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The COPD Pipeline XXXVII

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; neutrophil extracellular traps, **NETs**; forced expiratory volume in 1 second, **FEV_1**; CXC chemokine receptor type 2, **CXCR2**; phosphoinositide 3-kinase delta, **PI3Kδ**; dry powder inhaler, **DPI**; once daily, **QD**; twice daily, **BID**; respiratory assist system, **RAS**; spontaneous breathing trials, **SBT**

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Danirixin

Danirixin is the subject of 9 chronic obstructive pulmonary disease (COPD) studies, and 2 additional trials in acute influenza. Two relatively small Phase 2 studies of danirixin are projected or in trials. For these trials, primary outcomes are neutrophil extracellular traps (NETs) (NCT03250689)[1] and rate of decline of forced expiratory volume (FEV_1) (NCT03170232).[2]

From the GlaxoSmithKline trial of danirixin:

> "The inflammation associated with chronic obstructive pulmonary disease (COPD) is characterized by a prominent infiltration of neutrophils in lung tissue and airways. The CXC chemokine receptor type 2 (CXCR2) plays a pivotal role in neutrophil recruitment to the lungs resulting in progressive fibrosis, airway stenosis, and destruction of the lung parenchyma characteristic of COPD. There is a paucity of novel therapies that target these symptoms, and there are no currently available therapies that modify disease progression in COPD. Danirixin (GSK1325756) is a selective CXCR2 antagonist being developed as a potential anti-inflammatory agent for the treatment of COPD and influenza. This study is a mechanistic study which aims to evaluate the effect of danirixin in reducing neutrophil extracellular traps (NETs) or NETosis. Subjects will be randomized (3:1) to receive danirixin hydrobromide (HBr) 35mg orally twice daily or matching placebo for 14 days. Subjects may continue to use rescue medication(s) and inhaled COPD maintenance medication(s) during the study. The study will consist of a screening period of up to 30 days, a 2-week treatment period, and a 1-week follow-up visit via phone call."[1]

GSK2269557

GSK2269557 is a potent and selective phosphoinositide 3-kinase delta (PI3Kδ) inhibitor. It is being developed as an anti-inflammatory agent for the treatment of COPD and other inflammatory lung diseases. The agent is in 11 trials in clinicaltrials.gov and 1 trial that is not mentioned there. Briefly, NCT02522299[3] is a safety study in phase 2 with primary outcomes related to changes in mRNA transcriptomics in induced sputum from patients experiencing an acute exacerbation of COPD in addition to the usual safety and tolerability concerns. NCT03315559[4] is a phase 1 study that investigates pharmacokinetics following administration of GSK2269557 by mouth, by inhalation, and by intravenous injection. Shortly to be initiated is NCT03345407,[5] a dose finding study of GSK2269557 alternatively named "nemiralisib" for administration of the drug to 1250 participants with various degrees of acute exacerbations of COPD in phase 2. NCT02294734[6] is a similar phase 2 study in participants with exacerbations of COPD. As with some other anti-inflammatory molecules, this drug is also being studied in individuals with asthma (NCT03315559).[4]

CHF6333

A novel potent inhaled inhibitor of neutrophil

elastase study will investigate the safety, tolerability and pharmacokinetics of single and repeat doses of CHF6333 in 72 healthy males (NCT03056326)[7] the trial is in phase 1.[7,8]

Ellipta Dry Powder Inhaler

Per clinicaltrials.gov:

> "A randomized, cross over study aims to find out the benefits of delivering triple therapy using a single ELLIPTA® dry powder inhaler (DPI) (fixed-dose combination triple therapy) versus delivering triple therapy using Ellipta Dry Powder with two different types of inhalers (open triple therapy) including DISKUS® with HandiHaler® to subjects with COPD. Correct inhaler use, critical errors and performance attributes will also be assessed. Approximately 240 subjects with COPD will be randomized in the study. The study will be conducted in 3 visits and will be completed in approximately 56 days. At Visit 1 (Day 1) and Visit 2 (Day 28) subjects will be randomized to receive a placebo ELLIPTA inhaler once daily (QD) or a placebo DISKUS twice daily (BID) with placebo Handhaler QD inhaler in 1:1 ratio in a cross-over manner for the study period (28 days for each period). At Visit 3 (Day 56), subjects will be asked to complete preference questionnaire 1 or 2. There will be no active treatment and subjects will continue to take their own prescribed COPD maintenance and rescue medication during the entire study period. ELLIPTA and DISKUS are the registered trademarks of GlaxoSmithKline group of companies. Handhaler is the registered trademark of Boehringer Ingelheim group of companies" (NCT03227445).[9]

