

Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



The COPD Pipeline XXXVIII

Nicholas J. Gross, MD, PhD¹

Abbreviations: chronic obstructive pulmonary disease, **COPD**; electronic health records, **EHR**; forced expiratory volume in 1 second, **FEV₁**; area under the curve, **AUC**; structured light plethysmography, **SLP**

Citation: Gross N. COPD pipeline XXXVII. *Chronic Obstr Pulm Dis*. 2018;5(2):144-147. doi: <https://doi.org/10.15326/jcopdf.5.2.2018.0134>

¹ St. Francis Hospital and University Medical Research LLC

Address correspondence to:

Nicholas Gross, MD, PhD
grossnicholas1@gmail.com

Keywords

Pioneer; INS1007; doxofylline; QVA; Gala treatment; Nemiralisib; CHI3L1; YKL-40

Introduction

The Food and Drug Administration announced that they approved 46 new drugs in 2017 — about twice as many as the usual number and a new high for the past decade.¹ (That number does not include new combinations of previously included molecules such as trelegy, the triple combination of fluticasone, umeclidinium, and vilanterol.) The only new pulmonary drug in 2017 was the AstraZeneca drug benralizumab (Fasenra). We also have mepolizumab (Nucala), and reslizumab (Cinqair). It is likely that we will also have dupilumab (Dupixent), tralokinumab, and tezepelumab² all coming soon and all for asthma. But no monoclonals were approved for chronic obstructive pulmonary disease (COPD).

Sensor and Electronic Health

A new study related to electronic health records (EHRs) has been scheduled. It is described as: “a pilot study that will evaluate the feasibility of collecting increasing amounts of clinical study data from subjects through sensor and web/app-based methods and integrating it with data from their EHR to facilitate more efficient and meaningful research with acceptable quality. Approximately, 100 subjects with asthma and 100 subjects with chronic obstructive pulmonary disease

(COPD) will be prospectively enrolled. The subjects will be identified through integrated EHR records following which eligible subjects will receive study devices and training on proper use of the devices at a baseline visit. Data will be collected remotely from subject reports, devices and sensors over six months” (NCT03357341).³ This means more work, of course, but it sounds like a good idea.

PIONEER CHF6001

PIONEER CHF6001 is a selective phosphodiesterase-4 inhibitor described as “a novel phosphodiesterase 4 inhibitor, suitable for topical pulmonary administration with a wide therapeutic window.”⁴ The trial is a phase II, randomized, double-blind, double-dummy, placebo and active controlled multinational, multicenter, dose-ranging, 6-arm parallel-group study to identify the optimal dose of CHF6001 (NCT02986321).⁵ Patients will be assessed after 3, 6, 12, 18 and 24 weeks of treatment. The primary outcome is the change from baseline in predose morning forced expiratory volume in 1 second (FEV₁) at 12 weeks. A second study of the same agent, CHF6001, has also been initiated (NCT03004417).⁶ It is a dose response study.

GLIMMER

GLIMMER is a 6-week dose-ranging study of the Chiesi agent CHF5259, an extra fine glycopyrrolate, powdered, meter-dose inhalation in individuals with COPD.⁷ Per ClinicalTrials.gov, “the study is a phase II, multicenter, randomized, double-blind, placebo and active controlled dose-ranging 6-arm parallel group study to identify the optimal dose of CHF5259 with respect to lung function and clinical efficacy and safety outcomes.”⁷ The primary

outcome is the change from baseline in FEV₁ area under the curve (AUC)(0-12h) normalized by time at week 6.

Structured Light Plethysmography

Structured light plethysmography (SLP) is a different way to characterize lung structure. The idea is that SLP may become a tool used to “differentiate between different respiratory diseases. SLP measurements are recorded in a range of diagnostic conditions that affect breathing and in healthy normal subjects” (NCT02626468).⁸ The primary outcome will be the “difference in SLP breath timing indices and measured in seconds and between patients and healthy subjects.”⁸ No intervention or drug administration is involved. De Boer et al first presented this topic in their 2010 publication.⁹

