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The COPD Pipeline XXXV

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Abbreviations: long-acting muscarinic antagonist, **LAMA**; forced expiratory volume in 1 second, **FEV₁**; whole-body vibration training, **WBVT**; CXC chemokine receptor, **CXCR2**; muscarinic antagonist-beta2-agonist, **MABA**

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Introduction

Dealmakers in biopharma ended April with much disappointment and grumbling. This was the year that Mergers and Acquisitions were supposed to take off, with a new president bullishly asserting plans to reform taxes in a way that would free up billions in “big pharma” cash held overseas. As one trade journal states: “Didn’t happen. Donald Trump is so far bogged down on Obamacare reform and not able to deliver a much-ballyhooed tax reform pledge – for now.”¹ Most people are disappointed with the pace of mergers and acquisitions. In the first quarter, pharmaceutical dealmakers were down 13% compared to the same period a year ago.¹

Revefenacin

Revefenacin is a long-acting (24 hour) muscarinic antagonist (LAMA) being developed for COPD by Mylan and Theravance. Phase III studies, recently completed, show meaningful efficacy in terms of increased forced expiratory volume in 1 second (FEV₁) versus placebo (NCT03064113).² Adverse events included dry mouth in less than 0.5% of participants.³ There were no reports of vision impairment, narrow-angle glaucoma or worsening of urinary symptoms. One’s unique interest in this agent is that it will be the

first nebulized once-daily LAMA for COPD patients who, for a number of potential reasons, need or prefer to get their bronchodilator by nebulization. It is estimated that about 9% of patients who use a long-acting agent use it by nebulization.³ One expects that a combination of Revefenacin with a nebulized long-acting beta-agonist will shortly be developed.

Whole-Body Vibration Training

Whole-body vibration training (WBVT) is a physical treatment consisting of the administration of vibrations delivered to the whole body. Physical retraining is a recognized goal of rehabilitation in COPD, however it is rarely practiced correctly or in full. Whole-body proponents opine that “vibration training could be a new and time-saving exercise approach aimed at increasing exercise performance in patients with COPD.”⁴ Participants in a randomized placebo controlled clinical trial with chronic bronchitis received 2 treatments of WBVT per month for 3 months. Whole body vibrations were delivered while standing on a vibrating platform. The control group received “relaxation and breathing retraining in combination with calisthenics exercises.”⁴ Participants who received vibrations experienced statistically improved results on the St George’s Respiratory Questionnaire, 6-minute walk tests, sit-to-stand tests, peak force and Berg balance tests. The control group experienced no changes. Unavoidably, the trial was not double-blinded. Clinicaltrials.gov shows 76 studies of “whole body vibration training,” 10 of which were for “pulmonary” studies, mostly of a bronchitic nature.

The Gala Airway Treatment System is somewhat similar in nature but more intense. High frequency vibrations are delivered to the lungs via a proprietary catheter through a bronchoscope under general

anesthesia.⁵ Treatments last about 60 minutes and there are just 2 treatments in total, 1 for each lung. A device-based, energy delivery system delivers high frequency short duration energy to the airway epithelium and sub-mucosal tissue layers. The energy is delivered via a proprietary catheter through the bronchoscope. Three months after treatments, bronchoscopy will be performed to obtain tissue for histology. A clinical trial will enroll 12 participants, the primary outcome being safety (NCT03107494).⁵

Chiesi

Chiesi has several agents in development. CHF6001 is a phosphodiesterase type 4 inhibitor that has or shortly will be in 7 trials for COPD. Trial NCT02986321 the most recent, is a dose-ranging study called PIONEER.⁶

Chiesi also has a p38 MAP Kinase inhibitor in phases 1 and 2, CHF-6297, which, if I am not mistaken, is aimed at addressing the acute exacerbation itself (NCT02815488), a novel and interesting approach to COPD management.⁷

Clinicaltrials.gov shows that Chiesi has or had 59 clinical trials limited to “pulmonary” in phases I, II, or III in recent years.

RPL554

On the subject of phosphodiesterases for COPD, the dual phosphodiesterase 3/4 inhibitor RPL554, a Verona Pharma agent, is in 2 trials for COPD (NCT02542254 and 03028142)^{8,9} as well as one trial in asthma and another in cystic fibrosis. The drug stimulates the cystic fibrosis transmembrane conductance regulator and ciliary beat frequency in primary cultures of bronchial epithelia.¹⁰ Both PDE3/4 COPD trials are in Phase II, the primary objective being FEV₁ over the first 8 hours of administration.

