





Marketing authorisation application maa biology essay

[Science](#), [Biology](#)



ANORO ELLIPTA[®] is combination of 2 investigational bronchodilator molecules - GSK573719 or umeclidinium bromide (UMEC), a long-acting muscarinic antagonist (LAMA) and vilanterol (VI), a long-acting beta2 agonist (LABA), administered using the ELLIPTA[®] inhaler. UMEC/VI is one of pipelined project in the GSK respiratory which includes fluticasone furoate/vilanterol (FF/VI, RELVAR[®] and BREO[®]), VI monotherapy and MABA (GSK961081), developed in collaboration with Theravance, as well as GSK's[®] investigational medicines FF monotherapy, UMEC monotherapy and anti-IL5 MAb (mepolizumab). ANORO[®], RELVAR[®], BREO[®] and ELLIPTA[®] are trademarks of the GSK. Clinical trials were conducted to evaluate the efficacy and safety of GSK573719/GW642444 and the individual components delivered once-daily via a novel dry powder inhaler (nDPI) in subjects with COPD. Treatment with UMEC/VI 125/25 mcg, UMEC 125 mcg, and VI 25 mcg resulted in statistically significant improvements in the primary efficacy endpoint (PEE) of trough FEV1 at Day 169 compared with placebo. In another phase 3 study, subjects were randomized in a 3: 3: 3: 2 ratio to UMEC/VI, UMEC, VI and placebo for 24 weeks. Treatment with UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, and VI 25 mcg resulted in statistically significant improvements in the (PEE) of trough FEV1 at 169th day compared to placebo. A multicenter clinical trial was conducted to compare the efficacy and safety of GSK573719/GW642444 with GSK573719 and with tiotropium over 169 days in subjects with COPD. Treatment with once-daily UMEC/VI 125/25 resulted in a statistically significant improvement in lung function as measured by the primary endpoint (PE), trough FEV1 at in 24th week as compared to TIO. The comparison of UMEC/VI 125/25 and UMEC 125 with

evaluations were performed in the 3 trials. Results for the other two placebo controlled trials were similar to the results for Trial B. Mean peak improvements in FEV1, for TUDORZA PRESSAIR relative to baseline were assessed in all patients in trials B, C and D after the first dose on day 1 and were found to be similar at week 12. (Fig 2) Table and fig to be used from pack insert FDA On July, 2012, Almirall was granted European Commission marketing approval for Eklira/Bretaris Genuair (acclidinium 322 mcg twice daily) in all EU member states, plus Iceland and Norway. Clinical efficacy studies showed that acclidinium provides significant and sustained bronchodilation from the 1st dose (within half hour). Reduction in moderate and severe exacerbations by approximately 30% was observed. In addition the studies demonstrated that acclidinium provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI][3]) and disease-specific health status (assessed using the St. George's Respiratory Questionnaire [SGRQ][4]). In the six month study, patients receiving Acclidinium 322 mcg twice daily experienced a improvement in FEV1. Significant bronchodilatory effects were observed from day one and were maintained over the six month treatment period. Almost similar observations were found with Acclidinium in the 3 month study. Acclidinium demonstrated clinically improvements in breathlessness assessed by TDI mean changes vs baseline = 1 unit ($p < 0.001$) and disease-specific health status assessed using SGRQ: mean change vs baseline -4.6 units ($p < 0.0001$). It was observed that patients treated with acclidinium required less rescue medication than those treated with placebo (a reduction of 0.95 puffs per day at 6 months [$p = 0.005$]). Acclidinium reported to improve daily

symptoms of COPD and night-time and early morning symptoms. The pooled efficacy analysis (6-month and 3-month placebo controlled) revealed a statistically significant reduction in the moderate to severe exacerbations rate, with aclidinium 322 mcg twice daily compared to placebo. Inavir  Dry Powder Inhaler Inavir is an influenza antiviral product (laninamivir octanoate hydrate) for dry powder inhalation This is developed by Daiichi Sankyo Company, Limited. Inavir was found to significantly reduced the incidence of influenza infection compared to placebo in a phase 3 clinical study.  Clinical finding In an efficacy study, Inavir was investigated to prevent influenza virus infection of patients with infection from influenza A or B virus. Inavir  statistically significantly reduced the incidence of the clinical influenza virus infection among household contacts, the primary endpoint of efficacy, demonstrating its protective efficacy. Daiichi Sankyo intends to apply for approval to manufacture and sell of Inavir  in Japan for a prophylaxis indication by the end of 2012. AeroVanc AeroVanc, (Savara Pharmaceuticals) a DPI formulation of vancomycin, is the first inhaled antibiotic being developed for the treatment of respiratory methicillin-resistant Staphylococcus aureus (MRSA) infection in patients with CF. When given by parenteral delivery Vancomycin is choice for the treatment of MRSA-related bronchopneumonia, however, parenteral administration, causes poor penetration into the lungs and systemic toxicities limit its use in a chronic setting. AeroVanc is the first inhaled antibiotic being developed for the treatment of MRSA infection in cystic fibrosis patients. AeroVanc is supposed to improve clinical efficacy and reduce side effects due to systemic drug exposure, when given by inhalation route at the site of infection. The phase