Doxofylline

Doxofylline is known and used worldwide under at least a score of names. Not strictly a U.S. COPD pipeline medication, it has properties that make it worthy of consideration to become one. Matera et al explains that its structure differs only slightly from theophylline whose phosphodiesterase inhibitory action it shares, but with important differences.¹⁰ Although closely related to theophylline, it lacks some of theophylline’s drug-drug interactions, and may therefore be safer in older patients with comorbidities. Instead, per Matera et al, it is said to have “no significant effect on any of the known phosphodiesterase isoforms, no significant adenosine receptor antagonism, no direct effect on histone deacetylases or interaction with adrenoceptors and therefore, should not be considered as just a modified theophylline.”¹⁰ It has been shown to reduce study research dropouts as compared to that with theophylline. It has also been shown to have superior gastric tolerability as compared to theophylline, and does not increase myocardial oxygen demand, hypertension, or affect cardiovascular side-effects. It may become more effective and more usable than theophylline for bronchial asthma or COPD. Matera et al suggest that the use of doxofylline be “considered as an alternative to expensive biologics.”¹⁰

QVA

QVA is Novartis’s fixed combination of indacaterol and glycopyrronium bromide and was in a phase

3 randomized, placebo controlled, double-blind trial (NCT02487446).¹¹ The combination was delivered as a single-dose, dry powder inhaler which is compared with a similar Food and Drug Administration-approved combination of umeclidinium and vilanterol. The purpose of the trial was to show that QVA is similar in efficacy to the GlaxoSmithKline’s combination product umeclidinium/vilanterol. The pre-specified endpoint for both agents is FEV₁ AUC0-24h while maintaining an acceptable safety profile. While both agents are long-acting muscarinic antagonists/long-acting beta2-agonists, umeclidinium/ vilanterol is a once-daily agent whereas QVA would be a twice-daily bronchodilator.

Gala Treatment

Gala treatment for chronic bronchitis appears to be a form of bronchial hyperthermia but for COPD rather than asthma (NCT03385616).¹² The description of the treatment and its clinical trial (per ClinicalTrials.gov) is “a device-based, energy delivery system that 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. Two sessions of treatment will be delivered one month apart. The right lung is treated at the first treatment session and the left lung is treated at the second treatment session, approximately one month after the right side. Treatment will be delivered by a respiratory physician (an interventional pulmonologist) in a tertiary teaching hospital during a bronchoscopic procedure [under general anesthesia]. It is anticipated that the bronchoscopic procedure will last less than 60 minutes in total.”¹² A third bronchoscopy will be performed 3 months following the second treatment to determine the efficacy of the treatments. A similar trial, NCT03107494, was previously registered with Clinicaltrials.gov.

Nemiralisib (GSK2269557)

As mentioned in my January Pipeline column, Nemiralisib (GSK2269557) is also being developed by GlaxoSmithKline as an anti-inflammatory agent. A new dose-finding study to measure the lung function (FEV₁) in individuals with an acute moderate or severe exacerbation of COPD compared to FEV₁ during health is underway. NCT03398421 is in phase 1 with an enrollment of 20 individuals, the aim is to evaluate the effect of itraconazole on nemiralisib.¹³

The DISCOVER Targeted Lung Denervation

In a clinical trial description, Nuvaira™ states “Targeted Lung Denervation is a simple, one-time bronchoscopic procedure that disrupts overactive nerves in the lungs, thereby opening up the airways to improve breathing” (NCT02058459).¹⁴ More information on this procedure was provided in my January column, but Gompelmann et al provide this information, “this reversible technique leads to lobar atelectasis and thus significant lobar volume reduction in patients with severe emphysema and low collateral ventilation.”¹⁵

Chitinase-3-like Protein 1

Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is an interesting molecule looking for a problem. It is described as a “secreted glycoprotein that is approximately 40kDa in size that in humans is encoded by the *CHI3L1* gene. The name YKL-40 is derived from the three N-terminal amino acids present on the secreted form and its molecular mass. YKL-40 is expressed and secreted by various cell-types including macrophages, chondrocytes, fibroblast-like synovial cells, vascular smooth muscle cells, and hepatic stellate cells. The biological function of YKL-40 is unclear. It is not known to have a specific receptor. Its pattern of expression is associated with pathogenic processes related to inflammation, extracellular tissue remodeling, fibrosis and solid carcinomas and asthma.”¹⁶ I include it in the pipeline because some reports have suggested it might be a potential biomarker for COPD.¹⁷

Lonhala Magnair

Lonhala magnair is a twice daily delivery of aqueous glycopyrrolate that will be delivered via a novel device, the Magnair. No dosage adjustment is required for geriatric patients nor patients with renal disease or hepatic impairment. The delivery device requires some training and manual dexterity to put together the 7 components for each delivery.¹⁸

Acknowledgements

Many of the items in this report are due to the generous support of Johan Karlberg, MD, PhD, via his e-publication *Clinical Trials Magnifier Weekly*. I am grateful to Dr. Scott Caveney for his review and correction of some GlaxoSmithKline items.