INS1007

INS1007 is a product of Insmed Incorporated. Their product is an oral agent for non-cystic fibrosis bronchiectasis, now in phase 2. A novel agent, it is described as "an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP1), [an] enzyme that catalyzes the activation of neutrophil serine proteases, which play a key role in the pathology of chronic inflammatory lung diseases such as non-cystic fibrosis."[10,11,12] The primary outcome is "time to first pulmonary acute exacerbation" (NCT03218917).[13] A total of 240 adult individuals will be enrolled and studied in a randomized controlled trial for 24 weeks.[13]

Another Triple?

Hard on the heels of the Food and Drug Administration approval of GlaxoSmithKline's triple Trelegy Ellipta, approved this September, comes Boehringer-Ingleheim with a phase 4 trial of a fixed combination of a corticosteroid and Stiolto Respimat, their olodaterol/tiotropium(NCT03265145).[14] A total of 3200 COPD individuals who are "not controlled on current therapy" will be enrolled into a 12-week study lasting 12 months. The primary outcome will be time to first acute exacerbation.[14]

Mepolizumab for COPD?

Having succeeded with mepolizumab (as Nucala) for asthma, GlaxoSmithKline is looking to explore and possibly develop that drug as a therapy for COPD.[15] Mepolizumab recognizes and blocks interleukin-5. The aim has been to reduce the incidence of acute exacerbations in patients who exacerbate despite regular use of triple drug inhaled therapy which proved positive ($p<0.036$) in one of 2 phase-3 studies, an elevated blood or sputum eosinophil count being a relevant factor (NCT02105961).[15,16] The outcome, whether the drug is used and in which patients it might be used, is considered uncertain as yet. Other pharmaceutical companies are considering whether to go for a similar monoclonal that addresses airways inflammatory disorders.

Targeted Lung Denervation

The Discovery TLD registry is a multicenter, prospective, single-arm post-market release study designed to record the clinical outcomes of Targeted Lung Denervation (TLD), using the CE-marked Nuvaira™ Lung Denervation System, in a subset of its CE-marked approved indication. This study is being conducted in Europe (NCT03213080).[17] According to Nurvaira, "the one-time non-surgical procedure involves passing a special catheter through a bronchoscope into the lungs. The catheter delivers radiofrequency (RF) energy to the nerves located on the outside of the airways. Once the energy has been delivered, the catheter and bronchoscope are removed. The procedure takes about one hour."[18] A total of 200 individuals with severe COPD will be enrolled. The primary outcome will be the change in quality of life as measured by the St George's

Respiratory Questionnaire at 6, 12 and 24 months.[17]

CO2 Removal with the Hemolung Respiratory Assist System

According to clinicaltrials.gov, a new study will evaluate:

> "the safety and efficacy of using the Hemolung respiratory assist system (RAS) to provide low-flow extracorporeal carbon dioxide removal (ECCO2R) as an alternative or adjunct to invasive mechanical ventilation for patients who require respiratory support due to an acute exacerbation of COPD. It is hypothesized that the Hemolung RAS can be safely used to avoid or reduce time on invasive mechanical ventilation compared to COPD patients treated with standard-of-care mechanical ventilation alone (NCT03255057)."[19]

A total of 500 eligible patients will be randomized to receive lung support with either the Hemolung RAS plus standard-of-care mechanical ventilation, or standard-of-care mechanical ventilation alone. The primary outcome is ventilator-free days at 60 days from randomization. A secondary outcome will be the in-hospital mortality.[19]

A Study to Test the Vaccine

Non-typeable Hemophilus influenza and Moraxella catarrhalis are 2 frequent causes of respiratory infections. A vaccine against these organisms has been developed by GlaxoSmithKline. The present study evaluating GSK3277511A aims to investigate the efficacy of the vaccine(NCT03281876).[20] A total of 600 patients aged 40 to 80 years with a history of acute exacerbations of COPD will receive 2 doses of the investigational vaccine or placebo intramuscularly. The primary outcomes will include the frequency of acute exacerbations and the immune response.

