

# Albuterol–budesonide fixed-dose combination rescue inhaler for asthma: a plain language summary of the MANDALA study

*Ther Adv Respir Dis*

2024, Vol. 18: 1–14

DOI: 10.1177/  
17534666241232264

© The Author(s), 2024.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

Alberto Papi<sup>1</sup> , Bradley E. Chipps<sup>2</sup>, Richard Beasley<sup>3</sup>, Reynold A. Panettieri Jr<sup>4</sup>, Elliot Israel<sup>5</sup>, Mark Cooper<sup>6</sup>, Lynn Dunsire<sup>6</sup>, Allison Jaynes-Ellis<sup>7</sup>, Robert Rees<sup>7</sup>, Frank C. Albers<sup>8</sup> and Christy Cappelletti<sup>9</sup> 

## Summary

### What is this summary about?

This summary describes the results of a clinical study called MANDALA that was published in the *New England Journal of Medicine* in 2022. In the MANDALA study, researchers looked at a new asthma rescue inhaler that contains both **albuterol** and **budesonide** in a single inhaler (known as **albuterol–budesonide**, AIRSUPRA™). This summary describes the results for people aged 18 years and older who took part in the study.

### Why was the MANDALA study done?

In people with asthma, **albuterol** works by quickly relaxing and opening the constricted airways to make breathing easier. **Budesonide** decreases inflammation (swelling) in the lungs. Inflammation in

### How to say...

- **Albuterol:** Al-byoo-tuh-rol
- **Budesonide:** Byoo-deh-suh-nide
- **Exacerbation:** Ig-za-ser-BAY-shun
- **Corticosteroid:** KAW-ti-koh-STEER-oyd

<sup>1</sup>Department of Respiratory Medicine, University of Ferrara Medical School, Ferrara, Italy

<sup>2</sup>The Capital Allergy and Respiratory Disease Center, Sacramento, CA, USA

<sup>3</sup>The Medical Research Institute of New Zealand; Capital and Coast District Health Board, and Victoria University of Wellington, Wellington, New Zealand

<sup>4</sup>Rutgers Institute for Translational Medicine and Science; Child Health Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, NJ, USA

<sup>5</sup>Brigham and Women's Hospital, Harvard Medical School, Boston, USA

<sup>6</sup>BioPharmaceuticals Research and Development, AstraZeneca, Cambridge, UK

<sup>7</sup>Avillion, London, UK

<sup>8</sup>Avillion, Northbrook, IL, USA

<sup>9</sup>BioPharmaceuticals Research and Development, AstraZeneca, Durham, NC, USA

Received: 2 November 2023; revised manuscript accepted: 25 January 2024.

### Corresponding author:

Christy Cappelletti, BioPharmaceuticals Research and Development, AstraZeneca, Durham, NC, USA.

Email: christy.cappelletti1@astrazeneca.com



the lungs can lead to bronchoconstriction (narrowing of the airways) causing breathing difficulties and asthma attacks (**exacerbations**). In the MANDALA study, researchers wanted to learn whether the **albuterol–budesonide** inhaler used ‘as needed’ was more effective than an **albuterol** inhaler also used ‘as needed’ in preventing asthma attacks in people with moderate-to-severe asthma who were also using daily inhaled medication for their asthma. ‘As-needed’ refers to when a person uses their inhaler when they experience asthma symptoms, or before exposure to an asthma trigger.

Asthma medications that are used as needed are often called rescue therapies, and asthma medications that are used daily are often called maintenance or controller therapies. The people included in the MANDALA study were already using regular maintenance therapy and continued to use this during the study. The MANDALA study also looked at the safety of **albuterol–budesonide** compared with **albuterol**.

### What were the main results in adults and what do they mean?

People with asthma who used the **albuterol–budesonide** inhaler as needed had a 28% lower risk of having a severe asthma attack (i.e. an asthma attack requiring oral or injected steroids or a visit to hospital) than those using the **albuterol** inhaler. The amount of steroids they were given as pills or injections to treat severe asthma attacks was 32% lower on average. **Albuterol–budesonide** was well tolerated. The percentage of people who had a side effect with the **albuterol–budesonide** inhaler was similar to the percentage of people using the **albuterol** inhaler. Side effects may or may not be due to the medicine being studied. The most common side effects reported in both groups were common cold (also known as nasopharyngitis), headache, and infections of the upper airways.

These results led to the approval in the USA of the **albuterol–budesonide** rescue inhaler for the as-needed treatment or prevention of bronchoconstriction (airway tightening) and to help prevent **exacerbations** (severe asthma attacks requiring oral or injected steroids) in people with asthma aged 18 years and above.

### Who should read this summary?

This summary is intended for people with asthma, their family members and carers, patient advocates, and healthcare professionals who do not specialize in asthma but who treat people with asthma in their medical practice.

