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The COPD Pipeline XXXII

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Abbreviations: phosphodiesterase, **PDE**; forced expiratory volume in 1 second, **FEV_1**

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Here Come the Triples!

The excellent website *clinicaltrialmagnifier.org* run by Johan Karlberg, MD, PhD and the equally excellent government website *clinicaltrials.gov* make it possible to track all new clinical studies in real time. From these sources I find that over the last 6 months an average of about 125 new trials categorized as *respiratory* are initiated each week; about 6250 a year. Of these, about 45% are lung oncology trials, and another 12% are trials directed against lung infections. However, readers of this journal will be mostly interested in a subcategory called *Resp COPD*. That section accounts for about 21% or about 26 new trials each week. I do not usually include trials subcategorized as *cystic fibrosis* or *bronchiectasis* although I may include them when they seem to cover something new and interesting. Nor do I include any trials described as sleep disorder, respiratory failure, embolism, devices and such. Under the heading "Phase," fully two-thirds of the *Resp COPD* trials being initiated do not state the phase of the trial; no explanation is provided. Among those that do state the phase of the trial, the majority by far are Phase II and III trials in about equal proportions. Phase I trials account for only 2% or 3% of each week's new trials, which means that 97% or 98% of all new COPD trials are for agents in Phases II, III, or IV, --not what one might expect or wish for as those 2% or 3% in Phase I are the ones that might be of most interest for this column. I assume that most readers of this column already know about late stage clinical trials of COPD as many of them/us are involved with these one way or another.

Having said that, I excuse myself for addressing the issue of fixed-component triples simply to bemoan the overabundance of doubles, and, more recently, triples in late stage development. This is not because one disapproves of fixed combinations. Rather it is because one fears that too much work and capital of all sorts is being devoted to agents that seem to be of apparently equal safety and efficacy. In the absence of head-to-head trials, comparisons among fixed dose combinations of 2 agents appear to be almost identical, as was recently very well pointed out.[1] One expects that the triples now in late stage development will also turn out to have properties that are very similar to each other. Will the battle for sales among pharmaceutical agents and their products then be between different delivery devices and other secondary features? One wishes that more of the time, energy, and capital currently being spent on reinventing the wheel would be given to other important tasks such as the development of drugs that address the airways inflammation of COPD.

For the record then, in the last month GlaxoSmithKline initiated 3 Phase III trials of fixed *triples* consisting of fluticasone/umeclidinium/vilanterol (NCT02731846, NCT 02345161, and NCT02729051)[2,3,4] and 2 early phase trials of an antimuscarinic/adrenergic muscarinic antagonist-beta-2 agonist in combination with fluticasone fuorate (NCT02666287 and NCT02573870).[5,6] Chiesi initiated 2 trials of its fixed combination of beclomethasone, formoterol, and glycopyrrolate (NCT02467452 and NCT02743013).[7,8] Chiesi also initiated a Phase I

trial of the same agents (CHF 5993) delivered as a dry powder (NCT02743013).[9] An interesting feature of that trial is that the end point will be AUC of the active ingredients at 72 hours. Pearl initiated 3 Phase III triples of their combination called PT010. The components of the fixed combination are budesonide/formoterol/glycopyrrolate (NCT02465567, NCT02536508 and NCT02497001).[10,11,12] Note that the components of Chiesi's triples are identical to those of Pearl's triple although the dosages and methods of delivery differ somewhat.

GSK2269557

GSK2269557 is described by GlaxoSmithKline, the company, as "...a potent and highly selective inhaled phosphodiesterase 3-kinase delta inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases."[13] The present trial (NCT02691325)[13] follows 7 previous trials which included 1 asthma trial, 1 trial in preparation in an immunologic disorder, the rest being for COPD, mostly in acute exacerbations. The drug will be delivered by the GSK's Ellipta dry powder inhaler system to healthy volunteers and will consist of 3 phases: a pharmacokinetic/pharmacodynamic trial followed by a randomized, double blind, placebo-controlled study, and then by an open label, randomized, cross-over phase. Apart from the general knowledge that phosphodiesterase (PDE) kinases are active in some models of inflammation, the rationale of the present PDE3 kinase inhibitor is not common knowledge. Nor have the results of any of the completed trials of the present agent been reported.

COPD Cachexia

There is interesting news of treatments for the difficult problem of COPD cachexia. CK-2127107 a product of Astellas and Cytokinetics, is described as a novel fast skeletal muscle troponin activator. It "slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers" which leads to an increase in skeletal muscle contractility.[14] Its role has been explored in disorders of muscle weakness and fatigue such as spinal muscular atrophy. One assumes that the present trial (NCT02662582),[15] the first trial of this agent in COPD, will address its potential for improving muscle activity in those COPD patients whose muscular activity is declining. The trial is in Phase II and will assess the effect of the drug on physical function, constant work rate endurance time and similar outcomes in a placebo-controlled cross-over study in individuals with COPD. I believe the agent is oral, however that is not stated.

