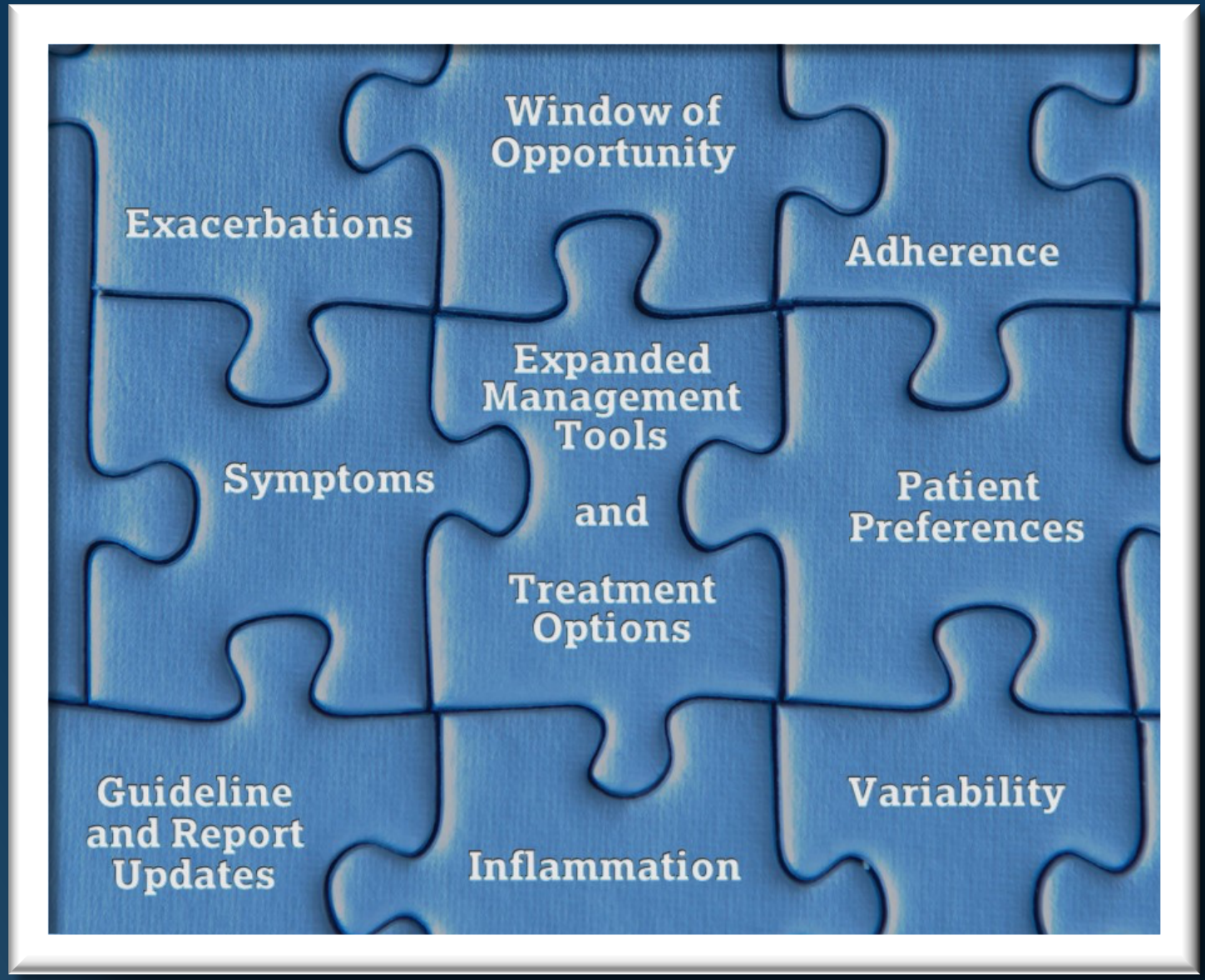
Reframing Rescue Therapy to Help Prevent Asthma Exacerbations



Martina Holder, PharmD, BCPS

Tuesday, June 4, 2024

An Industry Program presentation at the SBHPP Conference

This presentation is sponsored by AstraZeneca and is open to all SBHPP Conference attendees.

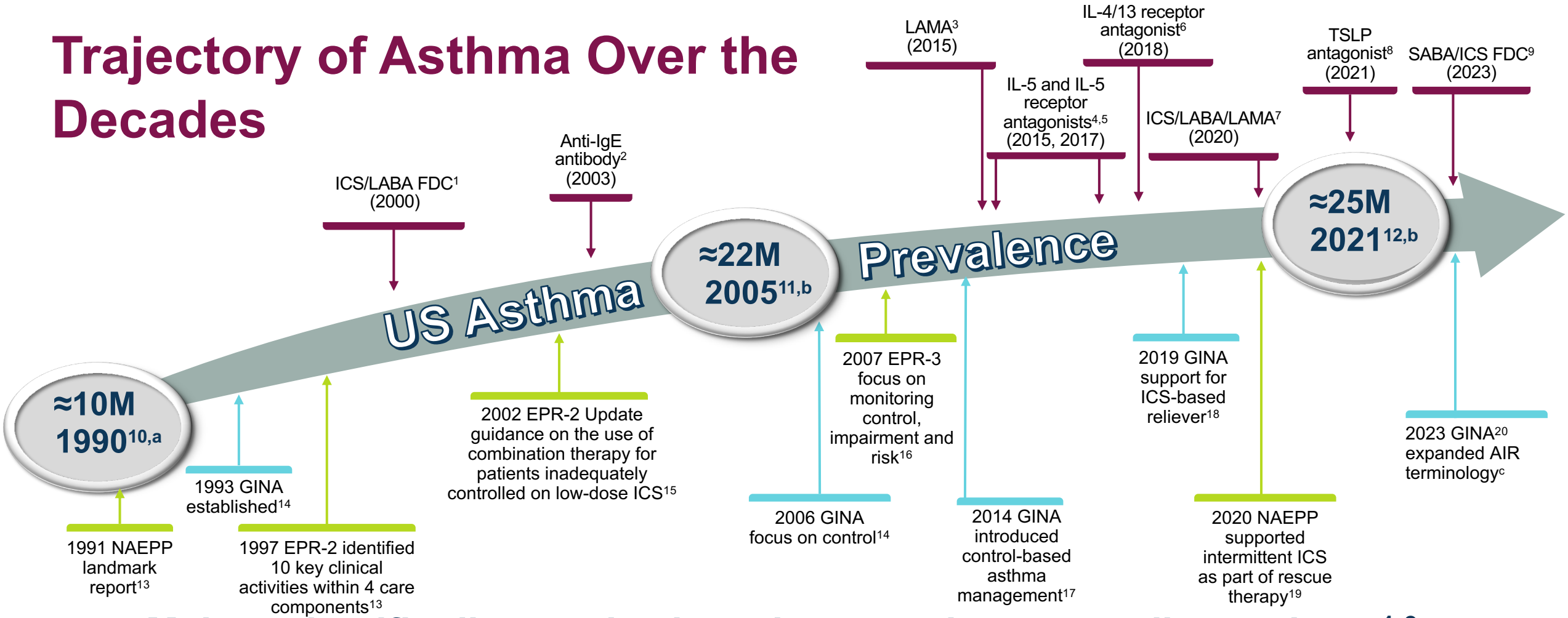
AstraZeneca

Objectives

- Recognize the impact of asthma exacerbations on burden of disease for patients with asthma in the United States
- Gain an understanding of the role of variable airway inflammation in the occurrence of asthma exacerbations and the consequent burden of systemic corticosteroid exposures
- Appreciate patient preferences for immediate symptom relief and fewer asthma attacks
- Review recent recommendations from GINA and NAEPP
- Examine data on a rescue-therapy treatment option

GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program.