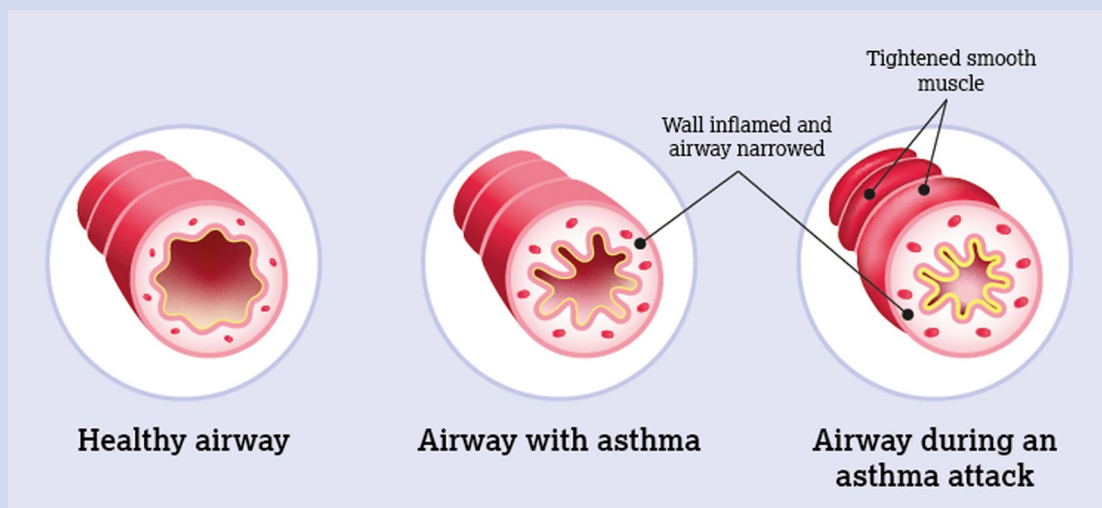
### Who sponsored these studies?

The MANDALA study was sponsored by Bond Avillion 2 Development LP. This summary of the study results was sponsored by AstraZeneca.

## What is asthma?

Asthma is a long-term condition that affects the airways (the tubes carrying air in and out of the lungs). When a person is suffering from asthma, the lining of the airways become inflamed (swollen) and narrowed at times. This makes breathing difficult and can cause symptoms of wheezing (a whistle-like sound when breathing out), shortness of breath, a tight chest, and coughing. Importantly, airway inflammation varies over time and in intensity in people with asthma, resulting in variability and unpredictable worsening of symptoms.

When asthma symptoms get considerably worse, it is known as an asthma attack (or **exacerbation**). Asthma attacks range in severity. Severe asthma attacks can be life-threatening. They may require immediate treatment with steroid pills (or injections), a visit to the emergency department, and/or admission to hospital.



Although asthma cannot be cured, treatments are available to control it. The main goals of treatment are to:

- Control symptoms and underlying inflammation.
- Relieve symptoms when they occur.
- Prevent future symptoms and asthma attacks.

Two main types of inhaler are used to treat asthma:

- **Maintenance inhalers** are also known as controller inhalers. They are used every day to keep airways open and decrease underlying inflammation that can result in symptoms and asthma attacks. The most common include a type of anti-inflammatory medication called an inhaled **corticosteroid**.
- **Rescue inhalers** are used to rapidly treat the symptoms as they occur. They traditionally only contain a fast-acting medication that relaxes the muscles in the airway (also called a bronchodilator).

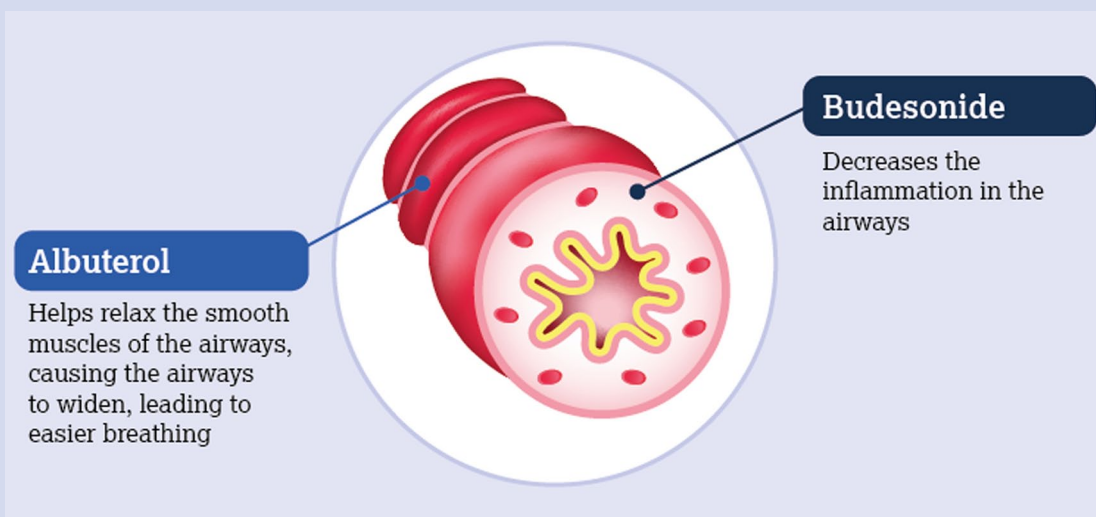
Many people with asthma who use a rescue inhaler will also require a daily maintenance inhaler. Some may need to use a daily maintenance inhaler that includes both an anti-inflammatory medicine and a bronchodilator in the same inhaler.