Declaration of Interest

The author states he received reimbursement for travel and overnight facilities for training and presentation of the Lonhala Magnair.

References

1. Food and Drug Administration (FDA). Novel drug approvals for 2017. FDA website. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm>. Published February 2, 2018. Accessed March 2018.
2. Coran J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Eng J Med*. 2017;377:936-946. doi: <https://doi.org/10.1056/NEJMoa1704064>
3. National Institutes of Health. Sensor and electronic health records (EHR) integration pilot study. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT03357341>. Published November 29, 2017. Updated February 12, 2018. Accessed March 2018.
4. Villetti G, Carnini C, Battipaglia L, et al. CHF6001: A novel phosphodiesterase 4 inhibitor, suitable for topical pulmonary administration—in vivo preclinical pharmacology profile defines a potent anti-inflammatory compound with a wide therapeutic window. *J Pharmacol Exp Ther*. 2015;352(3):568–578.
5. National Institutes of Health. A 24-wk dose ranging study to evaluate the efficacy and safety of 4 doses of a new pde4 inhibitor in patients with COPD (PIONEER). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02986321>. Published December 8, 2016. Updated January 10, 2018. Accessed March 2018.
6. National Institutes of Health. Pharmacodynamics, pharmacokinetics and safety of two doses of chf6001 dpi in subjects with moderate, severe COPD. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT03004417>. Published December 28, 2016. Updated January 18, 2018. Accessed March 2018.
7. National Institutes of Health. A 6-week dose ranging study of CHF5259PMDI in subjects with chronic obstructive pulmonary disease (GLIMMER). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT03084796>. Published March 21, 2017. Updated November 27, 2017. Accessed March 2018.
8. National Institutes of Health. Validation of structured light plethysmography - health and disease (SLP-RESPDIS). ClinicalTrials.gov website <https://clinicaltrials.gov/ct2/show/NCT02626468>. Published December 10, 2015. Accessed March 2018.
9. de Boer WH, Lasenby J, Cameron J, et al. SLP: A zero-contact non-invasive method for pulmonary function testing. In: Labrosse F, Zwiggelaar R, Liu Y, Tiddeman B, eds, *Proceedings of the British Machine Vision Conference*. BMVA Press: Aberystwyth, United Kingdom. 2010.
10. Matera MG, Page C, Cazzola M. Doxofylline is not just another theophylline! *Int J of COPD*. 2017;12: 3487-3493.
11. National Institutes of Health. Efficacy and safety study of QVA149 in COPD patients. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02487446>. Published July 1, 2015. Updated December 26, 2017. Accessed March 2018.
12. National Institutes of Health. Gala treatment for chronic bronchitis in Canada. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT03385616>. Published December 28, 2017. Accessed March 2018.
13. National Institutes of Health. A study to evaluate the effect of itraconazole on the pharmacokinetics (PK) of nemoralisib. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT03398421>. Published January 12, 2018 Updated March 12, 2018. Accessed March 2018.
14. National Institutes of Health. Targeted lung denervation for patients with moderate to severe COPD (AIRFLOW). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02058459> Published February 10, 2014. Updated May 3, 2017. Accessed March 2018.
15. Gompelmann D, Eberhardt R, Herth FJF. Novel endoscopic approaches to treating chronic obstructive pulmonary disease and emphysema. *Semin Respir Crit Care Med*. 2015;36(04):609-615. doi: <https://doi.org/10.1055/s-0035-1555614>
16. Sino Biological. CHI3L1/YKL40 summary. Sino Biological website. <http://www.sinobiological.com/CHI3L1-YKL40-a-5149>. Published 2017. Accessed March 2018.
17. Tong X, Wang D, Liu S, et al. The YKL-40 protein is a potential biomarker for COPD: a meta-analysis and systematic review. *Int J COPD*. 2018;13:409-418.
18. U.S. Food and Drug Administration (FDA). LONHALA MAGNAIR (glycopyrrolate) inhalation solution, for oral inhalation use: Highlights of prescribing information. FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208437lbl.pdf. Published December 2017. Accessed March 2018.