completed phase 1 study enrolled 12 healthy participants who received the agent by dry powder inhalation. The primary outcomes, apart from the usual pharmacokinetic and safety outcomes, were a range of lung function measurements over the following 6 days (results pending) (NCT 01762878).⁴

RPL554

RPL554 is a dual phosphodiesterase (PDE) 3/4 inhibitor nebulized for acute exacerbations of COPD. The molecule displays simultaneously bronchodilator and anti-inflammatory properties. In a recently completed trial, 40 individuals with COPD were entered in a phase 2 trial with 3 arms, namely 2 doses of RPL554 plus tiotropium and a control group that received only tiotropium. The primary outcome was peak FEV₁ on day 3 of treatment (NCT03028142) (results pending).⁵

Colistimethate Sodium

Colistimethate sodium, also known as polymixin E, is a well-known antibiotic that is effective against most gram-negative bacilli. It fell out of use due to renal toxicity but remains a last resort against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter*. In a placebo-controlled trial including 264 participants, the primary outcome will be time to first exacerbation.⁶

A Triple for COPD?

A trial of a fixed combination of fluticasone furoate/umeclidinium/vilanterol has been announced in clinicaltrials.gov (NCT03046069).⁷ Previous developments of fixed combinations of 2 components have faced the FDA “combination rule” that the optimal dose of each component must be determined in the presence of the other component. The rationale has been that the optimal dose of a drug cannot be assumed to be the same in the presence of another drug as it was in isolation. This rule often required trials of 8 or more arms to find acceptable doses of each component and often several such multi-armed trials were needed.

The costs of these trials often went into 7 figures. The mathematics of a triple required a logarithmic increase in the number of arms each trial would require—a daunting task. Which is why molecules with 2 actions, e.g., an antimuscarinic moiety and an adrenergic moiety, are being developed as single agents by some pharmaceutical companies. (That tactic has brought its own problems including the finding that it has been difficult to fashion a hybrid molecule in which the 2 moieties have significant and roughly equal potencies). The NCT03046069 trial seems to suggest either that the large number of arms and trials will be undertaken or that the FDA rule has been relaxed.

The present study, by GlaxoSmithKline, will put all 3 components, beta-agonist, anticholinergic, and corticosteroid, on the same molecule. It is referred to as a “single inhaler triple”. Enrollment will be a single participant. Yes, 1 patient. The dual primary outcomes will be “evaluation of the key relevant attributes of COPD treatment (time frame: up to 368 hours)” and “evaluation of the preferences, priorities and treatment goals of subjects with COPD for inhaled treatments.”⁷

Acumapimod

Acumapimod (BCT-197) is an oral p38 MAP kinase inhibitor that is being developed as a therapy for acute exacerbations of COPD. Previous studies undertaken by Novartis, showed the drug has the capacity to reduce the inflammatory marker TNF α and to increase FEV₁. Previous studies showed the drug to be well tolerated in the target population. The aim is to shorten the duration of acute exacerbations of COPD, something that would be novel. A placebo-controlled randomized study will enroll 255 individuals with COPD who will receive either the drug or placebo to standard of care for the treatment of an acute exacerbation in a phase 2 trial (NCT02700919).⁸ Primary outcomes are safety and pharmacokinetics.

Emera 003COPD

Emera 003COPD is an antioxidant and metal chelator that is being developed by Emeramed for patients with “COPD with bronchitis” (NCT 03123692).⁹ The double-blind placebo controlled trial will be in phase 2. The only previous trial of this agents was as a treatment for mercury intoxication (NCT02486289).¹⁰ I cannot find any other information about this agent.

AZD8871

AZD8871 is another bifunctional molecule with both anti-muscarinic and beta-adrenergic functions being developed for both asthma and COPD. It is in phase 1 and if successful will probably be married up with a corticosteroid to form, effectively, a triple inhalation for airways disorders that seems to have become the holy grail for inflammatory airways disorders. In addition to the present study (NCT02573155),¹¹ 3 other trials are registered in clinicaltrials.gov.