### What is albuterol–budesonide?

The **albuterol–budesonide** inhaler is a new type of asthma rescue inhaler. It can be prescribed in the United States of America (USA) under the brand name **AIRSUPRA™** for people with asthma who are 18 years of age and older to use as needed to treat or prevent bronchoconstriction (airway tightening) and to help prevent **exacerbations** (asthma attacks requiring oral or injected steroids).

The **albuterol–budesonide** rescue inhaler combines two medicines in one inhaler: **albuterol** and **budesonide**.

- **Albuterol** helps to relax the smooth muscles of the airways, causing the airways to widen, leading to easier breathing.
- **Budesonide** decreases airway inflammation. Inflammation in the airways can lead to breathing difficulties by narrowing the airways (also called bronchoconstriction) and can increase the risk of asthma attacks.



**Albuterol–budesonide** is delivered from the inhaler in a propelled spray. Two puffs (inhalations) should be used as needed. No more than 12 puffs should be used in a 24h period. **Albuterol–budesonide** should be used like traditional rescue medications, as needed in response to symptoms and prior to triggers. This way, the **budesonide** can decrease the rising inflammation that leads to increased symptoms.

### Why was the MANDALA study needed?

In people with asthma, airway inflammation varies over time. Maintenance inhalers reduce airway inflammation. However, sometimes inflammation continues to rise, leading to worsening of symptoms and asthma attacks.

A rescue inhaler containing only **albuterol** can quickly relieve the symptoms of asthma as they occur. It does not treat the rising inflammation that leads to symptoms or prevent an asthma attack from occurring. By combining **albuterol** with an inhaled **corticosteroid** in a rescue inhaler, both symptoms and rising inflammation can be addressed at the same time.

Researchers wanted to look at whether an **albuterol–budesonide** inhaler used as needed could reduce the risk of people with moderate-to-severe asthma having a severe asthma attack compared with using an **albuterol** only inhaler as needed.

### Who took part in the study?

The MANDALA study included 3132 people with asthma from North America, South America, Europe, and South Africa.

People who took part in the study:

- Had a diagnosis of asthma and were experiencing asthma symptoms.
- Had been using maintenance inhalers containing inhaled steroids to treat their asthma for at least 3 months before the start of the study.
- Had one or more severe asthma attacks in the 12 months before the study started.

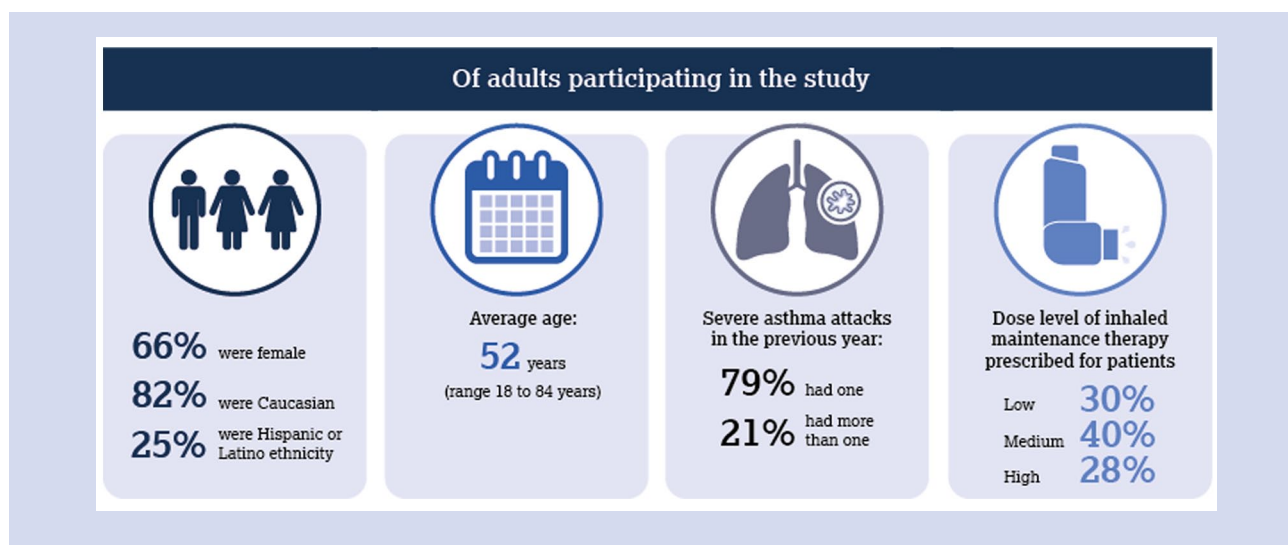
People in MANDALA had moderate-to-severe asthma, that is asthma that requires daily treatment with an inhaler containing a medium-to-high dose of an inhaled steroid or one that contained a low- to high-dose of an inhaled steroid and a bronchodilator in the same inhaler.

