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PT027, a novel fixed-dose combination of albuterol and budesonide, used as an as-needed rescue medicine, significantly reduced the risk of a severe exacerbation compared to albuterol by 27% in patients with asthma

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First time an albuterol/budesonide fixed-dose combination rescue medication has been shown to reduce severe exacerbations

MANDALA Phase III trial results published in the New England Journal of Medicine and presented at ATS 2022 International Conference

Full results from the positive MANDALA Phase III trial showed that PT027 (albuterol/budesonide) at two different strengths of budesonide, an inhaled corticosteroid (ICS), used as an as-needed rescue medicine, demonstrated a statistically significant reduction in the risk of a severe exacerbation versus albuterol rescue in patients with moderate to severe asthma.[1,2]

PT027 is a potential first-in-class inhaled, fixed-dose combination rescue medication containing albuterol, a short-acting beta2-agonist (SABA), and budesonide in the US. It is being developed by AstraZeneca and Avillion.

Globally, more than 176 million asthma attacks are experienced each year.[3]

Compared with albuterol rescue, PT027 at the 180mcg albuterol/160mcg budesonide dose reduced the risk of a severe exacerbation by 27% ($p<0.001$) in adults and adolescents.[1,2] In the trial, patients were randomised to receive PT027 or albuterol rescue, on top of their usually prescribed maintenance ICS, with or without additional controller medicines.[1,2]

In secondary endpoints, PT027 (180mcg albuterol/160mcg budesonide) demonstrated a 33% reduction in mean annualised total systemic corticosteroid exposure ($p=0.002$) and a 24% reduction in annualised severe exacerbation rate ($p=0.008$).[1,2] A numerically higher odds of patients experiencing an improvement in symptom control and quality of life was also observed after 24 weeks of treatment with PT027 compared to albuterol rescue.[1,2]

Adverse events (AEs) were similar across the treatment groups in the trial and consistent with the known safety profiles of the individual components, with the most common AEs including nasopharyngitis and headache.[1]

Bradley E. Chipps, Past President of the American College of Allergy, Asthma & Immunology and Medical Director of Capital Allergy & Respiratory Disease Center in Sacramento, US, said:

“The MANDALA Phase III trial results demonstrated that PT027, a novel fixed-dose combination of albuterol/budesonide used as-needed, provided additional anti-inflammatory treatment in response to patient symptoms, which led to a reduced risk of severe exacerbations compared with albuterol alone. These data further strengthen the growing body of evidence around the value of as-needed anti-inflammatory treatment in asthma and support PT027’s potential to transform the current rescue treatment approach.”

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: “Asthma is an inflammatory, variable disease and patients are at risk of experiencing a severe exacerbation regardless of disease severity and adherence to treatment. The results from these Phase III trials support the clinical benefit of PT027, an albuterol/budesonide rescue inhaler, which has the potential to be a first-in-class treatment approach that can prevent asthma attacks over and above their current maintenance therapies.”

In the MANDALA trial, PT027 at a lower budesonide dose (180mcg albuterol/80mcg budesonide), also demonstrated a statistically significant reduction of 17% in the risk of severe exacerbation versus albuterol rescue ($p=0.041$), when used as an as-needed rescue medicine in adults, adolescents, and children aged 4–11 years.[1,2]

The results were published in the *New England Journal of Medicine* and will be presented at the American Thoracic Society (ATS) 2022 International Conference.[1,2,4]

Also being presented at the ATS International Conference this week are the positive DENALI Phase III trial results. In this trial, PT027 demonstrated a statistically significant improvement in lung function measured by forced expiratory volume in one second (FEV1), compared to the individual components albuterol and budesonide, and compared to placebo in patients with mild to moderate asthma aged 12 years or older. Onset of action and duration of effect were similar for PT027 and albuterol. The safety and tolerability of PT027 in DENALI was consistent with the known profiles of the components.[5]

Notes

Asthma

Asthma is a chronic, inflammatory, variable respiratory disease that affects as many as 339 million adults and children worldwide,[6] including over 25 million in the US.[7]

