AstraZeneca

Airsupra (PT027) approved in US for asthma

11 January 2023 13:00 GMT

Airsupra (PT027) approved in the US for asthma

First and only rescue medication approved in the US for as-needed use to reduce risk of asthma exacerbations

Airsupra (albuterol/budesonide), formerly known as PT027, has been approved in the US for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in people with asthma aged 18 years and older.

The approval by the Food and Drug Administration (FDA) was based on results from the MANDALA and DENALI Phase III trials.[1,2] In MANDALA, *Airsupra* significantly reduced the risk of severe exacerbations compared to albuterol in patients with moderate to severe asthma when used as an as-needed rescue medication in response to symptoms.[1] Importantly, in the secondary endpoint of mean annualised total systemic corticosteroid exposure, *Airsupra* demonstrated a significant reduction compared to albuterol at the approved dose of 180mcg albuterol/160mcg budesonide.[1] In DENALI, *Airsupra* significantly improved lung function compared to the individual components albuterol and budesonide in patients with mild to moderate asthma.[2]

Airsupra is a first-in-class, pressurised metered-dose inhaler (pMDI), fixed-dose combination rescue medication containing albuterol, a short-acting beta2-agonist (SABA), and budesonide, an anti-inflammatory inhaled corticosteroid (ICS) in the US. It is being developed by AstraZeneca and Avillion.

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: "People with asthma are at risk of severe exacerbations regardless of their disease severity or level of control. Current albuterol rescue inhalers alleviate acute symptoms, but do not treat the underlying inflammation in asthma. The approval of *Airsupra* means that for the first time, adults with asthma in the US have a rescue treatment to manage both their symptoms and the inflammatory nature of their disease."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: "With patients experiencing more than 10 million asthma exacerbations each year in the US and uncontrolled asthma expected to cost the US economy billions of dollars in direct medical costs alone over the next 20 years, today's positive decision is good news for those adults with asthma who make up more than 80% of asthma patients in the US. Physicians will be able to offer their patients *Airsupra*, an important new rescue treatment that reduces the risk of asthma exacerbations."

Asthma is a chronic, inflammatory respiratory disease with variable symptoms that affects as many as 262 million people worldwide.[3] In the US over 21 million adults have asthma, representing more than 80% of the total number of people with asthma.[4] Adults have 8.5 million exacerbations each year in the US.[4] Uncontrolled asthma will cost the US economy an estimated $300 billion (in 2018 dollar values) in the next 20 years in direct medical costs alone.[5]

The safety and tolerability of *Airsupra* in both trials were consistent with the known profiles of the components,[1,2] with the most common adverse events including headache, oral candidiasis, cough and dysphonia.[6]

Results from the MANDALA trial were published in the *New England Journal of Medicine* in May 2022.[1]

Notes

Asthma

Asthma is a chronic, inflammatory respiratory disease with variable symptoms that affects as many as 262 million people worldwide,[3] including over 25 million in the US.[4]

Patients with asthma experience recurrent breathlessness and wheezing, which varies over time, and in severity and frequency.[7] These patients are at risk of severe exacerbations regardless of their disease severity, adherence to treatment or level of control.[8,9]

There are an estimated 136 million asthma exacerbations globally per year,[10] including more than 10 million in the US;[4] these are physically threatening and emotionally significant for many patients[11] and can be fatal.[3,12]

Inflammation is central to both asthma symptoms[8] and exacerbations.[13] Many patients experiencing asthma symptoms use a SABA (e.g. albuterol) as a rescue medicine;[14-16] however, taking a SABA alone does not address inflammation, leaving patients at risk of severe exacerbations,[17] which can result in impaired quality of life,[18] hospitalisation[19] and frequent oral corticosteroid (OCS) use.[19] Treatment of exacerbations with as few as 1-3 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.[20] International recommendations from the Global Initiative for Asthma no longer recommend SABA alone as the preferred rescue therapy.[7]

MANDALA, DENALI and the CREST (Combination REliever STudies) programme

The CREST clinical trial programme studied the efficacy and safety of PT027 and included the MANDALA,[1,21,22] DENALI[2,23,24] and TYREE[25] Phase III trials.

MANDALA[1,21,22] was a Phase III, randomised, double-blind, multicentre, parallel-group, event-driven trial evaluating the efficacy and safety of *Airsupra* 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: *Airsupra* 180/160mcg (excluding children aged 4-11 years), albuterol/budesonide 180/80mcg or albuterol 180mcg, taken as an as-needed rescue medicine. *Airsupra* and the albuterol comparator were delivered in a 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.

Results from the positive MANDALA Phase III trial showed that *Airsupra* demonstrated a statistically significant reduction in the risk of a severe exacerbation versus albuterol rescue in patients with moderate to severe asthma.[1,22] Compared with albuterol rescue, *Airsupra* at the 180mcg albuterol/160mcg budesonide dose reduced the risk of a severe exacerbation by 27% (p<0.001) in adults and adolescents.[1,22]

Primary and secondary endpoint results in adults and adolescents[1,22]
(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)**
Airsupra 180/160mcg	1013	207 (20.4)	0.73 (0.61, 0.88)	<0.001
Albuterol 180mcg	1014	266 (26.2)		
Annualised severe exacerbation rate (rate ratio)	**n**	**Number of Severe Exacerbations [a, b]**	**Annualised rate (95%CI)**	**Rate Ratio (95%CI)**
Airsupra 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)	
Annualised total SCS dose (mg/year)	**n**	**Mean (SD) [b]**	**%reduction in mean**	
Airsupra 180/160mcg	1012	86.2 (262.86)	33.4%	
Albuterol 180mcg	1011	129.3 (657.19)		

[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[1,22]
(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)**
Albuterol/budesonide 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

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.[1,22]

DENALI[2,23,24] was a Phase III, randomised, double-blind, placebo-controlled, multicentre, parallel-group trial evaluating the efficacy and safety of *Airsupra* 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: *Airsupra* 180/160mcg four times daily (excluding children aged 4-11 years), albuterol/budesonide 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. *Airsupra*, 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 *Airsupra* compared to budesonide to assess the effect of albuterol and change from baseline in trough FEV1 at Week 12 of *Airsupra* 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.