#### What was considered a severe asthma attack in the MANDALA study?

In the MANDALA study, a severe asthma attack was considered to have occurred if a person's asthma symptoms worsened or new symptoms of asthma developed leading to one or more of the following:

1. Three or more consecutive days of treatment with steroid pills (or a steroid injection).
2. A visit to an emergency room or urgent care center that resulted in treatment with steroid pills (or a steroid injection).
3. A stay in hospital of 24 h or more.

Adults, adolescents, and children (over 4 years) could participate in the study. However, as the **albuterol–budesonide** inhaler is approved in the USA for people aged 18 years old and above, this summary only describes results for the approved adult population.



### What happened in the study?

MANDALA was a large clinical study that compared two separate dose combinations of **albuterol–budesonide** with **albuterol**. This allowed researchers to find out if one or both doses of **albuterol–budesonide** was better than **albuterol** in preventing severe asthma attacks, and if one of the doses was better than the other.

#### MANDALA was a double-anonymized study

- This means the healthcare providers and the people participating in the study did not know who was receiving which of the study inhalers. The inhalers looked identical.
- Some studies are done this way because knowing what treatment the participants are given can affect the results of the study.

People participating in the study (participants) were assigned at random to one of three groups:

- One group received a higher dose combination of the **albuterol–budesonide** inhaler that delivered 180 micrograms (mcg) of **albuterol** and 160 mcg of **budesonide** in two puffs.
- One group received a lower dose combination of the **albuterol–budesonide** inhaler that delivered 180 mcg of **albuterol** and 80 mcg of **budesonide** in two puffs.
- One group received an **albuterol** inhaler that delivered 180 mcg of **albuterol** in two puffs.

**This summary only shows the results of the dose of **albuterol–budesonide** with 180 mcg of **albuterol** and 160 mcg of **budesonide**. This is the dose that is approved for use in the USA as this dose consistently showed better results than the lower dose and with the same safety profile as the lower dose.**

Participants continued to use their usual daily asthma maintenance inhaler during the study.

Participants were told to use two puffs (one dose) of their study inhaler as needed in response to symptoms. It could also be used before exercise. No more than 12 puffs (6 doses) were to be used per day.

The main questions that the researchers wanted to answer in the study were:



Did using the **albuterol–budesonide** inhaler as needed reduce the risk of people with asthma having a severe asthma attack compared with using the **albuterol** inhaler as needed?



Did using the **albuterol–budesonide** inhaler as needed reduce the amount of steroids that were given as pills or injections to treat severe asthma attacks compared with using the **albuterol** inhaler as needed?

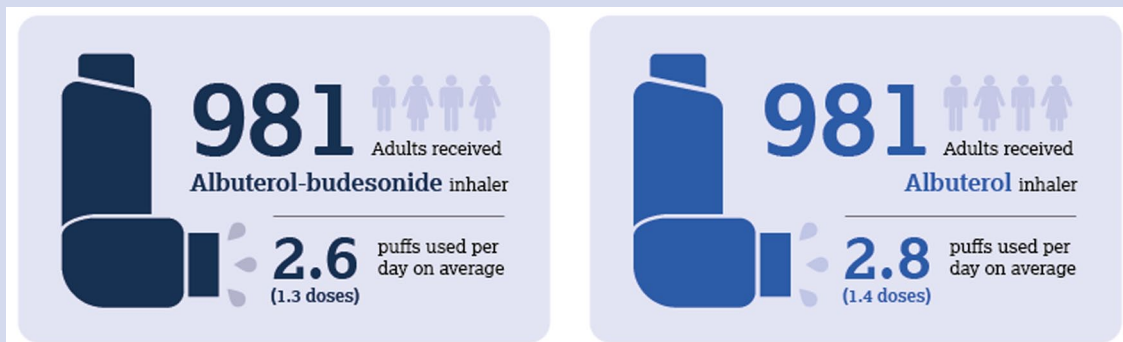


Did people with asthma report an improvement in how well their asthma was controlled or in their quality of life from using the **albuterol–budesonide** inhaler as needed compared with using the **albuterol** inhaler as needed?



How did the side effects that people had using the **albuterol–budesonide** inhaler compare with those in people using the **albuterol** inhaler during the study?