Trajectory of Asthma Over the Decades



Major scientific discoveries have been made surrounding asthma,[1-9] generating multiple updates by GINA and NAEPP[13-20]…

[a]Estimated annual number of persons with self-reported asthma (1980-1996) during the preceding 12 months. [b]Includes persons who answered "yes" to the questions: "Have you ever been told by a doctor or other health professional that you had asthma?" and "Do you still have asthma?" [c]AIR (ICS-formoterol and ICS-SABA) was added to distinguish between AIR-only in Steps 1-2 and maintenance and reliever therapy (MART) with ICS-formoterol in Steps 3-5.

AIR, anti-inflammatory reliever; EPR, Expert Panel Report; FDC, fixed-dose combination; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting β_2-agonist; TSLP, thymic stromal lymphopoietin.

1. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2008/021077s029lbl.pdf. 2. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2016/103976s5225lbl.pdf. 3. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/spl/data/dfdb2df1-8b3e-49cd-a9c6-bbfea46ccd57/dfdb2df1-8b3e-49cd-a9c6-bbfea46ccd57.xml. 4. FDA Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2015/125526Orig1s000Lbl.pdf. 5. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2019/761070s005lbl.pdf. 6. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/ 2019/761055s014lbl.pdf. 7. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/spl/data/ 8e185265-fd78-4306-bf66-302ea0d52a56/8e185265-fd78-4306-bf66-302ea0d52a56.xml. 8. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2021/761224s000lbl.pdf. 9. FDA. Accessed November 2, 2023. https://www.accessdata.fda.gov/drugsatfda_dSCS/label/2023/214070s000lbl.pdf. 10. Mannino DM, et al. *MMWR Surveill Summ*. 2002;51(6):1-16.11. CDC. Asthma Data Visualizations. Accessed November 2, 2023. https://www.cdc.gov/asthma/data-visualizations/default.htm. 12. CDC. Most Recent National Asthma Data. Accessed November 2, 2023. https://www.cdc.gov/ asthma/most_recent_data.htm. 13. Williams SG, et al. National Asthma Education and Prevention Program. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. *MMWR Recomm Rep*. 2003;52(RR-6):1-8. 14. GINA. Global strategy for asthma management and prevention, 2006. Accessed November 2, 2023. https://ginasthma.org/wp-content/uploads/2019/01/2006-GINA.pdf. 15. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR Update 2002). NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003. 16. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma, 2007. Accessed November 2, 2023. https://www.ncbi.nlm.nih.gov/books/NBK7232/pdf/Bookshelf_NBK7232.pdf. 17. GINA. Global strategy for asthma management and prevention, 2014. Accessed November 2, 2023. https://ginasthma.org/wp-content/uploads/2019/01/2014-GINA.pdf. 18. GINA. Global strategy for asthma management and prevention, 2019. Accessed November 2, 2023. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. 19. NHLBI. 2020 Focused Updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program coordinating committee expert panel working group. Accessed November 2, 2023. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines. 20. Global Initiative for Asthma, 2023. Accessed November 2, 2023. https://www.ginasthma.org.

…YET, the burden of asthma persists[1,2]

Severe exacerbations[a] contribute significantly to asthma morbidity.[3]

≈65%[2,b]

Patients ≥12 years old with persistent asthma used OCS

2012-2017

2020

≈990,000[1,c]

Annual ED visits

≈95,000[1,c]

Annual hospitalizations

Among patients with asthma

2021

≈9.8 million[1,d,e]

Annual asthma attacks[f]

NAEPP 2020 and GINA 2023 support a shift in the rescue paradigm[4,5]

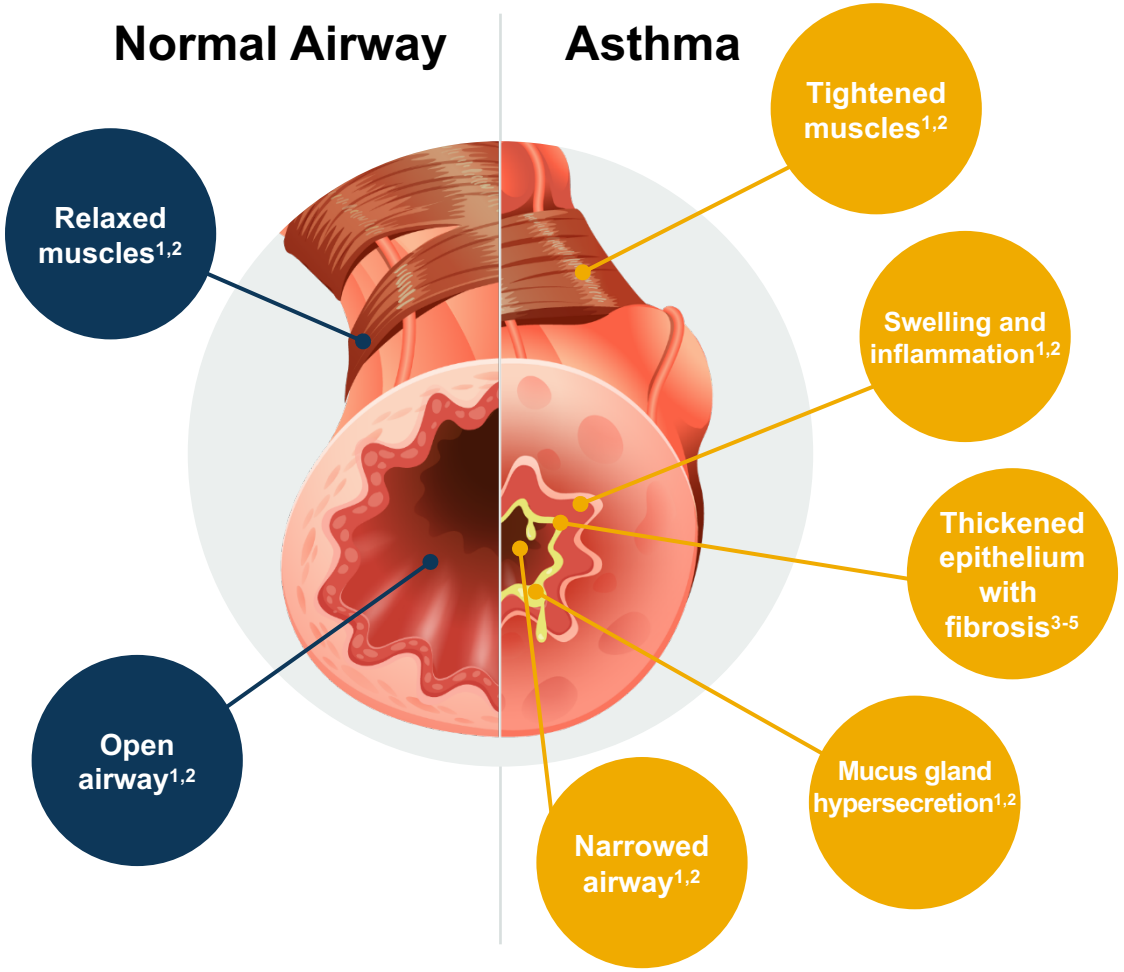
[a]Worsening asthma events requiring treatment with, or increase in, SCS in association with a health care provider encounter; an ED or UC visit resulting in SCS treatment; hospitalizations with SCS use or ICU admission/intubation; death (all cause and asthma related). [b]The IBM MarketScan Commercial Claims and Encounters, Medicare Supplemental, and Medicaid Multistate Claims research databases were used to identify 435,675 patients ≥12 years old with persistent asthma and without COPD or other excluded conditions from January 1, 2012, to December 31, 2017; all patients were followed for OCS use from the day after the index date to the end of follow-up. [c]Asthma as the primary diagnosis (ICD-10-CM Code: J45). [d]Current prevalence includes persons who gave an affirmative response to the questions: "Have you ever been told by a doctor or other health care professional that you had asthma?" and "Do you still have asthma?" Data from NHIS. [e]Having had 1 or more asthma attacks in the past 12 months among people with current asthma. [f]Also referred to as an *exacerbation*; a sudden worsening of symptoms (ie, coughing, chest tightness, wheezing, and trouble breathing) due to airway inflammation and swelling.

COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; NHIS, National Health Interview Survey; OCS, oral corticosteroid; SCS, systemic corticosteroid; UC, urgent care.

1. CDC. Most recent national asthma data. Accessed November 2, 2023. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. 2. Tran TN, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):338-346. 3. Fuhlbrigge A, et al. *J Allergy Clin Immunol*. 2012;129(3 suppl):S34-S48. 4. GINA. Global strategy for asthma management and prevention, 2023. Accessed November 2, 2023. https://ginasthma.org. 5. NHLBI. 2020 Focused Updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program coordinating committee expert panel working group. Accessed November 2, 2023. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines.

Airway Inflammation Is Central to Asthma Symptoms and Exacerbations

Inflammation augments airway narrowing, resulting in asthma symptoms[1,2]



Inflammation and symptoms[6]:

- Vary over time
- Vary in intensity

Lead to exacerbations

1. Sockrider M, et al. *Am J Respir Crit Care Med*. 2020;202(9):P25-P26. 2. Physiopedia. Asthma. Accessed November 2, 2023. https://www.physio-pedia.com/Asthma. 3. Bartemes KR, et al. *Clin Immunol*. 2012;143(3):222–235. 4. Holgate ST. *Immunol Rev*. 2011;242(1):205-219. 5. Cohen L, et al. *Am J Respir Crit Care Med*. 2007;176(2):138-145. 6. GINA. Global strategy for asthma management and prevention, 2023. Accessed November 2, 2023. https://ginasthma.org.

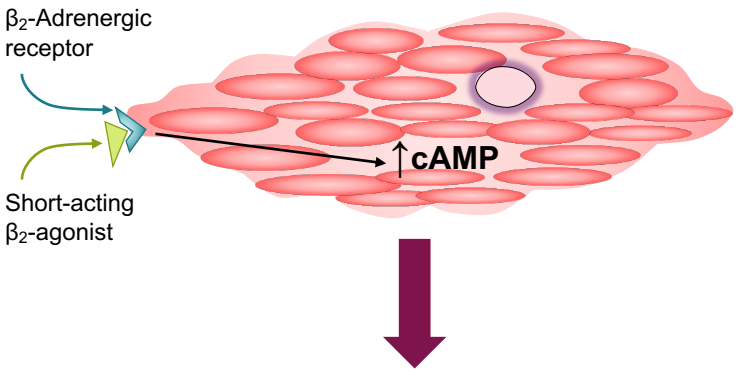
SABA Treats Symptoms Through Bronchodilation, and ICS Addresses Underlying Inflammation

SABA

Direct Agonism[1]

- Binds to β_2-adrenergic receptors, producing rapid ASM relaxation

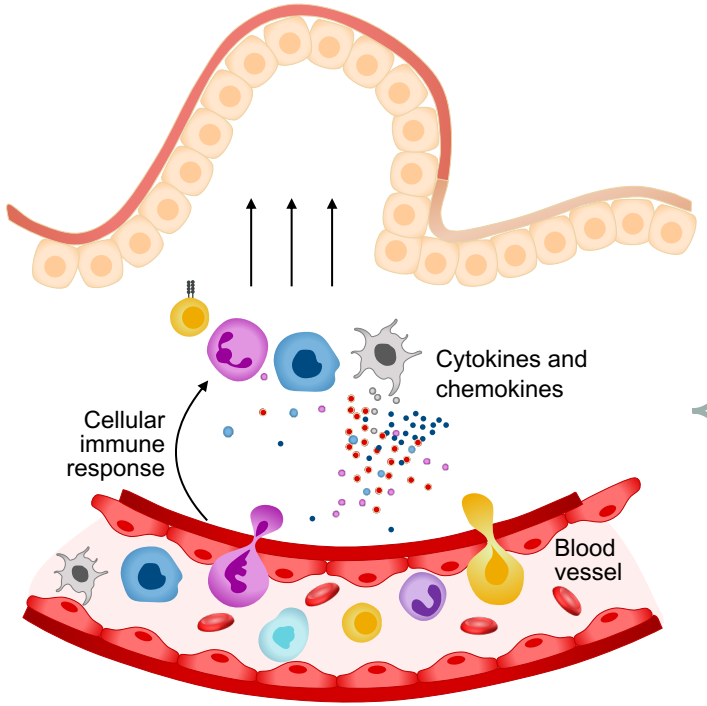
Airway smooth muscle cell



ASM relaxation

Adapted from Amrani Y, et al. *Adv Immunol*. 2017;136:1-28.

