Breztri Aerosphere Phase III ETHOS trial met

This announcement contains inside information

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***Breztri Aerosphere* Phase III ETHOS trial met its primary endpoint in chronic obstructive pulmonary disease**

At both standard and low budesonide doses, the triple-combination therapy showed a statistically-significant reduction in the rate of moderate or severe exacerbations compared with dual-combination therapies

First time the benefit of two doses of a fixed triple-combination therapy has been established in a Phase III chronic obstructive pulmonary disease trial

AstraZeneca today announced positive results from the Phase III ETHOS trial for triple-combination therapy *Breztri Aerosphere*, formerly PT010, in patients with moderate to very severe chronic obstructive pulmonary disease (COPD).

At the standard budesonide dose, *Breztri Aerosphere* (budesonide/glycopyrronium/formoterol fumarate 320/14.4/9.6mcg) demonstrated a statistically-significant reduction in the rate of moderate or severe exacerbations compared with dual-combination therapies *Bevespi Aerosphere*(glycopyrronium/formoterol fumarate 14.4/9.6mcg) and PT009 (budesonide/formoterol fumarate 320/9.6mcg).

At half of the budesonide dose, *Breztri Aerosphere* (budesonide/glycopyrronium/formoterol fumarate 160/14.4/9.6mcg) also demonstrated a statistically-significant reduction in the rate of moderate or severe exacerbations compared with *Bevespi Aerosphere* and PT009.

The dual-combination therapies used as comparators in the trial represent recommended therapeutic classes for the treatment of COPD.1

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "Exacerbations are devastating events for patients and can lead to a permanent loss of lung function. The Phase III ETHOS trial builds on the Phase III KRONOS data which together show *Breztri Aerosphere's*ability to reduce exacerbation risk in a broad range of patients with COPD, irrespective of whether they have had an exacerbation in the previous twelve months. We look forward to sharing these results with health authorities as soon as possible."

Klaus Rabe, Professor of Pulmonary Medicine at the University of Kiel, Director of the Department of Pneumology at Clinic Grosshansdorf, Germany, and Lead Investigator of the ETHOS trial, said: "The Phase III ETHOS trial results are exciting and demonstrate that *Breztri Aerosphere*significantly reduces the rate of exacerbations. This is also the first time we have seen the benefit of fixed-dose triple-combination therapy at two inhaled corticosteroid doses, which could transform treatment practice by allowing physicians to select the optimal dose for individual patients."

The safety and tolerability of *Breztri Aerosphere* were consistent with the known profiles of the dual comparators. In the trial, all combination therapies were administered in a pressurised metered-dose inhaler (pMDI) using *Aerosphere* delivery technology.

The ETHOS trial results will be presented at an upcoming medical meeting. *Breztri Aerosphere*has been approved in Japan and is under regulatory review in China, where it has been granted Priority Review by the National Medical Products Administration. It is also under regulatory review in the US and EU.

About ETHOS
ETHOS is a randomised, double-blinded, multi-centre, parallel-group, 52-week trial to assess the efficacy and safety of *Breztri Aerosphere* in symptomatic patients with moderate to very severe COPD and a history of exacerbation(s) in the previous year.2 Outcomes in the ETHOS trial included, as a primary endpoint, the rate of moderate or severe exacerbations. Full trial design details are published in *Respiratory Medicine*.3

Bevespi Aerosphere is a fixed-dose dual bronchodilator in a pMDI, combining glycopyrronium, a long-acting muscarinic antagonist (LAMA), and formoterol fumarate, a long-acting beta2-agonist (LABA). PT009 is a single inhaler, fixed-dose dual-combination therapy of budesonide, an inhaled corticosteroid (ICS), and formoterol fumarate, a LABA. It was developed as a relevant comparator in clinical trials for *Breztri Aerosphere*.4,5

ETHOS involved more than 8,500 patients who had experienced ≥1 moderate/severe exacerbation in the previous year and were receiving at least two inhaled maintenance treatments at entry into the trial.2,3

