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The COPD Pipeline XXXI

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Abbreviations: Food and Drug Administration, **FDA**; Centers for Drug Evaluation and Research, **CDER**

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New Drugs in 2015

A recent Food and Drug Administration (FDA) report begins: "FDA's Center for Drug Evaluation and Research (CDER) supports the pharmaceutical industry at every step of the process."[1] The FDA approved 45 new drugs last year, substantially more than the usual 25–30 new entities ("me-toos," of which hundreds are approved each year, are not included here). Sixteen of the 45 novel drugs were considered to be *First-in-Class*, and 21 of the 45 approvals, almost half, were for *orphan* drugs. Only 3 of the 45 new molecular entities were for pulmonary disorders. One of them, the fixed combination of lumacaftor/ivacaftor (Okambi) was approved for cystic fibrosis due to homozygous F*508del* mutations,[1,2] the most common cause of cystic fibrosis. Okambi is designated as an orphan drug. Mepolizumab (Nucala, a First-in-Class drug) was approved "for use with other asthma medicines for the maintenance treatment of asthma in patients aged 12 years and older."[1] It is a humanized, interleukin-5 antagonist monoclonal antibody. The third pulmonary approval was for selexipag (Uptravi),[1] to treat pulmonary arterial hypertension. It is an oral prostacyclin receptor agonist. No new molecular entities for COPD were approved by the FDA.

An updated summary of the FDA's current drug development and approval process was published in January of this year.[3]

Treprostinil

Treprostinil, a prostaglandin analog,[4] was approved for the treatment of pulmonary artery hypertension (WHO group I) in 2002. It is now or has been in 81 trials for a variety of indications and formulations as Tyvaso™. The latest trial, just initiated (NCT02633293),[5] is a phase 2/3 multicenter, open-label, 2-year trial to evaluate the safety and efficacy of inhaled treprostinil in individuals with pre-capillary pulmonary hypertension associated with interstitial lung disease including combined pulmonary fibrosis and emphysema, comorbidities that are presently outside the Tyvaso indication.

BI 1026706

A new Boehringer Ingelheim agent, BI 1026706, seems to be looking for an indication. In 5 completed trials it has been tested as an antifungal agent, as an anti-epileptic, as an analgesic and as a non-steroidal anti-inflammatory.[6] The present study is its first trial in COPD patients. It is a dose-response study in Phase I and the primary outcome is safety and tolerability. A total of 120 individuals with COPD will be enrolled into a 4 week study (NCT02642614).[7] There is no public information about the action of this agent but one presumes the trial is to test its anti-inflammatory activity in COPD patients.

PT003

Pearl Therapeutics has a new glycopyrronium/formoterol (14.4/9.6gm) fixed combination, PT003. It will employ Pearl's "...proprietary formulation

technology that uses lipid-based porous particles to create stable cosuspensions with drug crystals in HFA propellants, and high performance aerosols upon actuation."[8] A trial will enroll 20 COPD individuals in a placebo controlled 2-week, cross-over Phase III study. The outcomes will be lung volumes and resistance as determined by imaging (NCT02643082).[9]

CHF5259

CHF5259 is Chiesi's glycopyrronium bromide dry powder inhaler. Currently, a randomized, double blind, placebo-controlled, 3-way cross-over study of doses from 6.25 to 25mg twice daily to evaluate efficacy and safety in individuals with moderate to severe COPD is being conducted. In this phase II trial 300 individuals will receive treatments of 4 weeks duration over 3 periods. The primary outcome is forced expiratory volume in 1 second, area under the curve from 0–12 hours at the end of each study period (NCT02680197).[10]

Philip Morris P3L Nicotine Delivery Device

Two new trials are being tested for Philip Morris' P3L nicotine delivery device. The first trial, NCT02643693, will assess the safety and tolerability of Philip Morris's "...Nicotine Lactate Delivery System (P3L) after ad libitum use and the ability of combustible cigarette smokers to use P3L to maintain their customary nicotine intake."[11] A second trial, NCT02649556, known as the ZRHR-ERS-09-EXT-US study, has the objective of further assessing the effect of the Tobacco Heating System 2.2 (THS 2.2), compared to conventional cigarettes, on the components of the *smokers' health profile* for a prolonged period of 26 weeks.[12] This will provide additional information to the results of the original study ZRHR-ERS-09-US of 26-week exposure (NCT02396381). In total, the ZRHR-ERS-09-EXT-US study will extend the exposure period to 52 weeks. Neither study states a phase number.

Vismodegib

Vismodegib byErivedge® is a drug that was approved for basal-cell carcinoma in 2012. It has since been tested in over 60 trials for a wide variety of diseases mostly associated with malignancies of the prostate, colorectal, ovaries, stomach, lymphomas and several more. It is the first hedgehog signaling pathway-targeting agent to gain FDA approval. Initially developed by Genentech, it is now undergoing a small, single-arm phase I safety and tolerability trial of the drug in combination with pirfenidone in patients with idiopathic pulmonary fibrosis (NCT02648048).[13]

Batefenterol

Batefenterol, a GlaxoSmithKline molecule, has just entered 2 phase 1 trials. It is "..a bifunctional bronchodilator that is being developed for the treatment of COPD. Absorption, metabolism and excretion of batefenterol have been studied in animals, in vitro, and in previous clinical studies; however, the elimination routes and metabolic pathways of batefenterol have not been fully elucidated in humans."[14,15] Like some other emerging bi-functional molecules for COPD, its action consists of anti-muscarinic and beta-adrenergic pharmacophores joined by an inert spine. In the 2 phase 1 safety studies, 6 and 48 healthy individuals will receive the agent by intravenous infusion, orally, or by inhalation of the dry powder (NCT02663089 and NCT02666287).

GSK2269557

GSK2269557 is a potent and highly selective inhaled phosphoinositide 3-Kinase delta inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airway diseases, according to its developer, GlaxiSmithKline (NCT02691325).[16] Additional information about this new molecule is available from *Expert Opinion on Therapeutic Patents*.[17]

Moracin M

The moracins are 2-arylbenzofuran derivatives that are derived from an oriental tree bark. They have been found to inhibit interleukin-6 production from IL-1β-treated lung epithelial cells.[18] Among the several moracin molecules, moracin M shows the strongest inhibitory effect. Downregulation of IL-6 expression by moracin M was mediated by interrupting the JNK/c-Jun pathway. Its action includes selective inhibition of PDE4D2 and PDE5A2, interfering with NF-kB activation, and inhibition of inducible nitric oxide synthase (iNOS)-catalyzed NO. When orally administered to mice, moracin M (20-60mg/kg) showed comparable inhibitory action to dexamethasone (30mg/kg) against LPS-treated lung

inflammation. The interference with activation of NF-κB inhibition of inducible nitric oxide synthase (iNOS) is seen both in vitro and in vivo. The moracins, in particular moracin M, might have therapeutic potential in treating lung inflammatory disorders, as has been suggested (F), but trials of moracins have not yet been registered in clinicaltrials.gov.

GLPG1837

The S1251N mutation of cystic fibrosis is one of the earliest to have been identified[19] and one of the more common ones of the hundreds of known mutations. A trial of a treatment for patients with CF due to that mutation is about to begin (NCT02690519).[20]

New Lipid Formulation Trial

NCT02646995 describes a clinical trial of a novel lipid formulation aimed at increasing the bioavailability of fatty acids in cystic fibrosis patients.[21]

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