### What were the results?



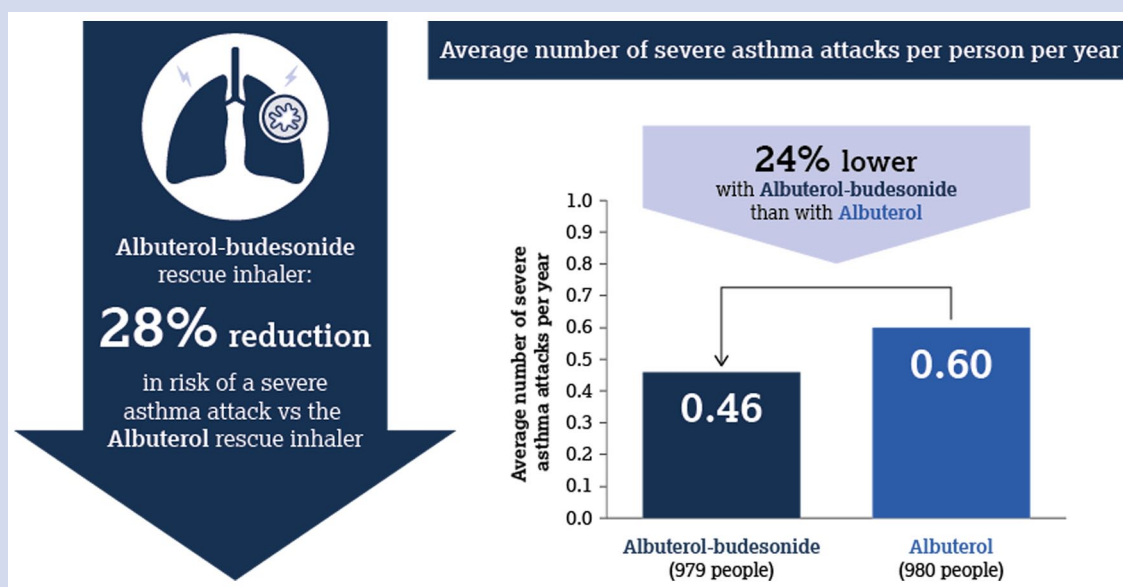
Did using the **albuterol–budesonide** inhaler as needed reduce the risk of people with asthma having a severe asthma attack compared with using the **albuterol** inhaler as needed?

Yes. Using the **albuterol–budesonide** inhaler as needed reduced the risk of people with asthma having a severe asthma attack by 28% compared with using the **albuterol** inhaler as needed.

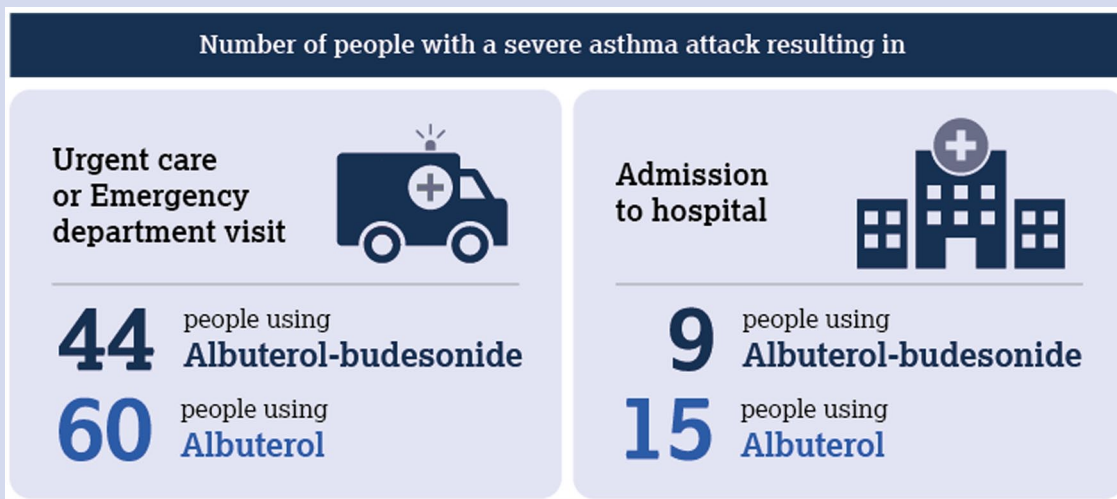
To answer this question, the researchers recorded the time from when each person started study treatment (**albuterol–budesonide** inhaler or **albuterol** inhaler) to when they had their first severe asthma attack. From this, they calculated the risk of a person having a severe asthma attack if they were using the **albuterol–budesonide** inhaler, or if they were using the **albuterol** inhaler, and compared the risks for the two groups.

They also recorded the total number of severe asthma attacks that each person had during the study and calculated the average number of severe asthma attacks per person per year.

These results are shown in the figures below.



Researchers also recorded the number of people in the study who had an asthma attack so severe that they needed to visit an urgent care or emergency department or were admitted to hospital. The results are in the panel below.





**Did using the **albuterol–budesonide** inhaler as needed reduce the amount of steroids that were given as pills or injections to treat severe asthma attacks compared with using the **albuterol** inhaler as needed?**

Yes. The average amount of steroids that were needed to be given as pills or injections to treat severe asthma attacks was 32% lower for people using the **albuterol–budesonide** inhaler compared with those using the **albuterol** inhaler.

Minimizing the amount of systemic steroids that a person receives is important, since these medications have a cumulative effect on a person over their lifetime and can cause significant side effects and risks.

**What is the difference between systemic steroids and inhaled steroids?**

Systemic steroids are swallowed or injected into the body. The medicine goes throughout the body.

Inhaled steroids are inhaled into the lungs. For people with asthma, this is where the steroid is needed. Only a portion of that then goes into the body from the lungs.

The doses of systemic steroids are in milligrams (mg). The doses of inhaled steroids are in micrograms (mcg; which is 1/1000th of a mg).

- Each dose of the **albuterol–budesonide** inhaler provides 160mcg of inhaled steroids into your airways.
- A typical 5-day course of steroid pills to treat a severe asthma attack provides about 200 mg of steroids to your body. 200 mg is the same as 200,000 mcg.