SPX-101

The epithelial sodium channel (ENaC) is responsible for reduced airway hydration causing mucus dehydration and decreased mucociliary clearance.¹² It is therefore a target for the management of cystic fibrosis. SPX-101 inhibits ENaC. It is an inhalation in a recently completed phase 1 trial (NCT03056989)¹³ for 5 individuals with cystic fibrosis independent of their underlying cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation. If successful, one wonders whether it might be of interest in COPD.

IC14

IC14 is an anti-CD14 antibody that blocks TNF α production.¹⁴ (It was first published in the early 2000's as an agent that might address the problem of inflammation in severe sepsis. After a flurry of about 6 or 7 publications, it seems that trials on its potential to address sepsis were disappointing. A further analysis of its potential is about to be renewed [NCT03017547]).¹⁵ In a phase 2 study, 160 individuals with acute respiratory distress syndrome (ARDS) will be randomized to receive either the IC14 or placebo by intravenous injection in daily doses for 4 days. The primary outcome will be safety, secondary outcomes will be changes in ARDS markers, e.g., IL-8, sTNFR1, and IL-6.

ZL-2102

ZL-2102 is a novel agent from China. The drug is in phase 1 in a double-blind, placebo-controlled, randomized trial. None of the other trials of the same agent, nor its sponsor, Zai Lab Pty Ltd, provide any information about the action of ZL-2102. There are no citations of ZL-2102 in Pub Med. However, the drug's

sponsor claims that it aims to transform patients' lives rather than simply relieve symptoms, (more or less exactly what we need). Asthma and COPD are stated targets in a 14-day, 3-stage trial involving 104 normal healthy participants (NCT02397005).¹⁶

Viral and Bacterial Pathogens in the Respiratory Tract

A new study will examine the occurrence of potential bacterial and viral pathogens in both stable and acute exacerbations of COPD in several Asian Pacific regions (NCT03151395).¹⁷ It has been suggested that the infectious etiology of acute exacerbations of COPD (AECOPD) varies according to geographical region: "the primary purpose of this study (which will be conducted in several countries in Asia Pacific) is to evaluate the occurrence of bacterial and viral pathogens in the sputum of stable COPD patients and at the time of AECOPD. Given the increasing and projected burden of COPD in the Asian Pacific region, this study will also evaluate the frequency, severity and duration of AECOPD, as well as the impact of AECOPD on health-related quality of life, health care utilization and lung function," as stated on ClinicalTrials.gov.¹⁷

Yet Another LAMA/LABA

Just when you thought we had enough doubles, there is another. However, with at least 3 LAMAs and 5 or 6 long-acting beta2-agonists and several delivery pathways, and durations of actions, etc, one may compute 100 possibilities for essentially the same treatment. They are or will all be safe and effective. You have seen them all advertised and detailed to you and have yourself detailed them to your colleagues and this column is not about things you already know very well.

Chaperones for Cystic Fibrosis

It is estimated that about 30% of cases of cystic fibrosis are due to protein misfolding due in turn to genetic abnormalities. The misfolded nascent proteins are, for one reason or another, unable to do their fluid and electrolyte duties at the cell surface. Chaperone proteins are proteins that promote the correct folding and assembly of other proteins. It is postulated that molecules can be synthesized that correct misfolded proteins in a chaperone manner. The pharmaceutical

company Vertex has obtained FDA approval for 2 drugs that can perform that function in cystic fibrosis: ivacaftor (Kalydeco) and a fixed combination of lumacaftor and ivacaftor (Orkambi). The same company has at least 4 other studies in phase 2 of fixed combinations of, essentially, triple combinations of either VX-659, or VX-440, or VX-445, or VX-152 in combination with a tezacaftor/ivacaftor combination.¹⁸ The concept is that each agent (chaperone) has its own effect and improves the overall outcome.

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