

Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



The COPD Pipeline XXVII

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Abbreviations: Food and Drug Administration, **FDA**; cystic fibrosis, **CF**; forced expiratory volume in 1 second, **FEV₁**

Funding Support: n/a

Date of Acceptance: April 2, 2015

Citation: Gross N. The COPD pipeline: XXVII. *J COPDF*. 2015; 2(2): 191-194. doi: <http://dx.doi.org/10.15326/jcopdf.2.2.2015.0137>

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Keywords:

FDA overhaul; reporting trial results; lumacaftor; ivacaftor; VX661; p38 MAPK inhibitors; AQX-1125; new clinical trials

The Food and Drug Administration

On February 3 of this year, *FDANews* published some details of the Food and Drug Administration's (FDA) regulatory overhaul. Among those that might impact our specialty are "...an overhaul of agency procedures to increase orphan drug development, streamline clinical trials oversight, give industry incentives to find new uses for old drugs."¹ One hopes that a large portion of the incentives goes towards more basic science. COPD treatment does not need more "me-too" drugs.

Another feature of the discussion and subsequent white paper on the initiative that catches one's eye is the statement that "...in a perfect world, research and development dollars would flow toward the areas of highest need where the severity or burden of disease was most pronounced. However, as noted by the President's Council of Advisors on Science and Technology, the current system in many ways discourages investment in therapies for scientifically complex diseases with longer development times. Dr. Collins has encouraged Congress to tackle this problem since today's patent framework often makes it economically unviable to bring such therapies to market, even when they have shown early promise."²

Reporting Trial Results

The clinicaltrials.gov registry was initiated in 2000; and in 2007 the FDA mandated that all clinical trials at Phase II or higher were required not only to be registered in advance but also to report the trial results "no later than 12 months after the [trial] Completion Date."³ This has not happened. I drew attention to this in an early *Pipeline* column and a detailed study now shows the extent of the problem.⁴ Only 38% of trials had reported results at any subsequent date; far fewer within 1 year of trial completion. However, trials sponsored by industry were significantly more likely to be in compliance with the reporting requirements than trials with academic sponsorship.

To see how COPD trials reporting compared with the 13,327 studies that were included in the comprehensive study referred to above, I reviewed the data in clinicaltrials.gov accessing all trials under the search term *COPD OR emphysema OR bronchitis*, limiting the search to completed trials. Of 1,387 completed COPD trials on that site only 269, or 19%, reported any results. Several of those "reports" were to a package insert or to a publication that did not provide useful data.

Lumacaftor-Ivacaftor

Ivacaftor was developed as a treatment for cystic fibrosis (CF) in patients with the G551 mutation in the CFTR. It acts by increasing the time the receptor is open thus permitting more chloride ions to pass through the surface epithelium. The drug modestly improves sweat chloride tests, some aspects of lung function and may reduce the frequency of acute exacerbations. It was FDA approved in 2012, brand name Kalydeco™. Only about 5% of CF patients have the G551 mutation, thus additional treatments that modify the CFTR have been sought.

Lumacaftor is a molecule that is being developed by the same pharmaceutical company that developed ivacaftor. It addresses the CFTR conformational abnormality due to a deletion of its 508 phenyl alanine. This mutation is found in about 60% of CF patients. Like ivacaftor, it improves sweat chloride levels in CF patients. However, in Phase II it did not improve lung function, acute exacerbations or disease status. The combination of ivacaftor and lumacaftor is thus now being developed and 13 clinical trials of the combination have been completed (according to clinicaltrials.gov none have provided results). Meeting abstracts of Phase II trials indicate modest improvements in sweat chloride levels with various combinations of the 2 agents and also small improvements in the decline in forced expiratory volume in 1 second (FEV₁) over 24 weeks. Both drugs appear to be well tolerated.⁵

Another agent, VX661, is being developed for CF by the same company. This agent is being studied as a monotherapy and also in combination with ivacaftor. Preliminary results indicate a reduction in sweat chloride tests and also a small but statistically significant improvement in FEV₁ with the VX661-ivacaftor combination. Interestingly, the improvement disappeared when the drugs were stopped. Drug tolerance was again good; however, there were a few withdrawals due to adverse events.⁶

New to the CF field is Flatley Discovery Lab LLC with a "CFTR corrector," FDL169. The agent "promotes CFTR folding and processing, thereby increasing the level of functional protein on the cell surface. FDL169 restores CFTR dependent chloride transport when used alone or in combination with a drug that potentiates CFTR."⁷ Like some other CF agents, the benefit is expected to be limited to CF patients with the relatively common 508 deletion. The agent is in a Phase I clinical

trial on healthy volunteers and is currently recruiting (NCT02359357). The trial is randomized, double-blind, placebo-controlled, dose-escalation and first-time-in-human, the primary outcome being safety and tolerability.

