

# Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



## The COPD Pipeline, XXIX

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**Abbreviations:** Clinical Trials Monitor, **CTM**; inhaled corticosteroids, **ICS**; Food and Drug Administration, **FDA**; metered dose inhaler, **MDA**; forced expiratory volume in 1 second, **FEV<sub>1</sub>**

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### The Status of COPD Clinical Research

*Clinical Trials Monitor* (CTM) is an e-journal produced by Johan Karlberg, MD, PhD, which provides subscribers with information about all clinical trials reported to [clinicaltrials.gov](http://clinicaltrials.gov). The data are updated weekly and list new trials, new results, new study data, and similar useful information. The publication, which is invaluable, is the source of much of the information in this column. From CTM I have compared the research activity into COPD with that of the overall clinical research activity over the last 3 months.

On average, 122 new clinical trials of all types are registered with [clinicaltrials.gov](http://clinicaltrials.gov) each week. Of these, an average of 10% of all new trials or 12.3 trials per week, are associated with all aspects of the respiratory system. Excluding lung cancer, pediatric conditions, sleep, novel devices, procedures, and observational studies reduces the number to 5 new trials per week. Of that number between 2 and 3 new trials per week are specific to COPD.<sup>1</sup> Nearly all of these COPD trials are related to classes of molecules that are well known

to us and are often already in use, namely long-acting beta agonists, long-acting muscarinic agonists, inhaled corticosteroids (ICS), and fixed combinations of those agents. The preponderance of the new COPD studies involving fixed combinations of these molecules are in late phase development, -late Phase II, Phases III or IV. Among novel molecules, there is a trickle of studies, some of which are reported in this column as they enter clinical trials. The pharma industry is not required to report agents in preclinical stages, and their details are nearly always proprietary. Other sources report that there are many novel pulmonary agents in early and preclinical development.<sup>2</sup> In 2014 it was estimated that about 80 new COPD agents were in early stage or preclinical development. Approximately 15 agents were structural protein modulators; about 40 agents were non-ICS anti-inflammatories; and a further 10 agents were of unclassified nature. One only rarely has access to detailed information about the preclinical agents for obvious reasons. There were also about 10 new agents consisting of bronchodilators and fixed combinations that will be similar to those that have already been approved and are in current use.<sup>2</sup>

CTM also reports the number of closed clinical trials that report their results each week. If all trials reported their results within a year of trial conclusion as required, their number should be approximately the same as the number of trials that are initiated. However, for COPD, only an average of 26 closed trials have reported their results each week, which, compared to 122 new trials each week, suggests considerable non-compliance with the requirements of the [clinicaltrials.gov](http://clinicaltrials.gov) program, as pointed out elsewhere.<sup>3</sup> It is possible that some closed trials have been reported in a journal, for example, and not reported to [clinicaltrials.gov](http://clinicaltrials.gov).

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## Food and Drug Administration Approvals

Fifty-nine Food and Drug Administration (FDA) approvals were announced for the first 8 months of 2015, a record.<sup>4</sup> Infectious diseases topped the list with 7 approvals; cardiology, family medicine and oncology received 6 each; gastroenterology, immunology, and pediatrics received 4 approvals each. Pulmonary received 2 approvals. Stiolto Respimat (tiotropium bromide and olodaterol), by Boehringer Ingelheim, was approved for the maintenance of COPD. Orkambi (lumacaftor-ivacaftor combination) by Vertex Pharmaceuticals, was approved for the treatment of cystic fibrosis. Among other approvals was one included for “fat below the chin.” (How far below, one wonders).

## Two Head-to-Head Trials

In what may be the first of its kind, Novartis has initiated 2 trials comparing its glycopyrronium-indacaterol fixed combination DPI (QVA149) with GlaxoSmithKline’s umeclidinium-vilanterol fixed combination DPI (Anoro®); NCT02487446 and NCT02487498. This will be a “multi-center, randomized, double-blind, double-dummy, [placebo controlled], 2-period cross-over study.” Participants will be 354 patients with moderate to severe COPD. The primary outcome will be “non-inferiority of QVA149 compared to umeclidinium/vilanterol in terms of (forced expiratory volume in 1 second) FEV<sub>1</sub> AUC0-24h.”<sup>5</sup> (*It is possible that NCT02487446 is a reporting error, as no information about it has been received by clinicaltrials.gov for more than 2 years*).