Airway inflammatory cells and vasculature[2]



Adapted from Bio-Rad (https://www.bio-rad-antibodies.com/inflammation-antibodies.html)

ICS

Late effects, onset 4-24 hours (genomic)[3,4]

- ↑ anti-inflammatory gene transcription
- ↑ β_2-receptor gene transcription
- ↓ proinflammatory gene transcription

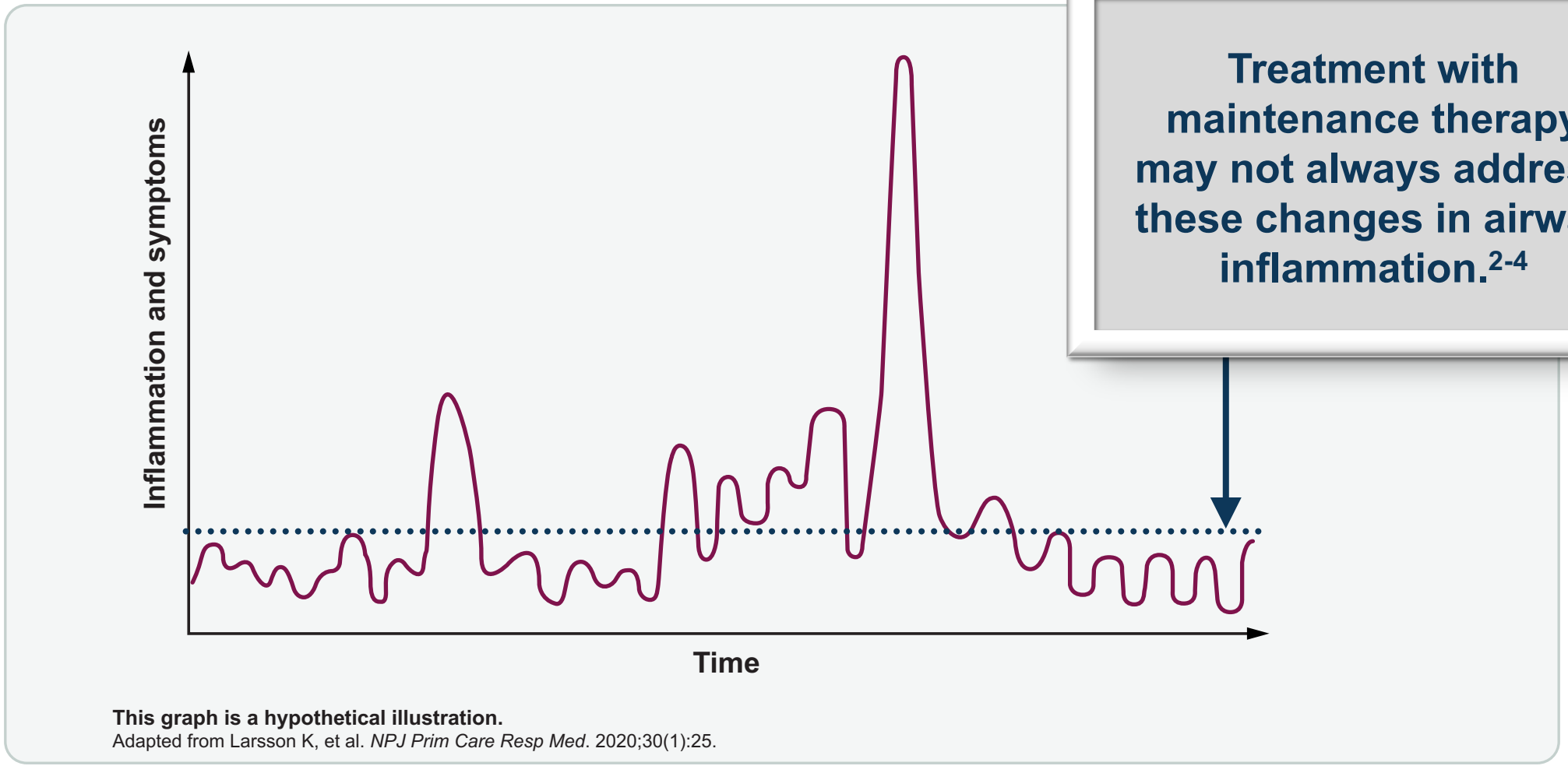
Early effects, onset within minutes (nongenomic)

- ↑ β_2-agonist–induced bronchodilation[5]
- ↓ bronchial vascular blood flow[3]
- ↓ immune mediators[6]

ASM, airway smooth muscle; cAMP, cyclic adenosine monophosphate; ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist.

1. Amrani Y, et al. *Adv Immunol*. 2017;136:1-28. 2. Bio-Rad Laboratories Inc. Inflammation. Accessed November 2, 2023. www.bio-rad-antibodies.com/inflammation-antibodies.htm. 3. Alangari AA. *Ann Thorac Med*. 2010;5(3):133-139. 4. Black JL, et al. *Chest*. 2009;136(4):1095-1100. 5. Koziol-White C, et al. *Am J Physiol Lung Cell Mol Physiol*. 2020;318(2):L345-L355. 6. Zhou J, et al. *Allergy*. 2008;63(9):1177-1185.

Episodic Exposure to Allergic and Nonallergic Triggers Can Lead to Rising Inflammation and Increasing Symptoms[1-3]

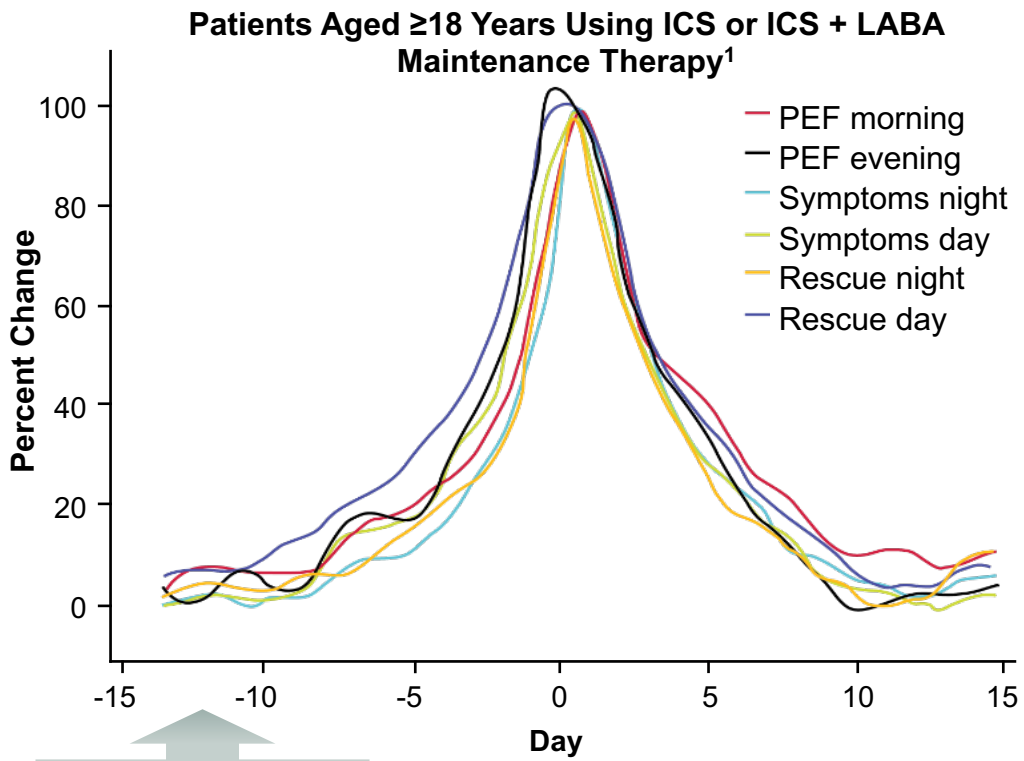


This graph is a hypothetical illustration.
Adapted from Larsson K, et al. *NPJ Prim Care Resp Med*. 2020;30(1):25.