Danirixin

Danirixin is a selective CXC chemokine receptor (CXCR2) antagonist being developed as a potential anti-inflammatory agent for the treatment of COPD. A phase II trial will evaluate several dosages, the primary outcome being the change from baseline in clinical outcomes as measured by the E-RS tool, a component of the EXACT tool (NCT03034967).¹¹ As previously published,¹² a limitation of the anti-inflammatory

approach by CXCR2 antagonists has been a decrease in circulating neutrophils that can be severe.

Batefenterol

Batefenterol, GSK961081, is a potent dual pharmacophore, or muscarinic antagonist-beta2-agonist (MABA), that demonstrates both antimuscarinic and beta-agonist pharmacology.¹³ In preclinical studies, both pharmacologies were functional and of long duration. If reproduced in man, GSK961081 has the potential to deliver a medicine that can be given once daily. The primary outcome of the latest trial (NCT00674817) will be bronchodilatation after inhalation of single doses of GSK961081 alone and in the presence of salbutamol and/or ipratropium.¹³ Any residual bronchodilatation post-inhalation of GSK961081 may provide an indirect assessment of the beta-agonist and antimuscarinic components of this agent. In a phase II trial of the same MABA, the primary outcome is the change in FEV₁ at 7 weeks, versus umeclidinium/vilanterol fixed combination (NCT02570165).¹⁴

The status of this agent, GSK961081, is unknown as the clinicaltrials.gov site has not received updates for more than 2 years.

Eosinophilia with COPD

Eosinophilia with COPD is a topic of interest in which pharmaceutical companies are trying to determine the frequency of blood eosinophilia in patients with COPD (NCT03018808).¹⁵ Besides being of concern in asthma patients, the topic has become one of interest for pulmonologists treating COPD.¹⁶ If this research shows a connection between eosinophilia and acute exacerbations of COPD, no doubt we will be using IL-5 inhibitors in the latter.

Lungpacer Medical, Inc

Lungpacer Medical, Inc., is a medical device company developing an intravenous catheter-based phrenic-nerve-pacing system. The company announced recently that it has received an Expedited Access Pathway designation for this device from the Food and Drug Administration. Lungpacer Medical states its system “is a novel therapeutic solution for preserving the integrity and strength of the diaphragm muscle in critically

ill patients who require mechanical ventilation. The proprietary Lungpacer system is designed to activate the diaphragm using a temporary, minimally invasive, transvascular nerve stimulation approach that is expected to save many lives, improve surviving patient outcomes and greatly reduce hospital care costs.”¹⁷ Ongoing trials are NCT03096639 (RESCUE2)¹⁸ and NCT03107949 (RESCUE1).¹⁹ The protocol indicates that diaphragm pacing intervention will be conducted 3 times a day using the Diaphragmatic Pacing Therapy System. A control group will receive no pacing.

Tetomilast

Tetomilast--what happened to it? It was a promising phosphodiesterase 4 inhibitor that was in 2 phase II studies for COPD and 5 studies for ulcerative colitis. Nothing since 2015.²⁰

N1,N3-bis(2-Mercaptoethyl) Isophthalamide (NBMI)

Emiramide is an antioxidant and metal chelator that is in its first clinical trial exploring safety for COPD. The study is a randomized, 2-arm, double-blind, placebo-controlled, cross-over trial. Participants will receive 14

days of administration and observation; the method of administration is not mentioned (NCT03123692).²¹ Many antioxidants, e.g., CoQ10 and N-acetylcysteine, have been tested in lung diseases before and found not to be very effective.

Colistin

Colistin, also known as polymyxin E, is an antibiotic produced by certain strains of the bacteria *Paenibacillus polymyxa*. It belongs to the class of polymyxins and is effective against most Gram-negative bacilli. An old drug, it fell out of favor in human medicine due to kidney toxicity. A double-blind placebo controlled trial is in phase III. A total of 264 participants with non-cystic fibrosis bronchiectasis will be enrolled. The primary outcome is time to first exacerbation (NCT03093974).²²

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