Patients with asthma experience recurrent breathlessness and wheezing, which varies over time, and in severity and frequency.[8] These patients are at risk of severe exacerbations regardless of their disease severity, adherence to treatment or level of control.[9,10]

There are an estimated 176 million asthma exacerbations globally per year,[3] including more than 10 million in the US;[7] these are physically threatening and emotionally significant for many patients[11] and can be fatal.[6,12]

Inflammation is central to both asthma symptoms[8] and exacerbations.[13] Many patients experiencing asthma symptoms use a SABA as a rescue medicine; however, taking a SABA alone does not address inflammation, leaving patients at risk of severe exacerbations,[14] which can result in impaired quality of life,[15] hospitalisation[16] and frequent oral corticosteroid (OCS) use.[16] Treatment of exacerbations with as few as 1-2 short courses of OCS are associated with an increased risk of adverse health conditions including type 2 diabetes, depression/anxiety, renal impairment, cataracts, cardiovascular disease, pneumonia and fracture.[8,17,18] International recommendations from the Global Initiative for Asthma no longer recommend SABA alone as the preferred rescue therapy.[8]

MANDALA

MANDALA[1,19] was a Phase III, randomised, double-blind, multicentre, parallel-group, event-driven trial evaluating the efficacy and safety of PT027 compared to albuterol on the time to first severe asthma exacerbation in 3,132 adults, adolescents, and children (aged 4–11 years) with moderate to severe asthma taking ICS alone or in combination with a range of asthma maintenance therapies, including long-acting beta2-agonists (LABA), leukotriene receptor antagonists (LTRA), long-acting muscarinic antagonists (LAMA) or theophylline. The trial comprised a two-to-four-week screening period, at least a 24-week treatment period and a two-week post-treatment follow-up period.

Patients were randomly assigned to one of the following three treatment groups in a 1:1:1 ratio: PT027 180/160mcg (excluding children aged 4–11 years), PT027 180/80mcg or albuterol 180mcg, taken as an as-needed rescue medicine. PT027 and the albuterol comparator were delivered in a pressurised metered-dose inhaler (pMDI) using AstraZeneca's *Aerosphere* delivery technology. The primary efficacy endpoint was the time to first severe asthma exacerbation during the treatment period. Secondary endpoints included severe exacerbation rate (annualised), total systemic corticosteroid exposure (annualised), asthma control and health-related quality of life.

Primary and secondary endpoint results in adults and adolescents[1,2]
(pre-planned on-treatment efficacy analysis)

Treatment Group			Comparison versus albuterol 180mcg	
Time to first severe exacerbation	**n**	**Number (%) of Patients with a Severe Exacerbation [a, b]**	**Hazard Ratio (95% CI)**	**p value (2-sided)**
PT027 180/160mcg	1013	207 (20.4)	0.73 (0.61, 0.88)	<0.001
Albuterol 180mcg	1014	266 (26.2)		
Annualised total SCS dose (mg/year)	**n**	**Mean (SD) [b]**	**% reduction in mean**	
PT027 180/160mcg	1012	86.2 (262.86)	33.4%	
Albuterol 180mcg	1011	129.3 (657.19)		
Annualised severe exacerbation rate (rate ratio)	**n**	**Number of Severe Exacerbations [a, b]**	**Annualised rate (95% CI)**	**Rate Ratio (95% CI)**
PT027 180/160mcg	1013	334	0.45 (0.34, 0.60)	0.76 (0.62, 0.93)
Albuterol 180mcg	1014	413	0.59 (0.44, 0.78)	

[a]Deterioration of asthma requiring use of SCS for ≥3 days, or inpatient hospitalisation, or emergency room visit, that required SCS. [b]Before discontinuation of randomised treatment or change in maintenance therapy.