AZD8871

AZD8871 is AstraZeneca's bifunctional molecule that combines long-acting anticholinergic and beta-adrenergic functions, a muscarinic receptor antagonist and beta2-adrenoceptor. Delivered as a dry powder, it completed a phase 1 trial last year and now, in its 4th trial, is conducting a phase 2 trial in Japan. Twenty-four healthy participants, aged 20 to 55 years, will participate in receiving active or placebo dry powder inhalations (NCT03159442).[21] Three other trials of the same molecule have already been completed in phase 1, namely NCT02971293, NCT02814656, and NCT02573155. One expects that, if AZD8871 is successful, it will be paired with an inhaled steroid resulting in another triple. There are 9 co-primary outcomes that mostly deal with safety and tolerability.[21]

CHF5993

CHF5993, a Chiesi product, aims to evaluate the effect of inhaled extra fine metered-dose inhalation, monitoring the resulting airway volumes and airways resistance by functional respiratory imaging, in COPD patients (NCT03268226).[22] The study is a single arm phase 3 trial of the fixed combination of beclomethasone dipropionate, formoterol fumarate and glycopyrrhonium. A total of 30 participants with FEV_1 below 50% will be enrolled.

Phrenic Nerve Stimulator for Diaphragm Pacing

Clinical trial, NCT03107949, is described as "a therapy to recondition and strengthen the diaphragm of patients who have been intubated and invasively mechanically ventilated for > or = to7 days, have failed 2 or more spontaneous breathing trials (SBT), and were not hypervolemic during the latest SBT."[23] A total of 15 individuals will be studied. The primary outcome will be evidence of phrenic nerve stimulation and activity among other outcomes.

Zephyr EZB

Zephyr EZB is a valve that is being tested for its efficacy in COPD individuals with homogeneous emphysema, a treatment that typically responds only in patients with heterogeneous emphysema. Per the clinicaltrials.gov description:

> "The aim of this prospective, randomized, controlled, one-way crossover study is to assess and compare the efficacy of the Zephyr endobronchial valves versus Standard of Care (SoC) in patients suffering from COPD with homogeneous emphysema. Patients will be followed for 12 months after randomization and valve placement. Patients in the SoC arm will crossover to the EBV treatment arm after the 6-month visit and will

be followed up for 6 additional months. The primary objective is the variation of FEV_1 between baseline and 3-month follow-up visit. The secondary objectives will include quality of life, exercise capacity, dyspnea and safety outcomes(NCT02025205)."[24]

PT010, PT009 and PT003

The agents, PT010, PT009 and PT003 are, respectively, fixed combinations of budesonide/glycopyrronium/formoterol (a triple), budesonide/formoterol, and glycopyrronium/formoterol. A phase 3 study aims to assess the safety and tolerability of each combination in individuals with moderate to very severe COPD. Primary outcomes are bone mineral density and lens opacity (NCT03313570).[25] A total of 500 patients will each receive one of the above combinations for 52 weeks. Pearl (who sold the above triple, PTO10, to AstraZeneca) is also studying the same fixed triple combination with the primary outcomes being plasma concentration of the maximum concentration and area under the curve following the treatment with and without oral charcoal (NCT03311373).[26]

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References

1. National Institutes of Health. Randomized study evaluating the effect of danirixin on neutrophil extracellular traps (NETS) in chronic obstructive pulmonary disease (COPD). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03250689 Published August 2017. Updated November 2017. Accessed January 2018.

2. National Institutes of Health. A pilot study of danirixin for disease progression in chronic obstructive pulmonary disease (COPD). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03170232. Published May 2017. Updated January 2018. Accessed January 2018.

3. National Institutes of Health. A study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 in chronic obstructive pulmonary disease (COPD) subjects with acute exacerbation. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02522299. Published August 2015. Updated December 2017. Accessed January 2018.

4. National Institutes of Health. Absorption & elimination of radiolabelled GSK2269557. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03315559. Published October 2017. Updated November 2017. Accessed January 2018.

5. National Institutes of Health. Dose finding study of nemiralisib (GSK2269557) in subjects with an acute moderate or severe exacerbation of chronic obstructive pulmonary disease (COPD). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03345407. Published November 2017. Updated January 2018. Accessed January 2018.

6. National Institutes of Health. An efficacy study of gsk2269557 added to standard care in subjects with an acute exacerbation of chronic obstructive pulmonary disease. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02294734. Published November 2014. Updated March 2017. Accessed January 2018.