1. Frey U, et al. *Lancet*. 2008;372(9643):1088-1099; 2. Larsson K, et al. *NPJ Prim Care Respir Med*. 2020;30(1):25; 3. GINA. Global strategy for asthma management and prevention, 2023. Accessed November 2, 2023. https://ginasthma.org/.
4. NHLBI. 2020 Focused Updates to the Asthma Management Guidelines. Accessed November 2, 2023. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines.

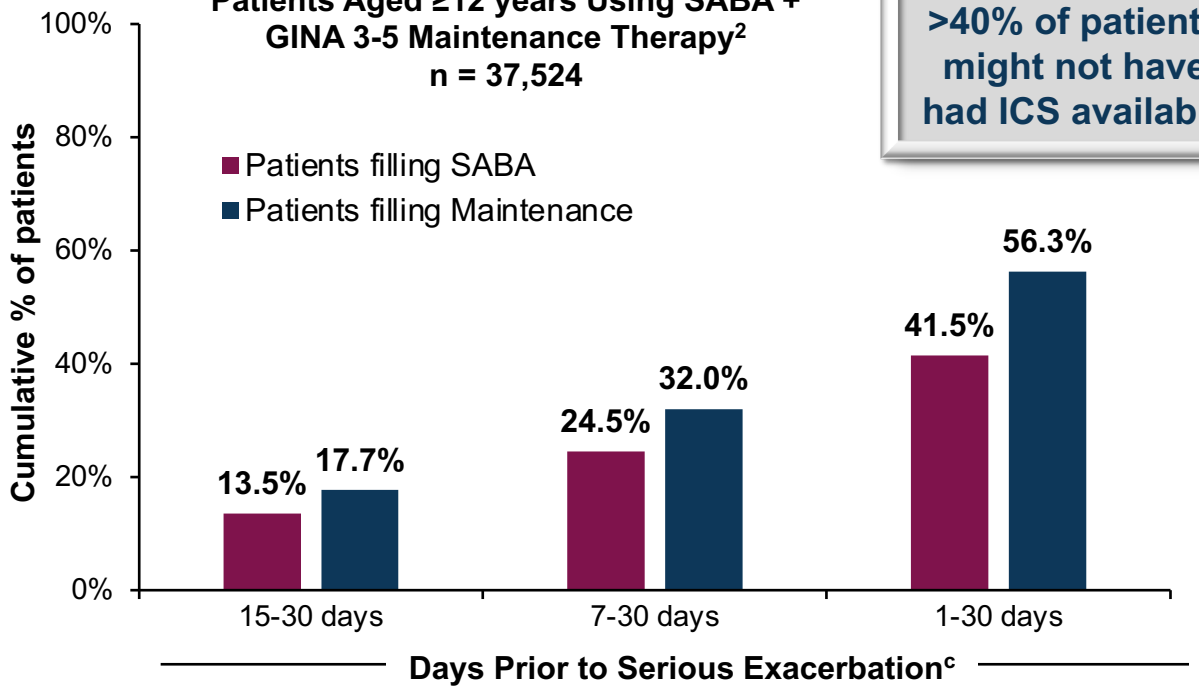
Increasing Symptoms Prior to an Exacerbation May Lead to an Increase in Rescue Use

Onset of Exacerbation[a]



This window is for illustrative purposes only and is not part of the published data set. Adapted from Tattersfield AE, et al. *Am J Respir Crit Care Med*. 1999;160(2)594-599.

In the days leading to an exacerbation, SABA and Maintenance fills increased[b]



At onset of an exacerbation, >40% of patients might not have had ICS available

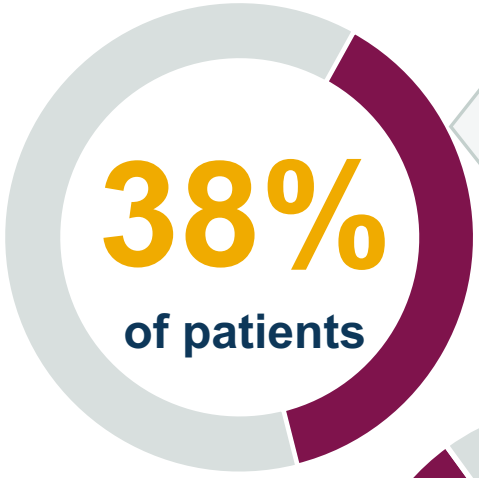
A window of opportunity may exist to help prevent an exacerbation if symptoms and inflammation are treated concomitantly.[3-6]

[a]Data for the rate of change in PEF, symptoms, and rescue use were standardized, with day −14 equal to 0% and day 0 equal to 100%. A severe asthma exacerbation was defined in this study as an exacerbation that required oral corticosteroids as judged by the clinical investigator or an episode in which morning PEF fell by more than 30% from mean morning PEF during the last 10 days of the run-in period (baseline) on 2 consecutive days. PEF, symptoms, and β_2-agonist use as rescue were studied in 425 severe exacerbations over 12 months in a double-blind, randomized, parallel-group study across 71 centers in 9 countries assessing more than 800 patients (FACET). [b]Merative MarketScan research databases of administrative claims from 2010–2017 identified 319,342 patients ≥4 years with moderate to severe asthma as defined by fills of GINA step 3–5 maintenance therapies during the post-index period. [c]Severe exacerbations were defined as ≥3 days of OCS use or equivalent SCS injection, an ED or outpatient visit with a diagnosis of asthma exacerbation and associated with a SCS prescription, or an inpatient admission with a primary diagnosis of asthma; serious exacerbations were a subset of severe exacerbations that were accompanied by an in-person, face-to-face healthcare provider encounter in an outpatient clinic, urgent care or ED, or hospitalization.

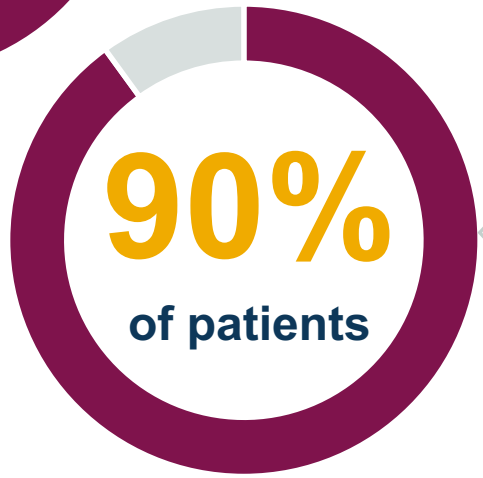
ED, emergency department; GINA, Global Initiative for Asthma; HCP, health care provider; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β_2-agonist; SCS, systemic corticosteroid; UC, urgent care.

1. Tattersfield AE, et al. *Am J Respir Crit Care Med*. 1999;160(2):594-599. 2. Lanz MJ, et al. *Ann Allergy Asthma Immunol*. 2023;131(4):458-465.e1. 3. Larsson K, et al. *NPJ Prim Care Respir Med*. 2020;30(1):25. 4. Papi A, et al. *Lancet Respir Med*. 2013;1(1):23-31. 5. Papi A, et al. *N Engl J Med*. 2022;386(22):2071-2083. 6. Israel E, et al. *N Engl J Med*. 2022;386(16):1505-1518.