CI, confidence interval; SCS, systemic corticosteroid; SD, standard deviation

Primary endpoint results in adults, adolescents, and children[1,2]

(pre-planned on-treatment efficacy analysis)

Treatment Group			Comparison versus albuterol 180mcg	
Time to first severe exacerbation	**n**	**Number (%) of Patients with a Severe Exacerbation [a, b]**	**Hazard Ratio (95% CI)**	**p value (2-sided)**
PT027 180/80mcg	1054	241 (22.9)	0.83 (0.70, 0.99)	0.041
Albuterol 180mcg	1056	276 (26.1)		

[a]Deterioration of asthma requiring use of SCS for ≥3 days, or inpatient hospitalisation, or emergency room visit, that required SCS. [b]Before discontinuation of randomised treatment or change in maintenance therapy.

CI, confidence interval

DENALI

DENALI[4,20,21] was a Phase III, randomised, double-blind, placebo-controlled, multicentre, parallel-group trial evaluating the efficacy and safety of PT027 compared to its components albuterol and budesonide on improvement in lung function in 1,001 adults, adolescents, and children aged 4–11 years with mild to moderate asthma previously treated either with SABA as-needed alone or in addition to regular low-dose ICS maintenance therapy. The trial comprised a two-to-four-week screening period, a 12-week treatment period and a two-week post-treatment follow-up period.

Patients were randomly assigned to one of the following five treatment groups in a 1:1:1:1:1 ratio: PT027 180/160mcg four times daily (excluding children aged 4–11 years), PT027 180/80mcg four times daily, albuterol 180mcg four times daily, budesonide 160mcg four times daily (excluding children aged 4–11 years) and placebo four times daily. PT027, the albuterol and budesonide comparators and placebo were delivered in a pMDI using AstraZeneca's *Aerosphere* delivery technology.

The dual primary efficacy endpoints were change from baseline in FEV1 area under the curve 0-6 hours over 12 weeks of PT027 compared to budesonide to assess the effect of albuterol and change from baseline in trough FEV1 at Week 12 of PT027 compared to albuterol to assess the effect of budesonide. Secondary endpoints included the time to onset and duration of response on day one, number of patients who achieved a clinically meaningful improvement in asthma control from baseline at Week 12 and trough FEV1 at Week 1.

PT027

PT027 is a potential first-in-class SABA/ICS rescue treatment for asthma in the US, to be taken as needed. It is an inhaled, fixed-dose combination rescue medication containing albuterol (also known as salbutamol), a SABA, and budesonide, a corticosteroid, and is being developed in a pMDI using AstraZeneca's *Aerosphere* delivery technology.

AstraZeneca and Avillion collaboration

In March 2018, AstraZeneca and Avillion signed an agreement to advance PT027 through a global clinical development programme for the treatment of asthma. Under the terms of the agreement, Avillion became the trial sponsor responsible for executing and funding the multicentre, global clinical trial programme for PT027 through NDA filing to a regulatory decision in the US. Following the successful approval of PT027, AstraZeneca has the option, upon certain financial payments, to commercialise the medicine in the US.

AstraZeneca in Respiratory & Immunology

Respiratory & Immunology, part of BioPharmaceuticals, is one of AstraZeneca's main disease areas and is a key growth driver for the Company.

AstraZeneca is an established leader in respiratory care with a 50-year heritage. The Company aims to transform the treatment of asthma and COPD by focusing on earlier biology-led treatment, eliminating preventable asthma attacks, and removing COPD as a top-three leading cause of death. The Company's early respiratory research is focused on emerging science involving immune mechanisms, lung damage and abnormal cell-repair processes in disease and neuronal dysfunction.

With common pathways and underlying disease drivers across respiratory and immunology, AstraZeneca is following the science from chronic lung diseases to immunology-driven disease areas. The Company's growing presence in immunology is focused on five mid- to late-stage franchises with multi-disease potential, in areas including rheumatology (including systemic lupus erythematosus), dermatology, gastroenterology, and systemic eosinophilic-driven diseases. AstraZeneca's ambition in Respiratory & Immunology is to achieve disease modification and durable remission for millions of patients worldwide.

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AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

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