In the trial, *Airsupra* 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 *Airsupra* and albuterol. The safety and tolerability of *Airsupra* in DENALI was consistent with the known profiles of the components.

Airsupra

Airsupra (albuterol/budesonide), formerly known as PT027, is a 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 has been 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 *Airsupra* 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 *Airsupra* through NDA filing to a regulatory decision in the US. Following the successful approval of *Airsupra*, AstraZeneca has the option, upon certain financial payments, to commercialise the medicine in the US.

AstraZeneca in Respiratory and 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.

AstraZeneca

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.

References

1. Papi A, *et al*. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. *N Engl J Med* 2022; 386 (22): 2071-2083.
2. Chipps BE, *et al*. Efficacy and safety of albuterol/budesonide (PT027) in mild-to-moderate asthma: Results of the DENALI study. *Am J Respir Crit Care Med* 2022; 205: A3414. Abstract. Available at: http://doi.org/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A3414 [Last accessed: November 2022].
3. The Global Asthma Network. The Global Asthma Report 2022. [Online]. Available at: http://globalasthmareport.org/index.html [Last accessed: November 2022].
4. CDC. Most Recent National Asthma Data. [Online]/ Available at: http://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. [Last accessed: November 2022].
5. Yaghoubi M, *et al*. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *Am J Respir Crit Care Med*. 2019; 200 (9): 1102-1112.
6. *Airsupra* (albuterol/budesonide) US prescribing information; 2023.
7. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2022. Available at: http://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. [Last accessed: November 2022].
8. Price D, *et al*. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med*. 2014; 24: 14009.
9. Papi A, *et al*. Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate-to-severe asthma. *J Allergy Clin Immunol Pract*. 2018; 6 (6): 1989-98.e3.
10. AstraZeneca Pharmaceuticals. Data on File. Budesonide/formoterol Data on File: Annual Rate of Asthma Exacerbations Globally. (REF-173201)
11. Sastre J, *et al*. Insights, attitudes, and perceptions about asthma and its treatment: a multinational survey of patients from Europe and Canada. *World Allergy Organ J*. 2016; 9: 13.
12. Fernandes AG, *et al*. Risk factors for death in patients with severe asthma. *J Bras Pneumol*. 2014; 40 (4): 364-372.
13. Wark PA, *et al*. Asthma exacerbations· 3: pathogenesis. *Thorax*. 2006; 61 (10): 909-15.
14. Johnson DB, *et al*. Albuterol. 2022 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. PMID: 29489143.
15. Montemayor T, *et al*. Albuterol: Often Used and Heavily Abused. *Respiratory Care* November 2021, 66 (Suppl 10) 3603775.
16. ClinCalc.com. Albuterol: Drug Usage Statistics, US 2013 - 2020. Available at: http://clincalc.com/DrugStats/Drugs/Albuterol. [Last accessed:

November 2022].

17. Nwaru BI, *et al*. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020; 55 (4): 1901872.

18. Lloyd A, *et al*. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Prim Care Respir J*. 2007; 16 (1): 22-7.

19. Bourdin A, *et al*. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *Eur Respir J*. 2019; 54 (3): 1900900.

20. Price DB, *et al*. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018; 11: 193-204.

21. Chipps BE, *et al*. Evaluation of the Efficacy and Safety of As-Needed PT027 Budesonide/Albuterol MDI) Compared to As-Needed Albuterol MDI in Adults and Children 4 Years of Age or Older with Uncontrolled Moderate to Severe Asthma: Design of the MANDALA Study. *Am J Respir Crit Care Med*. 2020; 201: A3015.

22. Papi A, *et al*. Efficacy and safety of as-needed albuterol/budesonide versus as-needed albuterol in adults, adolescents and children aged ≥4 years with moderate-to-severe asthma: Results of the MANDALA study. American Thoracic Society International Conference 2022. Oral Presentation. Abstract A3413 during B93. BREAKTHROUGHS IN PEDIATRIC AND ADULT ASTHMA CLINICAL TRIALS .

23. Clinicaltrials.gov. A Study to Assess the Efficacy and Safety of Budesonide/Albuterol Metered-dose Inhaler (BDA MDI/PT027) Used 4 Times Daily in Adults and Children 4 Years of Age or Older With Asthma (DENALI). Available at http://clinicaltrials.gov/ct2/show/NCT03847896. [Last accessed: November 2022].

24. AstraZeneca Pharmaceuticals. Data on File. DENALI clinical trial protocol Data on File (ID: 121792).

25. LaForce C, *et al*. Albuterol/budesonide for the treatment of exercise-induced bronchoconstriction in patients with asthma: The TYREE study. *Ann Allergy Asthma Immunol.* 2022; 128: 169-177.

Adrian Kemp
Company Secretary
AstraZeneca PLC

This information is provided by RNS, the news service of the London Stock Exchange. RNS is approved by the Financial Conduct Authority to act as a Primary Information Provider in the United Kingdom. Terms and conditions relating to the use and distribution of this information may apply. For further information, please contact rns@lseg.com or visit www.rns.com.