Patterns of Rescue and Maintenance Use Reflect Patient Attitudes Toward Asthma Management



Believed there was **no need to take medication** every day when they felt well



Wanted treatments that provide **immediate relief**

INSPIRE Study[a]
2006
(N = 3415)

Patient behavior downplays the need for daily maintenance medication and prioritizes quick relief when needed

[a]The INSPIRE study, which was conducted between October 2004 and February 2005, examined the attitudes and actions of 3415 patients in 11 countries, including the United States, aged ≥16 years with physician-confirmed asthma who were prescribed regular maintenance therapy with ICS or ICS + LABA.
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.
Partridge MR, et al. *BMC Pulm Med*. 2006;6:13.

The Treatment of Exacerbations With Systemic Corticosteroids Contributes to the Burden of Disease

Observational data have suggested that multiple bursts of SCS may result in a cumulative steroid burden affecting future health[1,2]

Significant risks are evident when crossing the 500-mg and 1000-mg thresholds of cumulative lifetime SCS exposure compared to a reference category of >0 to <500 mg SCS[2,a-c]

	500 to <1000 mg	1000 to <2500 mg
Type 2 diabetes	1.2×	1.4×
Depression/anxiety	1.2×	1.3×
Renal impairment		1.2×
Cataracts		1.3×
Cardiovascular disease		1.4×
Pneumonia		1.7×
Osteoporosis		1.9×

In a separate study, it was observed that within 30 days of OCS initiation, the incidence of acute adverse events such as sepsis, venous thromboembolism, and fracture approximately doubled[3,d]

[a]Incidence rates of each adverse outcome were calculated as cases per 100 patient-years of follow-up, and conditional multivariable Cox proportional hazard models were used to compare the risk of adverse outcomes between SCS and non-SCS arms. Adverse outcomes in SCS arms versus non-SCS arms from the Optimum Patient Care Research Database and Clinical Practice Research Datalink databases from 24,117 matched pairs of patients. Data shown are for the majority of outcomes. Of SCS prescriptions included in the analyses, 98% were for SCS and 2% were for parenteral corticosteroids. [b]Record availability before SCS initiation of 9.9 and 8.7 years and median follow-up of 7.4 and 6.4 years in SCS and non-SCS arms, respectively. Data not shown for cumulative exposures >2500 mg. [c]The estimated cumulative exposures of SCS were calculated as prednisolone equivalent. [d]Retrospective cohort study and self-controlled case series that enrolled adults aged 18 to 64 years between January 2012 and December 2014 using the Clinformatics DataMart database

SCS, systemic corticosteroid; OCS, oral corticosteroid.

1. Sullivan PW, et al. *J Allergy Clin Immunol*. 2018;141(1):110-116. 2. Price DB, et al. *J Asthma Allergy*. 2018;11:193-204. 3. Waljee AK, et al. *BMJ*. 2017;357:j1415.

Treatment of Exacerbations With as Few as 1 to 2 Short Bursts of SCS[a] Is Associated With an Increased Risk of Adverse Health Conditions[1-3]

	Burst 1			Burst 2			Burst 3		
Days	40 mg	50 mg	60 mg	40 mg	50 mg	60 mg	40 mg	50 mg	60 mg
3	120 mg	150 mg	180 mg	240 mg	300 mg	360 mg	360 mg	450 mg	540 mg
4	160 mg	200 mg	240 mg	320 mg	400 mg	480 mg	480 mg	600 mg	720 mg
5	200 mg	250 mg	300 mg	400 mg	500 mg	600 mg	600 mg	750 mg	900 mg
6	240 mg	300 mg	360 mg	480 mg	600 mg	720 mg	720 mg	900 mg	1080 mg
7	280 mg	350 mg	420 mg	560 mg	700 mg	840 mg	840 mg	950 mg	1260 mg
8	320 mg	400 mg	480 mg	640 mg	800 mg	960 mg	960 mg	1200 mg	1440 mg
9	360 mg	450 mg	540 mg	720 mg	900 mg	1080 mg	1080 mg	1350 mg	1620 mg
10	400 mg	500 mg	600 mg	800 mg	1000 mg	1200 mg	1200 mg	1500 mg	1800 mg

Below the **lifetime** high-risk SCS exposure threshold

≥500 mg cumulative SCS increases the risk of type 2 diabetes and depression/anxiety

≥1000 mg cumulative SCS increases the risk of renal impairment, cataracts, cardiovascular disease, pneumonia, and osteoporosis

[a]Of 305,110 SCS prescriptions analyzed, 2% were parenteral. Estimated cumulative exposure of SCS calculated as prednisolone equivalent.
Incidence rates of each adverse outcome were calculated as cases per 100 patient-years of follow-up, and conditional multivariable Cox proportional hazard models were used to compare the risk of adverse outcomes between SCS and non-SCS arms. Adverse outcomes in SCS arms versus non-SCS arms from the Optimum Care Research Database and Clinical Practice Research Datalink from 24,117 matched pairs of patients. Data shown are for the majority of outcomes. Record availability before SCS initiation of 9.9 and 8.7 years and median follow-up of 7.4 and 6.4 years in SCS and non-SCS arms, respectively. Data not shown for cumulative exposures >2500 mg.
SCS, systemic corticosteroid.

1. Price DB, et al. *J Asthma Allergy.* 2018;11:193-204. 2. Global Initiative for Asthma. 2023. Accessed November 2, 2023. https://www.ginasthma.org. 3. EPR-3. Expert panel report 3: guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. August 2007. Accessed November 2, 2023. https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosismanagement-of-asthma.

NAEPP and GINA Support ICS/Fast-acting Bronchodilators[a] as Rescue/Reliever in Patients ≥12 Years[1,2]

NAEPP Focused Updates 2020[1]

Preferred treatment steps	
Step 1	PRN SABA
Step 2	Daily low-dose ICS and PRN SABA, or PRN concomitant ICS and SABA
Step 3	Daily and PRN combination low-dose ICS-formoterol[*,b]
Step 4	Daily and PRN combination medium-dose ICS-formoterol[*,b]
Step 5	Daily medium-/high-dose ICS-LABA + LAMA and PRN SABA
Step 6	Daily high-dose ICS-LABA + SCS + PRN SABA

GINA 2023[2]

Track 1 (Preferred)	
RELIEVER: As-needed low-dose ICS-formoterol[*,c]	
Steps 1-2	As-needed-only low-dose ICS-formoterol[*,c]
Step 3	Low-dose maintenance ICS-formoterol[*]
Step 4	Medium-dose maintenance ICS-formoterol[*]
Step 5	Add on LAMA. Refer for phenotypic assessment ± biologic therapy. Consider high-dose ICS-formoterol[*]

SABA-only treatment of asthma is no longer recommended[2]

"The risk of severe exacerbations and mortality increases incrementally with higher SABA use, independent of treatment step."[2]

The use of ICS-formoterol is not approved for maintenance and rescue therapy or for as-needed rescue only in the United States. The recommendations for ICS-formoterol are based on clinical data evaluating the use of ICS-formoterol formulations and strengths not approved and not available in the United States.