7. National Institutes of Health. A study to investigate safety, tolerability and pharmacokinetics of single and repeat doses of CHF6333 in healthy subjects (CHF6333 FIH). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03056326. Published February 2017. Updated November 2017. Accessed January 2018.

8. Carnini C, Brogin G, Patacchini R, et al. CHF6333: Pharmacological and pharmacokinetic characterization of a novel potent inhaled inhibitor of neutrophil elastase. *Am J Resp Crit Care Med*. 2017;195: A4420

9. National Institutes of Health. Comparative study of Ellipta dry powder inhaler (DPI) versus diskus DPI used with handihaler DPI in subjects with chronic obstructive pulmonary disease (COPD). Clinicaltrials.gov. website. https://clinicaltrials.gov/ct2/show/NCT03227445. Published July 2017. Updated November 2017. Accessed January 2018.

10. Insmed Incorporated. INS1007-An investigational, novel oral reversible inhibitor of DDP1. Insmed website. http://www.insmed.com/about-ins1007/. Published 2018. Accessed January 2018.

11. Korkmaz B, Horwitze MS, Jenne DE, Gauthier F. Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human disease. *Pharmacol Rev*. 2010;62(4):726-759.

12. Stockley R, De Soyza A, Gunawardena K, et al. Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. *Respir Med*. 2013;107(4):524-533.

13. National Institutes of Health. Assessment of INS1007 in subjects with non-cystic fibrosis bronchiectasis.Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03218917. Published July 2017. Updated August 2017. Accessed January 2018.

14. National Institutes of Health. Assessment in a real world setting of the effect of inhaled steroid-based triple therapy versus the combination of tiotropium and olodaterol on reducing chronic obstructive pulmonary disease (COPD) exacerbations [AIRWISE]. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03265145. Published August 2017. Updated December 2017. Accessed January 2018.

15. Carroll J. Struggling in R&D, GSK lines up an FDA pitch on COPD with mixed data. *Endpoints News*. September 12, 2017. https://endpts.com Accessed January 2018.

16. National Institutes of Health. Efficacy and safety of mepolizumab as an add-on treatment in chronic obstructive pulmonary disease (COPD). Clinicaltrials.com website. https://clinicaltrials.gov/ct2/show/NCT02105961. Published April 2014. Updated September 2017. Accessed January 2017.

17. National Institutes of Health. Discovery of the impact of targeted lung denervation (TLD) on the severe and very severe COPD population (DISCOVER TLD). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03213080. Published July 2017. Updated November 2017. Accessed January 2018.

18. Nuvaira Inc. Nuvaira-The procedure. Nuvaira website.https://www.nuvaira.com/the-procedure/ Published 2017. Accessed January 2018.

19. National Institutes of Health. Extracorporeal CO2 removal with the Hemolung RAS for mechanical ventilation avoidance during acute exacerbation of COPD (VENT-AVOID). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03255057?term=Hemolung+RAS&rank=2. Published August 2017. Updated October 2017. Accessed January 2018.

20. National Institutes of Health. A study to test if the vaccine is working well in chronic obstructive pulmonary disease (COPD) patients aged 40 to 80 years old to reduce episodes of worsening symptoms and to gather further information on safety and immune response. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03281876. Published September 2017. Accessed January 2018.

21. National Institutes of Health. Safety, tolerability and pharmacokinetics of multiple ascending doses of AZD8871 in healthy male Japanese subjects. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03159442. Published May 2017. Updated Octobert 2017. Accessed January 2018.

22. National Institutes of Health. Functional Respiratory Imaging Study (FRI) (FRI) Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03268226. Published August 2017. Updated November 2017. Accessed January 2018.

23. National Institutes of Health. Percutaneous temporary placement of a phrenic nerve stimulator for diaphragm pacing (RESCUE1) (RESCUE1). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03107949. Published April 2017. Updated September 2017. Accessed January 2018.

24. National Institutes of Health. Improving patient outcomes by selective implantation of the Zephyr EBV - study (IMPACT). Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02025205. Published December 2013. Updated October 2017. Accessed January 2018.

25. National Institutes of Health. Study to assess the safety and tolerability of PT010, PT009 and PT003 in subjects with moderate to very severe chronic obstructive pulmonary disease. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03313570. Published October 2017. Accessed January 2018.

26. National Institutes of Health. A randomized, open-label, single-dose, single-center, crossover study in healthy subjects to assess the relative bioavailability of PT010. Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03311373. Published October 2017. Updated October 2017. Accessed January 2018.