BYM338

BYM338, bimagrumab is a monoclonal antibody targeting ActRIIB (a high affinity activin type 2 receptor that mediates the signaling by a subset of TGF-β family ligands including myostatin).[16] The agent is being developed by Novartis for the treatment of musculoskeletal diseases such as sporadic inclusion body myositisis (for which the Food and Drug Administration awarded it a "breakthrough therapy" designation). The agent is also in Phase II or III trials for the cachexia associated with cancer, and mechanically ventilated patients. The primary outcome of this 24 week study, NCT01669174, is a change in thigh muscle volume compared to placebo. The study will last for approximately 24 weeks.[17]

ARALAST NP and GLASSIA

Both ARALAST NP and GLASSIA are approved therapies for alpha-1 antitrypsin deficiency. They are now entering a Phase IV trial that will examine the safety and efficacy of these 2 agents, 2 doses of each, versus placebo, over 104 weeks. Primary outcome will be rate of change of lung density which will be measured every 26 weeks, NCT02722304.[18]

VX-661

A study is being created with the primary purpose of evaluating the treatment effect of VX-661 in combination with ivacaftor (VX-661/ivacaftor) on chest imaging endpoints using low-dose computed tomography at week 72.[19] The experimental treatment is an oral fixed dose combination of the 2 agents given once daily; ivacaftor monotherapy will be given in the evening. The trial will also examine the safety of VX-661/ivacaftor. The Phase II trial will be limited to patients with 1 copy of each G551D and F508del mutation (NCT02730208).[19] One expects that, in the future, there will be many similar combinations of –caftors and caftor-promoting agents.

BCT197

BCT197 is an orally active p38 MAP kinase inhibitor that turns off a key signaling pathway involved in

the regulation of proinflammatory cytokines.[20] Pharmaceutical chemists are becoming quite interested in molecules of this kind as potential ways to address chronic inflammation. This molecule had its first COPD outing 5 years ago (NCT01332097)[21] and its sponsor, Mereo Biopharma, evidently saw a role for the agent as a therapy for acute exacerbations of COPD rather than as a maintenance treatment. The present study is a randomized, double-blind, placebo-controlled phase II trial. The drug or placebo is given together with all usual therapy on initiation of an acute exacerbation. The primary outcome is the change in forced expiratory volume in 1 second (FEV_1) from baseline to day 7 of the exacerbation (NCT02700919).[22]

AZD7624

AZD7624 is another p38 MAP kinase inhibitor that has just completed a Phase II trial (NCT01817855).[23] A previous COPD trial of the agent following lipopolysaccharide-induced airway inflammation was reported (several times) at the annual ATS Conference in 2015. In anticipation of systemic side effects the agent will be administered by inhalation (NCT02238483).[24]

Cystic Fibrosis Therapies

There is much activity in this area. FDL169 is a *class II disease-modifying corrector* of the F508 deletion, meaning it inhibits the folding and stability of the CFTR protein.[25,26] It is in a Phase I dose-finding study of 9 single doses with an additional placebo-controlled double-blind component (NCT02359357).[27]

OligoG is described as an alginate oligosaccharide, a surface acting agent that mitigates antimicrobial resistance by acting as an anti-biofilm. Correspondingly, it will be delivered as a dry powder by inhalation. The present study is in Phase IIb (NCT02157922),[28] and follows 4 previous trials of the same agent.

N91115 inhibits its primary catabolizing enzyme thus providing a novel therapeutic strategy for cystic fibrosis and has been shown to improve the expression and function of the F508 deletion in experimental models. The Phase II study will enroll 30 individuals who are heterozygous for F508 del and already receiving ivacaftor (NCT02724527).[29]

Ivacaftor itself will be the subject of a clinical trial in children aged 3 to 5 years of age who are heterozygous for F508 del and a gating mechanism (NCT02742519).[30] Ivacaftor is not currently approved for children of that age and genotype.

GS5745

GS5745, a Gilead Sciences product, is a monoclonal antibody that inhibits matrix metalloprotease-9, an extracellular enzyme involved in matrix remodeling, tumor growth, and some proinflammatory molecules. The agent has been in 4 previous completed trials only 1of which was a Phase I trial in individuals with COPD. The results have not been published. The agent is now entering a Phase II placebo-controlled trial in adults with cystic fibrosis (NCT02759562).[31]

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