P38MAPK Inhibitors

Despite their efficacy in asthmatic inflammation, corticosteroids are disappointingly ineffective in addressing the inflammation of COPD. In COPD the inflammatory biomarkers IL-6, CRP, and fibrinogen are increased, as shown in the ECLIPSE study.⁸ p38MAPkinases, which are increased in lung macrophages in COPD, are reported to be activated by inflammatory signals. Activated p38MAPK itself phosphorylates and upregulates the transcription of several proinflammatory mRNAs. Inhibition of p38MAPkinase has been shown to suppress inflammatory mediator release from alveolar macrophages of patients with COPD. The possibility that such inhibition could extend to corticosteroid efficacy has now been tested.

In a small *in vitro* study, peripheral blood monocytes of healthy cigarette smokers and smokers with COPD were stimulated with lipopolysaccharide to promote the release of inflammatory biomarkers. Inclusion of dexamethasone diminished the release of IL-8 in the non-COPD monocytes; but the steroid effect was significantly reduced in the COPD monocytes. This provided a model to test the ability of p38MAPK inhibition to restore corticosteroid sensitivity. Using the experimental p38MAPK inhibitor, GW856553, the inhibition of steroid efficacy was restored to the COPD monocytes.⁹ This agent, named losmapimod, has been the subject of 6 clinical trials in COPD, 5 of which have been completed. At the time of this writing no results had been reported.

Ship1 Activator AQX-1125

The search for agents that address the mechanism(s) of inflammation in COPD is warming up. The phospholipid PIP₃ is a component of membranes but also holds a key place in inflammation, cell growth and survival. In response to a variety of stimuli it activates downstream signaling components including the protein kinase AKT. PI₃ kinase increases PIP₃ and the enzyme SHIP1 decreases it. One effect of an increase in PIP₃ is to promote the release of a variety of pro-inflammatory

signaling molecules, hence, inflammation. An agent that inhibits PIP₃ synthesis, namely a PI₃ kinase inhibitor, has not shown significant benefit against the inflammation of allergic asthma.¹⁰ But an agent that enhances PIP₃ catabolism, namely a SHIP1 enhancer, may be more effective.

The pharmaceutical company Aquinox has developed a small molecule agent, AQX-1125, that stimulates SHIP1. In rodent models of pulmonary inflammation and allergy, AQX-1125 suppresses leukocyte accumulation and inflammatory mediator release.¹¹ It is now a candidate for an anti-inflammatory role in a variety of inflammatory conditions. Against rheumatoid arthritis and asthma the effect of AQX-1125 has shown some reduction in neutrophils, macrophages and eosinophils. Better activity is anticipated in severe COPD. A Phase II trial is in progress with the primary outcome being a reduction in acute exacerbations of COPD.¹² See clinicaltrials.gov (NCT01954628).

New Clinical Trials

Chiesi Farmaceutici has just completed a phase I trial of a triple for COPD: beclomethasone/ formoterol/ glycopyrrolate versus placebo (NCT 02119234). The agents were administered with or without Aerochamber and spacer. The same company also has a dose-ranging study of their inhaled phosphodiesterase inhibitor, CHF6001, as well as a MABA and a p38MAPK inhibitor in preclinical stages.¹³

Novartis completed a Phase II trial of BYM338 versus placebo for the cachexia of advanced COPD, (NCT01669174). The agent is a human HuCAL monoclonal against activin receptor type 2B. It is also the subject of other cachexia trials such as inclusion body myositis, sarcopenia, and cancer. A trial in mechanically ventilated patients was withdrawn prior to enrollment for unstated reasons. The primary outcome of this, as in other trials, was the change in thigh muscle volume. A total of 67 patients were enrolled. The trial duration was 24 weeks. No results are available yet. Novartis also will shortly initiate a 12 week post-marketing trial comparing the safety and efficacy of their glycopyrronium agent NVA237 given once or twice daily. The endpoint will be trough (24 hr.) FEV₁. The study is a post-authorization commitment to the European Medicines Agency.

AstraZeneca will shortly initiate a Phase IV, 8-week placebo-controlled trial of its anticholinergic agent aclidinium. The primary outcome will be cough and

other COPD symptoms using the EXACT-Pro tool (NCT02375724).

Pearl Therapeutics has completed paired Phase III trials of MDI glycopyrrolate-formoterol fixed combination versus monotherapies of each, plus tiotropium, and placebo arms. (NCT01854645 & 01854658)

Spiration will subject its HUD IBV Valve System to a post-marketing study (NCT01166516). The valve is approved for air leaks following lobectomy, segmentectomy, or LVRS. The primary outcome is safety. The same company has initiated a randomized trial of a new valve system versus conventional tube drainage for lung leaks (NCT02382614). Time to air leak closure will be the primary outcome.

Pfizer has PF-03715455, a p38 inhibitor with broad anti-inflammatory actions in human lung cell and animal model systems and that maintains activity under in vitro conditions where corticosteroid efficacy is less effective. It is now in a Phase II randomized, double-blind, placebo-controlled 2-way crossover study to evaluate its efficacy and safety (NCT02366637). Eighty moderate to severe COPD participants will receive the agent or placebo by inhalation twice daily for 4 weeks. The primary outcome will be the change from baseline in trough FEV₁.

Acknowledgement

Many of the items in this report were due to the generous support of Clinical Trials Magnifier Weekly.¹⁴

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