## COPD Biomarker Assay

RespiVert, (recently acquired by Janssen Biotech) has an interest in identifying small molecules that are biomarkers of major diseases including COPD and asthma. A trial in COPD (NCT02490358) plans to obtain sputum from 60 individuals in 3 arms: healthy smokers, COPD smokers, and COPD ex-smokers. The nature of the biomarker(s) is not stated. In a recent publication,<sup>6</sup> it appears the company has patents for 4 multikinase inhibitors so one assumes the present trial will be assaying one or more of these agents for development as a biomarker for COPD.

## RNS60

RNS60 is a “therapeutic saline containing highly potent charge-stabilized nanostructures that decrease inflammation and cell death.”<sup>7</sup> Claimed to have anti-inflammatory properties providing an entirely new approach, RNS60 is also being developed for asthma and some other diseases with inflammatory features. The sponsors, Revalesio, provide information about the agent, its mechanism of action and its claimed benefits on their website.<sup>8</sup>

## Pearl’s Triple PT010

Pearl’s Triple PT010 is a fixed combination of budesonide, glycopyrrolate and formoterol to be delivered by a metered dose inhaler (MDI). In a randomized, double-blind, parallel-group, 24-week trial the agent will be compared to pairs of its components and Symbicort® Turbuhaler®. The participants will have moderate to very severe COPD (NCT02536508). A total of 1800 enrollees are predicted.<sup>9</sup> It is not stated whether the trial is Phase II or III. One wonders how Pearl will negotiate the FDA’s “combination rule” that requires that each component must be shown to make a contribution to the combination. The rule implies that dose responses must be determined for each component *in the presence of* the other components. This is difficult enough for 2 component combinations and exponentially more demanding for a triple.

## GSK2269557

This is a selective PI3K $\delta$  inhibitor being developed by GlaxoSmithKline. The agent has been in several Phase I and II studies for acute exacerbations of COPD and asthma. “The purpose of the study (NCT02522299) is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3K $\delta$ -dependent changes in messenger ribonucleic acid extracted from induced sputum in patients experiencing an exacerbation of COPD, with or without treatment with the agent. The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging and spirometry.”<sup>10</sup>

## GLASSIA

GLASSIA Kamada's flagship product, Aralast, is an alpha-1 proteinase inhibitor that is about to commence a Phase III/IV trial, NCT02525861. "The purpose of the study is two-fold: (1) to further evaluate the safety and potential immunogenicity of Glassia following IV administration via in-line filtration; and, (2) to assess the effects of Glassia augmentation therapy on the levels of A1PI and various biomarkers in the epithelial lining fluid following intravenous administration at a dosage of 60 mg/kg body weight /week for 25 weeks in subjects with emphysema due to congenital A1PI deficiency."<sup>11</sup>

## Lebrikizumab

Lebrikizumab is an injectable anti-IL-13 agent being developed by Hoffman-Laroche. It has been through a number of trials for severe asthma, atopic dermatitis and idiopathic pulmonary fibrosis. The present study (NCT02546700) is a Phase II placebo-controlled study in patients with severe COPD, the primary endpoint being the change from baseline in pre-bronchodilator FEV<sub>1</sub> after 24 weeks.<sup>12</sup>

## PneumRx

PneumRx, the company that makes the coil for volume reduction in emphysematous COPD, has initiated a further clinical trial. Its purpose is "to advance the understanding of the mechanism of action of the CE marked RePneu Coil by observing changes in lung physiology and cardiac performance in patients with emphysema treated with the RePneu Coils" NCT02499380.<sup>13</sup> The device has been approved by the European Medicines Agency in Europe but not by the FDA. The trial will be conducted entirely in Germany.

## TD-4208

TD-4208 is a long-acting muscarinic agonist being developed by Theravance. Delivery will be by nebulization. A Phase III trial has just begun (NCT02512510). It will be a 12-week placebo-controlled study of 2 active doses in individuals with moderate to very severe COPD. The primary outcome will be lung function not further described.<sup>14</sup> One presumes that this drug, if it performs well, will be taken over by GlaxoSmithKline, as were Theravance's (now

GSK961081) and their "closed triple" (Fluticasone/Umeclidinium/ Vilanterol).

## A Switching Study

A switching study will examine the effect (trough level) of switching patients who have been receiving b.i.d. Symbicort<sup>®</sup> to o.d. QVA149 (indacaterol/glycopyronium) (NCT02516592). The primary outcome will be trough FEV<sub>1</sub> level 12 weeks after the switch.<sup>15</sup>

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