[a]Fast-acting bronchodilators: SABA or formoterol.[2] [b]ICS-formoterol as daily controller and reliever is preferred over equivalent-dose ICS + LABA or higher-dose ICS as daily controller therapy and SABA reliever.[1]
[c]Anti-inflammatory reliever (AIR); ICS-formoterol should not be used as the reliever by patients who are taking a different maintenance ICS-LABA; for these patients, the appropriate reliever options are SABA or ICS-SABA.[2]
GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NAEPP, National Asthma Education and Prevention Program; SCS, systemic corticosteroids; PRN, as-needed; SABA, short-acting β_2-agonist.

1. NHLBI. 2020 Focused Updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program coordinating committee expert panel working group. Accessed November 2, 2023.https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines. 2. GINA. Global strategy for asthma management and prevention, 2023. Accessed November 2, 2023. https://ginasthma.org.

GINA 2023 Includes Recommendations for Concomitant Use of SABA and ICS Across All Steps of Therapy[1]

GINA 2023 Track 2 in patients ≥12 years

When Track 1 is not possible or if a patient is stable with good adherence and had no exacerbations on current therapy

Alternative **CONTROLLER** and **RELIEVER (Track 2)**: Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

Step 1	Step 2	Step 3	Step 4	Step 5
ICS whenever SABA is taken[a]	Low-dose maintenance ICS	Low-dose maintenance ICS-LABA	Medium-/high-dose maintenance ICS-LABA	Add-on LAMA. Refer for phenotypic assessment ± biologic therapy. Consider high-dose ICS-LABA

RELIEVER: as-needed SABA, or *as-needed ICS-SABA*[a]

Personalized asthma management: Assess, Adjust, & Review for individual patient needs

Note: Alternative treatment options are not shown from the NAEPP 2020 Focused Updates but are available at the website provided below.[2]

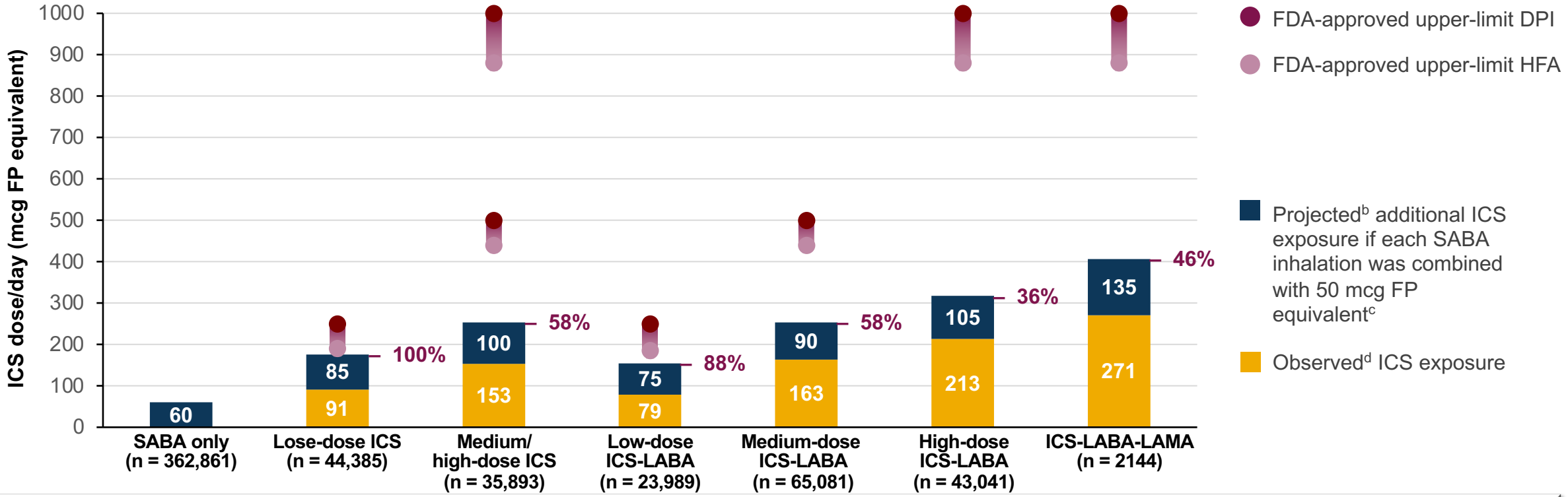
[a]Anti-inflammatory reliever (AIR), administered in separate or combination devices.[1]

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting β_2-agonist.

1. GINA. Global strategy for asthma management and prevention, 2023. Accessed November 2, 2023. https://ginasthma.org. 2. NHLBI. 2020 Focused Updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program coordinating committee expert panel working group. Accessed November 2, 2023.https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

Real-world Observed and Projected ICS Exposure if SABA and ICS Were Used Concomitantly for Symptoms

Merative® MarketScan® databases of 2010-2017 administrative claims for US patients[a] ≥12 years receiving SABA for asthma (Subset of total population n = 577,394)



Percentage values (maroon) indicate the percentage of FDA-approved maximum daily ICS dose reached with the daily ICS maintenance dose observed (yellow bars) in the study plus the additional projected as-needed ICS exposure (blue bars) if each SABA inhalation contained 50 mcg FP equivalent.[c]

DPI, dry powder inhaler; FDA, US Food and Drug Administration; FP, fluticasone propionate; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA; long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist.
[a]Patients were indexed on a random SABA claim, had 12 months' continuous eligibility pre- and post-index, and filled post-index ICS-based maintenance medication totaling ≥32 days' supply or ≥1 additional SABA if no maintenance. [b]Projected ICS exposure was calculated for the post-index year using mean SABA fills (inhalations/day). Each SABA inhalation was assumed to contain 50 mcg of FP equivalent. [c]50 mcg FP/80mcg budesonide equivalent. [d]Post-index ICS exposure was analyzed based on proportion of days covered of observed claims and assuming full claims use. ICS dose was converted to mcg/day of FP equivalents.

Lugogo N, et al. *J Asthma Allergy.* 2023;16:579-584.

Estimated Total ICS Exposure With As-Needed SABA + ICS Compared to Observed SCS Exposure

	SABA only (n = 362,861)	Low-dose ICS (n = 44,385)	Med-high dose ICS (n = 35,893)	Low-dose ICS/LABA (n = 23,989)	Medium-dose ICS/LABA (n = 65,081)	High-dose ICS/LABA (n = 43,041)	ICS/LABA/ LAMA (n = 2144)
Annual total estimated ICS exposure, mg, mean[a]	22	64	92	56	92	116	148
Patients with any SCS exposure, n (%)	187,731 (51.7)	15,298 (34.5)	13,127 (36.6)	7,558 (31.5)	27,011 (41.5)	22,327 (51.9)	1,206 (56.3)
Annual observed SCS exposure among patients with any SCS exposure, mg, mean (SD)[b]	451 (1214)	555 (1138)	574 (1334)	542 (1438)	590 (1365)	763 (1606)	1088 (2148)
Annual observed SCS relative to estimated ICS exposure	**21-fold**	**9-fold**	**6-fold**	**10-fold**	**6-fold**	**7-fold**	**7-fold**

[a]Inhaled corticosteroid dose/day in mcg of fluticasone propionate equivalents. [b]Cumulative annual systemic corticosteroid exposure in mg of prednisone equivalents.
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist; SCS, systemic corticosteroids; SD, standard deviation.
Lugogo N, et al. *J Asthma Allergy*. 2023;16:579-584.