About the ATHENA clinical trial programme
ATHENA is AstraZeneca's Phase III clinical trial programme for *Breztri Aerosphere*, which includes more than 15,500 patients globally across 11 trials.2,3,4,5,6 The four key trials are ETHOS, KRONOS, TELOS and SOPHOS.2,3,4,5,6

KRONOS is a Phase III randomised, double-blinded, parallel-group, 24-week, chronic-dosing, multi-centre trial that assessed the efficacy and safety of *Breztri Aerosphere*. The trial compared *Breztri Aerosphere* with *Bevespi Aerosphere*, *Symbicort Turbuhaler* (budesonide/formoterol fumarate) and PT009. Patients were given two inhalations twice a day of *Breztri Aerosphere*, *Bevespi Aerosphere*, *Symbicort Turbuhaler* or PT009. KRONOS involved approximately 1,900 patients with moderate to very severe COPD.6

In the KRONOS trial, *Breztri Aerosphere* met six of seven primary endpoints versus dual comparators, and PT009 met two non-inferiority endpoints to support the qualification of PT009 as an active comparator. As published in *The Lancet Respiratory Medicine*, in a key secondary endpoint, *Breztri Aerosphere* showed a statistically-significant 52% reduction in the rate of moderate or severe COPD exacerbations compared with *Bevespi Aerosphere* in a patient population that was not required to have had an exacerbation in the previous 12 months.6 *Breztri Aerosphere* also demonstrated reductions in the rate of moderate or severe COPD exacerbations versus PT009 and *Symbicort Turbuhaler* (18% and 17% respectively), which were numerically but not statistically-significant improvements. The incidence of adjudicated pneumonia was low and comparable in all treatment arms.6 The primary and secondary endpoints and treatment comparisons in the KRONOS trial differed according to regional regulatory requirements.6

About *Breztri Aerosphere*
Breztri Aerosphere has been approved in Japan and is under regulatory review for approval in China, where it has been granted Priority Review by the National Medical Products Administration. It is also under review in the US and EU.

Under the terms of the agreement to acquire Pearl Therapeutics Inc., AstraZeneca anticipates making a $150m milestone payment upon US regulatory approval of *Breztri Aerosphere* for COPD. This payment would be the final development and regulatory milestone under that agreement.

About COPD
COPD is a progressive disease which can cause obstruction of airflow in the lungs resulting in debilitating bouts of breathlessness.1 It affects an estimated 384 million people worldwide and is predicted to be the third leading cause of death by 2020.1,7 Improving lung function, reducing exacerbations and managing daily symptoms such as breathlessness are important treatment goals in the management of COPD.1

About AstraZeneca in respiratory diseases
Respiratory is one of AstraZeneca's main therapy areas, and our medicines reached more than 18 million patients as maintenance therapy in 2018. AstraZeneca's aim is to transform asthma and COPD treatmentthrough inhaled combinations at the core of care, biologics for the unmet needs of specific patient populations, and scientific advancements in disease modification.

The Company is building on a 40-year heritage in respiratory disease and AstraZeneca's capability in inhalation technology spans pressurised metered-dose inhalers and dry powder inhalers, as well as the *Aerosphere* delivery technology. The company also has a growing portfolio of respiratory biologics including *Fasenra* (anti-eosinophil, anti-IL-5 receptor alpha), now approved for severe, eosinophilic asthma and in development for severe nasal polyposis and other potential indications, and tezepelumab (anti-TSLP), which has been granted Breakthrough Therapy Designation by the US Food and Drug Administration in patients with severe asthma and is in Phase III trials. AstraZeneca's research aims at addressing underlying disease drivers by focusing on the lung epithelium, lung immunity, lung regeneration and neuronal functions.

About AstraZeneca
AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, CVRM and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit astrazeneca.com and follow us on Twitter @AstraZeneca.

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