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Breztri Aerosphere (PT010) approved in Japan for patients with chronic obstructive pulmonary disease

First global approval and only triple-combination therapy in a pressurised metered-dose inhaler device in Japan

AstraZeneca today announced that *Breztri Aerosphere* (budesonide/glycopyrronium/ formoterol fumarate), formerly PT010, has been approved in Japan as a triple-combination therapy to relieve symptoms of chronic obstructive pulmonary disease (COPD).

This is the first global regulatory approval for *Breztri Aerosphere* and is the first approval by the Japanese Ministry of Health, Labour and Welfare for a triple-combination therapy in a pressurised metered-dose inhaler (pMDI), which uses the innovative *Aerosphere* delivery technology.

The approval was based on positive results from the Phase III KRONOS trial in which *Breztri Aerosphere*demonstrated a statistically-significant improvement in trough forced expiratory volume in one second (FEV1), the primary endpoint for Japan, compared with the dual comparators *Bevespi Aerosphere*(glycopyrronium/formoterol fumarate) and PT009 (budesonide/formoterol fumarate).

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "Chronic obstructive pulmonary disease affects more than five million people in Japan, and *Breztri Aerosphere* offers these patients a new, powerful triple-combination therapy in a pressurised metered-dose inhaler. This first approval of *Breztri Aerosphere* is a significant step towards providing a new treatment choice to people living with chronic obstructive pulmonary disease globally."

Klaus Rabe, Professor of Pulmonary Medicine at the University of Kiel, Director of the Department of Pneumology at Clinic Grosshansdorf, Germany, and National Co-ordinating Investigator of the KRONOS trial, said: "The KRONOS trial demonstrated that *Breztri Aerosphere* provides rapid and sustained, clinically-relevant lung function improvements in patients with moderate to very severe chronic obstructive pulmonary disease. Triple-combination therapy is an increasingly important treatment option and will play a central role in helping patients manage their disease."

Data from the Phase III KRONOS trial has previously been published in *The Lancet Respiratory Medicine*.

The Chinese National Medical Products Administration has granted a priority review to *Breztri Aerosphere*, with an expected regulatory decision in the second half of 2019. The medicine is also under regulatory review in the US and EU with anticipated regulatory decisions in 2020.

About *Breztri Aerosphere*

Breztri Aerosphere (budesonide/glycopyrronium/formoterol fumarate), formerly known as PT010, is a single-inhaler, fixed-dose triple combination of budesonide, an inhaled corticosteroid, glycopyrronium, a long-acting muscarinic agonist, and formoterol fumarate, a long-acting beta2-agonist.

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

About KRONOS and the ATHENA clinical trial programme

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* (glycopyrronium/formoterol fumarate 14.4/9.6mcg pMDI), *Symbicort Turbuhaler*(budesonide/formoterol fumarate 400/12mcg) and PT009 (budesonide/formoterol fumarate 320/9.6mcg) using *Aerosphere* delivery technology in a pMDI. 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.

In the 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 inThe 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. *Breztri Aerosphere* also demonstrated reductions in the rate of moderate or severe COPD exacerbations versus PT009 and *Symbicort* (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.[1] The primary and secondary endpoints and treatment comparisons in the KRONOS trial differed according to regional regulatory requirements.[1]

The Phase III ATHENA clinical trial programme for *Breztri Aerosphere* includes more than 15,500 patients globally across 11 trials.[1,2,3,4] The four key trials are KRONOS, TELOS, SOPHOS and ETHOS.[1,2,3,4] The Phase III ETHOS trial is the last trial in the programme and data readout is anticipated in the second half of 2019.

About COPD

COPD is a progressive disease which can cause obstruction of airflow in the lungs resulting in debilitating bouts of breathlessness.[5] It affects an estimated 384 million people worldwide and is predicted to be the third leading cause of death by 2020.[5,6] Improving lung function, reducing exacerbations and managing daily symptoms such as breathlessness are important treatment goals in the management of COPD.[5]

About AstraZeneca in respiratory disease

Respiratory is one of AstraZeneca's three 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 treatment through 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-5R 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, Cardiovascular, Renal & Metabolism 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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