**Did people with asthma report an improvement in how well their asthma was controlled or in their quality of life from using the **albuterol–budesonide** inhaler as needed compared with using the **albuterol** inhaler as needed?**

Yes. After 24 weeks in the study, the proportion of people who reported a meaningful improvement in their asthma control and in their quality of life was greater among the group using the **albuterol–budesonide** inhaler as needed than the group using the **albuterol** inhaler as needed.

To answer this question, the researchers asked people in the study to complete two different questionnaires: the Asthma Control Questionnaire (ACQ-5) and the Asthma Quality of Life Questionnaire (AQLQ+12) (see **box**). They were asked to complete the questionnaires at the start of the study and again after being in the study for 24 weeks.

Researchers then calculated the scores from the questionnaires. For each person they compared the score at the start of the study with the score after being in the study for 24 weeks.

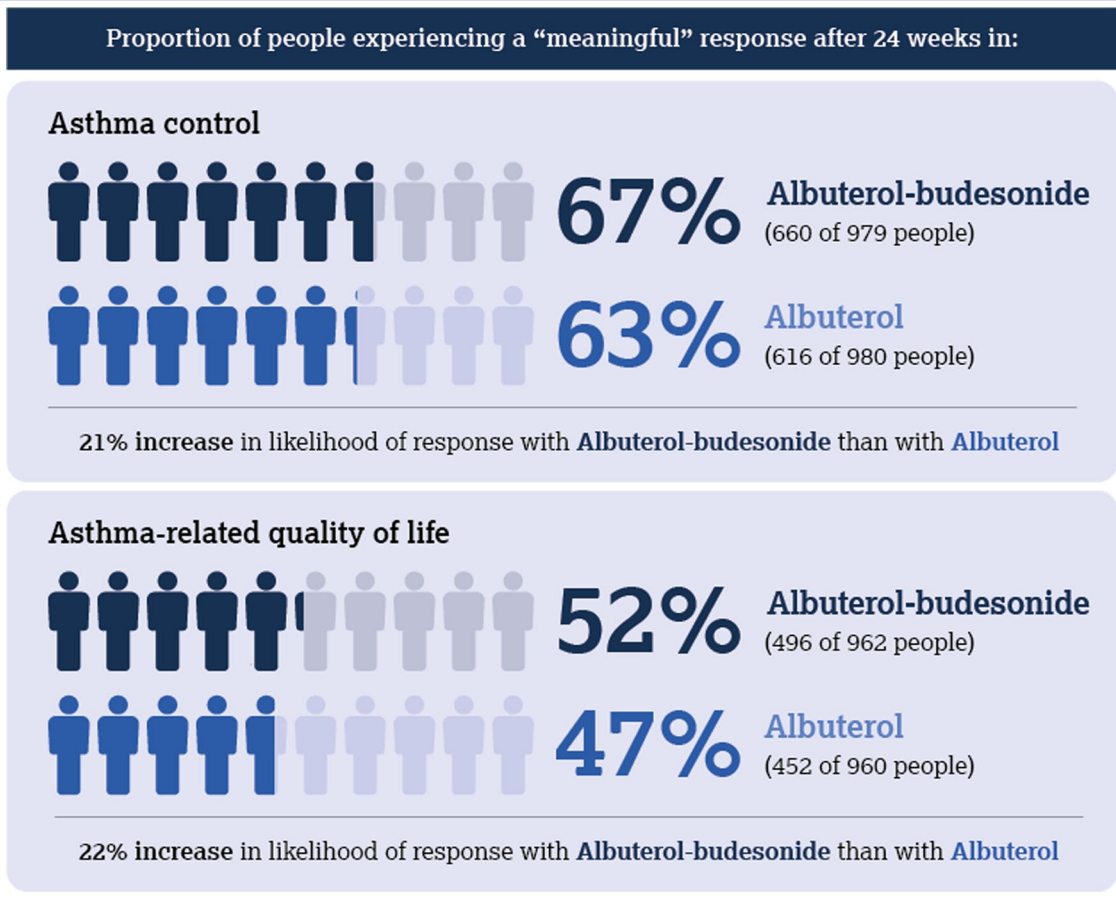
**Asthma Control Questionnaire (ACQ-5):**

- A questionnaire completed by the person with asthma to indicate how well their asthma is controlled.
- It includes questions about waking in the night from asthma, morning symptoms, wheezing, shortness of breath, and to what extent asthma affected their daily activities.

**Asthma Quality of Life Questionnaire (AQLQ + 12)**

- A questionnaire completed by the person with asthma to measure both the physical and the emotional impacts of asthma on their life.
- This questionnaire assesses symptoms, impact on daily activities, emotional well-being, and triggers from the environment that affect the person’s asthma.

The proportion of people who met the criteria for a meaningful improvement (the difference a person with asthma would think was an improvement) in asthma control and in asthma-related quality of life after 24 weeks are shown in the figures below.