A study in healthy and CF patients demonstrated positive safety and tolerability results, as a once- or twice-daily treatment for pulmonary MRSA infections. vancomycin concentration in sputum was found effective to kill MRSA. The Phase IIa study was planned in MRSA-infected patients. Savara Pharmaceuticals' vancomycin, first inhaled antibiotic DPI formulation designated by USFDA as orphan drug, for the treatment of pulmonary MRSA.

Colobreathe dry powder

On Feb 12, Forest Laboratories was granted EMA approval to market Colobreathe DPI colistimethate sodium for inhalation for treating CF patients aged 6 years and older with chronic lung infection caused by *P. aeruginosa*. The pivotal study which was submitted to EMA for approval was an open-label active comparator clinical study to compare the efficacy of Colobreathe to TOBI[®] (tobramycin nebuliser solution for inhalation). The clinical data from the pivotal study of Colobreathe showed that overall better tolerability and no emergence of antibacterial resistance.

In a phase 3 study (TRIAL REG NO: Eudra CT 2004-003675-36.) Patients with stable CF aged ≥ 6 years with chronic *P. aeruginosa* lung infection were randomised to Colobreathe dry powder for inhalation (CDPI, one capsule containing colistimethate sodium 1 662 500 IU, twice daily) or three 28-day cycles with twice-daily 300 mg/5 ml tobramycin inhaler solution (TIS). The duration of study was 24 weeks. 380 patients were randomised. The change in (FEV₁)% predicted at week 24 was -0.98% in the intention-to-treat population and -0.56% in the per protocol population. Colistin-resistant isolates in both groups was 1.1%. CDPI demonstrated efficacy by virtue of non-inferiority to TIS in lung function after 24 weeks of treatment. There was no emergence of resistance of *P. aeruginosa* to colistin.. QVA149QVA149

(indacaterol 110 /glycopyrronium bromide 50 mcg) is an investigational inhaled, once-daily, fixed dose combination of the long acting beta2-agonist (LABA) indacaterol, and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (NVA237). QVA149 is being investigated for the maintenance treatment of COPD in the Phase III IGNITE clinical trial program. Clinical data from the Novartis once-daily COPD clinical trial programs were presented at the ERS Congress. Overall, Novartis presented 14 abstracts, including data from the investigational QVA149, IGNITE Phase III clinical trial program, the glycopyrronium bromide (Seebri[®] Breezhaler[®]) GLOW Phase III clinical trial program and the indacaterol maleate (Onbrez[®] Breezhaler[®]) INERGIZE Phase III/IV clinical trial program. QVA149 responded superior bronchodilation compared to indacaterol 150 mcg, glycopyrronium 50 mcg, salmeterol/fluticasone 50/500 mcg BID, OL tiotropium 18 mcg and placebo[1],[2]. Seebri[®] Breezhaler[®] (glycopyrronium bromide) demonstrated rapid, sustained bronchodilation and reduced exacerbations similar to OL tiotropium 18 mcg in GLOW pooled data analysis[3],[4]. Onbrez[®] Breezhaler[®] (indacaterol maleate) was superior to OL tiotropium 18 mcg in improving severe breathlessness symptoms in pooled INERGIZE data[5]About the study designsSHINE was a 26 week, multicenter, placebo and active controlled pivotal trial of , 144 patients with moderate-to-severe COPD to assess efficacy in terms of trough FEV1[1]. ILLUMINATE assessed the efficacy, safety and tolerability of QVA149 compared to twice-daily fixed dose combination of salmeterol/fluticasone 50/500 mcg in COPD patients [2]. ENLIGHTEN was a 52 week pivotal trial of 339 COPD patients designed to assess the safety and tolerability [6]. GLOW1 was a 26 week study of

glycopyrronium 50 mcg or placebo. GLOW2 was a 52 week comparative study of glycopyrronium 50 mcg or placebo, and included an exploratory arm to compare the effects of once-daily OL tiotropium 18 mcg versus placebo[3],[4]. The investigational QVA149 IGNITE phase III clinical studies (SHINE, ILLUMINATE and ENLIGHTEN) showed that QVA149 significantly improved lung function compared to other COPD therapies [1],[2],[6]. Data from the GLOW program showed that glycopyrronium 50 mcg once daily responded rapid and sustained bronchodilation, and reduced exacerbations and symptoms in comparison to placebo, similar to the levels observed with open-label (OL) tiotropium 18 mcg[3],[4]. Pooled-analysis from the INERGIZE studies demonstrated that Onbrez  Breezhaler  300 mcg was superior to OL tiotropium 18 mcg in improving breathlessness in COPD patients who had more severe breathlessness symptoms on entry to the studies ($p < 0.05$)[5].