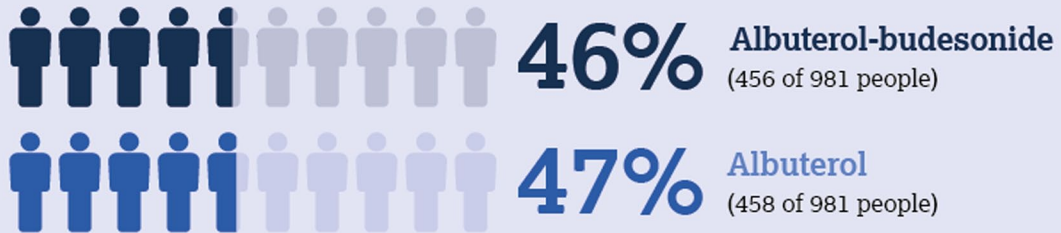


### How did the side effects that people had using the **albuterol–budesonide** inhaler compare with those in people using the **albuterol** inhaler during the study?

The researchers recorded all the side effects that the participants had during the study. Anything that happens during a study (e.g. catching a cold, having a sore throat) is recorded as a side effect. Side effects may or may not be caused by the medicines being studied. Therefore, the researchers were also asked to indicate how many of these side effects were in their opinion related to the study medicine.

The proportion of people in the study who reported side effects was similar between the group of people using the **albuterol–budesonide** inhaler and the group using the **albuterol** inhaler. The results are shown in the figures below.

#### How many people had side effects in the study?



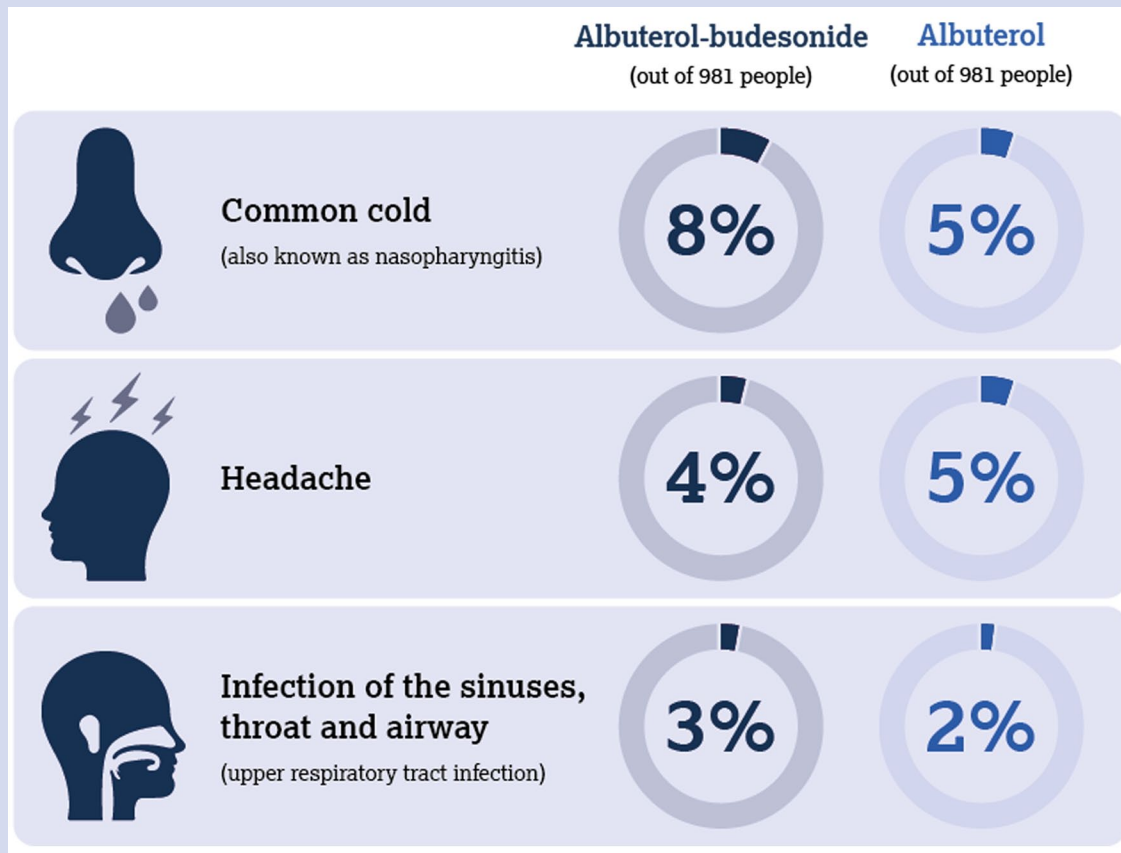
#### How many people had side effects considered related to the study medicine?



A side effect is considered serious when it is life threatening, causes lasting problems, or requires hospital care. In the study, 5% of people using the **albuterol–budesonide** inhaler and 5% of those using the **albuterol** inhaler had a serious side effect (which may or may not be related to the study medicine).

### What were the most common side effects?

The figure below shows the most common side effects during the study (which may or may not be related to the study medication) and the proportion of people who experienced them. There were other side effects in the study, but they happened in fewer people.



### What do the results of the study mean?

The results of the MANDALA study showed that in adults with moderate-to-severe asthma, those using an **albuterol–budesonide** inhaler as a rescue therapy had a lower risk of having a severe asthma attack and needed less steroid pills or injections than those who used an **albuterol** inhaler as a rescue therapy. Results are from people using regular inhaled **corticosteroid**-containing maintenance therapy and the benefits are in addition to what is provided from use of the maintenance inhaler. The proportion of people who met the criteria for a meaningful improvement in asthma control and in asthma-related quality of life was greater among the group using the **albuterol–budesonide** inhaler than the group using the **albuterol** inhaler.

The **albuterol–budesonide** rescue inhaler was well tolerated. The side effects that people had using the **albuterol–budesonide** inhaler were similar to those in people using the **albuterol** inhaler.

These results led to the approval in the USA of the **albuterol–budesonide** inhaler as a rescue therapy for people with asthma aged 18 years or older to treat bronchoconstriction (airway tightening) and to help prevent **exacerbations** (asthma attacks).

This should allow people with asthma in the USA to use a rescue inhaler that combines a bronchodilator with an anti-inflammatory medicine, which is recommended by asthma treatment guidelines and experts world-wide.

### Where can you find the original article on which this summary is based?

The original article is entitled **Albuterol–Budesonide** Fixed-Dose Combination Rescue Inhaler for Asthma and is available free of charge at <https://www.nejm.org/doi/full/10.1056/NEJMoa2203163>

The MANDALA results in patients aged 18 years and above for the primary efficacy analysis are available at [https://www.annallergy.org/article/S1081-1206\(23\)00644-0/fulltext](https://www.annallergy.org/article/S1081-1206(23)00644-0/fulltext) and at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/214070s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214070s000lbl.pdf).

More information on the MANDALA study can be found at ClinicalTrials.gov: <https://www.clinicaltrials.gov/study/NCT03769090>.

### Declarations

#### *Ethics approval and consent to participate*

The trial design was approved by the appropriate institutional and national regulatory authorities and ethics committees; all the patients or their guardians provided written informed consent (and assent, if appropriate).

#### *Consent for publication*

Not applicable.

#### *Author contributions*

**Alberto Papi:** Investigation; Writing – review & editing.

**Bradley E. Chipps:** Investigation; Writing – review & editing.

**Richard Beasley:** Investigation; Writing – review & editing.

**Reynold A. Panettieri Jr:** Investigation; Writing – review & editing.

**Elliot Israel:** Investigation; Writing – review & editing.

**Mark Cooper:** Investigation; Writing – review & editing.

**Lynn Dunsire:** Formal analysis; Writing – review & editing.

**Allison Jaynes-Ellis:** Conceptualization; Writing – review & editing.

**Robert Rees:** Conceptualization; Writing – review & editing.

**Frank C. Albers:** Conceptualization; Writing – review & editing.

**Christy Cappelletti:** Investigation; Writing – review & editing.

### *Acknowledgements*

AstraZeneca and Avillion would like to thank the clinical study participants and their family members and carers. They would also like to thank the investigators and staff at the study centers who cared for the participants in the clinical studies.

### *Funding*

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Medical writing support was provided by Tanya Jandu of inScience Communications, Springer Healthcare Ltd., United Kingdom (funded by AstraZeneca). We thank Jodi Spiler for giving a patient review of this manuscript, which was reimbursed at fair market value and funded by AstraZeneca.


### *Competing interests*


AP reports grants from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, TEVA, Sanofi, and consulting fees, honoraria for lectures or advisory boards from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi, IQVIA, Avillion, Elpen Pharmaceuticals, Menarini, Zambon, and Mundipharma. BEC is an advisor for, has received consultancy fees from, and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi Genzyme. RB reports receiving grants from AstraZeneca, Cure Kids, the Health Research Council of New Zealand, Genentech, and GlaxoSmithKline; receiving personal fees from AstraZeneca, Avillion, Cipla, and Theravance; serving on advisory boards for AstraZeneca, Avillion, and Theravance; and serving as the chair of the adolescent and adult asthma guidelines group for the Asthma and Respiratory Foundation NZ outside the submitted work. RAP Jr reports grants and advisory board support from AstraZeneca, Sanofi, Genentech, Medimmune, Origa Pharma, Amgen, RIFM, NIH, Regeneron, and Novartis. EI reports personal fees from AB Science, Allergy and Asthma Network, Biometry, Equillum, Merck, NHLBI, 4D Pharma, Pneuma Respiratory, PPS Health, Regeneron, Sanofi Genzyme, and Sienna Biopharmaceutical; grants and personal fees from Amgen, AstraZeneca, Avillion, and Novartis; personal fees and non-financial support from Genentech, GlaxoSmithKline, and TEVA; grants from Gossamer Bio; grants and non-financial support from Circassia; non-financial support from Boehringer Ingelheim; and other from Vorso Corp, outside the submitted work. CC, MC, and LD are employees of, and hold stock in, AstraZeneca. FCA, RR, and AJ-E are employees of Avillion.

### *Availability of data and materials*

Data underlying the findings described in this manuscript may be obtained in accordance with the data sharing policy of Avillion's codevelopment partner AstraZeneca, as described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>

### **ORCID iDs**

Alberto Papi  <https://orcid.org/0000-0002-6924-4500>

Christy Cappelletti  <https://orcid.org/0000-0002-7203-7721>