QAT 370 QAT 370 is an investigational compound of Novartis, it is under phase 3. The molecule is having antimuscarinic property. In Germany at 3 centres a multi-centre clinical study was conducted to assess the safety and tolerability of an efficacious dose of QAT370 or matched placebo compared to open-label tiotropium bromide in mild-to-moderate COPD patients. The study consisted of a randomized 3 way crossover design with QAT370, QAT370 matched placebo and tiotropium administered across three treatment periods within each of 6 treatment sequences. The dose of the investigational drug (QAT370) was 400 ? g or matching placebo. The dose of tiotropium was 18 ? g (the recommended single daily dose). QAT370 400 ? g significantly increased the FEV1 AUC 0-24h on Day 7 by 24% relative to placebo, and the increase by Tiotropium was 16% when compared to

placebo. The effect on FEV1 at trough, i. e. FEV1 AUC 23-24h, was also statistically significant but slightly lower in magnitude. The mean FEV1 improvement over placebo ranged between 10% and 24% on Day 7 and was statistically significant at all times. The overall comparison of QAT370 to placebo (averaging over all time points) was significant for FEV1 but did not reach statistical significance for Inspiratory Capacity, although it showed a positive trend at all time points examined which is consistent with AUC 0-24h results. QMF149 is combination of Novartis's experimental beta2-agonist indacaterol with Schering-Plough's inhaled corticosteroid mometasone furoate. It is under phase II study. Novartis's concept device Twisthaler is supposed to be used for these combination drugs. Other molecules are under development at phase I e. g. QBX258, QAB149B at Novartis. TOBI Podhaler 28 mg DPI comes as hard capsules. TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with CF. Phase III trial consisted of 2 studies and 612 treated patients having CF. In the multicentre placebo controlled, study, TOBI Podhaler significantly improved lung function compared to placebo. Spiriva HandiHaler (tiotropium bromide inhalation powder) HandiHaler is DPI formulation of tiotropium bromide, a product of Boehringer Ingelheim International GmbH. The clinical study revealed that the mean difference in change of isotime inspiratory capacity PE or the total normal exhaled air, from baseline to week 6 during rest and exercise between SPIRIVA and placebo was statistically significant in patients with GOLD 1 and 2 COPD.. The difference in change from baseline to week 6 in

exercise duration between SPIRIVA and placebo (secondary endpoint) was not statistically significant in the combined GOLD 1 and 2 groups or the GOLD 1 patient subgroup. The clinical study included 126 current or former smokers age 40 or older with a post-bronchodilator FEV1/FVC less than 70 percent and a FEV1 greater than or equal to 50 percent predicted airflow limitation. iSPERSE (by Pulmatrix) iSPERSE (by Pulmatrix) dry powders comprise proprietary cationic salt formulations developed for oral inhalation having unique small particle size, high density and high dispersibility. These properties make iSPERSE suitable to deliver macromolecules like proteins and peptides. Additionally, iSPERSE's proprietary powders allow for flexible formulation with straightforward manufacturing, supporting the formulation of small and large molecule drugs as well drug combinations, including triple drug combinations. Ref pulmitrex websites Easyhaler, Easyhaler, an in-house developed dry-powder inhaler. Orion has developed Easyhaler-adapted DPI of several generics (e. g. salbutamol, beclometasone, budesonide, formoterol) used in the treatment of asthma and COPD. At the moment under development are new combined formulations of budesonide formoterol, and fluticasone-salmeterol for the treatment of asthma and COPD. Ref Orion's website R343 R343 is an inhaled SYK inhibitor that is being evaluated as a potential treatment for allergic asthma, developed by Rigel Pharmaceuticals, Inc. A phase 2 study of R343, was designed in 270 adults with allergic asthma called SITAR (SYK Inhibition for Treatment of Asthma with R343), for 8 weeks of treatment with either of two different doses of the study agent or placebo. The PE of study will be the measurement of each patient's change in FEV1 from baseline to dosing

completion. Rigel will be using the 3M™ Taper Dry Powder Inhaler device for this trial. Rigel expects to complete this study in 2013. Civitas Therapeutics, Inc., is developing transformative therapeutics using the ARCUS™ respiratory delivery platform, announced today the initiation of a phase 2a clinical trial in Parkinson's patients evaluating CVT-301, an inhaled formulation of levodopa (L-dopa), for the rapid relief from motor fluctuations. CVT-301 provides immediate onset of a large and precise dose of L-dopa. ARCUS™ is a clinically proven dry powder pulmonary delivery platform of Civitas.