Putting Together the Puzzle of Asthma Burden

A Paradigm Shift to Address the Problem of Exacerbations

AIRSUPRA™
(albuterol 90 mcg/budesonide 80 mcg)
Inhalation Aerosol

Please see full Prescribing Information, including Patient Information, available at this presentation.

Indication and Dosage

AIRSUPRA is a combination of albuterol, a β_2-adrenergic agonist, and budesonide, a corticosteroid, indicated for the **as-needed** treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older

2 inhalations equal 1 dose delivering:

Short-acting β_2-agonist (SABA)

Albuterol 180 mcg

Inhaled corticosteroid (ICS)

Budesonide 160 mcg

Do not take more than 6 doses (12 inhalations) in a 24-hour period

Please see the full Prescribing information, including Patient Information, at this presentation.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023

Select Important Safety Information

- **Contraindications:** Hypersensitivity to albuterol, budesonide, or to any of the excipients
- **Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient continues to experience symptoms after using AIRSUPRA or requires more doses of AIRSUPRA than usual, it may be a marker of destabilization of asthma and requires evaluation of the patient and their treatment regimen
- **Paradoxical Bronchospasm:** AIRSUPRA can produce paradoxical bronchospasm, which may be life threatening. Discontinue AIRSUPRA immediately and institute alternative therapy if paradoxical bronchospasm occurs. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister
- **Cardiovascular Effects:** AIRSUPRA, like other drugs containing beta$_2$-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by pulse rate, blood pressure, and/or other symptoms. If such effects occur, AIRSUPRA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST-segment depression. Therefore, AIRSUPRA, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension

Please see additional Important Safety Information at the end of this presentation, and please see the full Prescribing Information, including Patient Information, at this presentation.

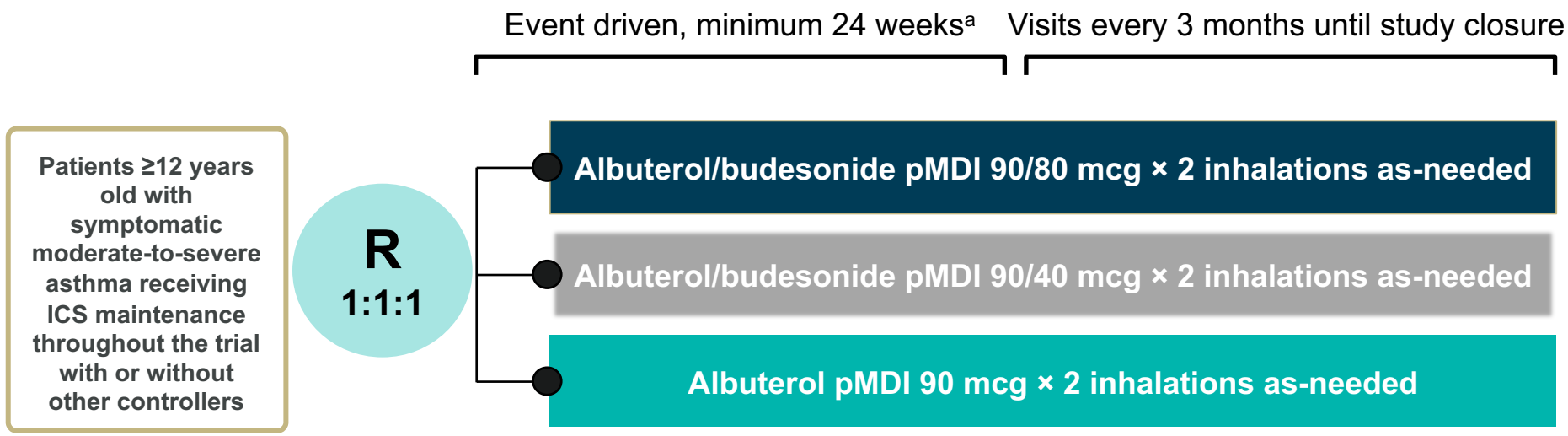
AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023

MANDALA Clinical Trial

Study Design

Phase 3 study evaluating the efficacy and safety of as-needed albuterol/budesonide pMDI compared to as-needed albuterol pMDI on the time to first severe asthma exacerbation (N = 3040)[1-4]



Background maintenance therapy:
Stable medium- to high-dose ICS or low- to high-dose ICS/LABA, with or without other controllers

While patients 12 to 17 years were included in MANDALA, AIRSUPRA is not approved in this age group; therefore, efficacy results are only presented for adults ≥18 years of age. Since albuterol/budesonide 180/80 mcg is not an approved dose, this presentation will not include results for this arm of the study.

Please see full Prescribing Information, including Patient Information, available at this presentation.

[a] Treatment period was event driven and continued until ≥570 first severe exacerbations events were recorded and 3000 adults and adolescents were randomized.[1]
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; pMDI, pressurized metered-dose inhaler; R, randomization; SABA, short-acting β_2-agonist; SV, screening visit; W, week.
1. Chipps BE, et al. *BMJ Open Respir Res.* 2021;8:e001077. 2. Papi A, et al. Article and supplementary appendix. *N Engl J Med*. 2022;386(22):2071-2083. 3. AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 4. Data on file, REF-174347, AZPLP.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Select Inclusion and Exclusion Criteria

Inclusion Criteria[1-3]

- Symptomatic patients with moderate to severe asthma
- Physician diagnosis of asthma documented for at least 1 year
- ≥1 severe asthma exacerbations in the previous 12 months
- Receiving 1 of the following scheduled asthma maintenance therapies for ≥3 months with stable dosing for ≥4 weeks prior to screening:
  - Medium- to high-dose ICS or low- to high-dose ICS in combination with LABA with or without 1 additional controller: LTRA, LAMA, or xanthines
- Prebronchodilator FEV_1 of ≥40 to <90% predicted normal (for patients aged 12 to <18 years old, ≥60%) and confirmed reversibility to albuterol
- ACQ-5 score ≥1.5 at Visit 2 (Day 1 of double-blind study medication) indicating uncontrolled asthma

Exclusion criteria[1,2]

- COPD or other significant lung disease
- SCS within 6 weeks prior to screening
- Chronic SCS use (≥3 weeks within 3 months prior to screening)
- Biologic treatment within 3 months or 5 half-lives before screening

While patients 12 to 17 years were included in MANDALA, AIRSUPRA is not approved in this age group; therefore, efficacy results are presented only for adults ≥18 years of age.

Please see full Prescribing Information, including Patient Information, available at this presentation.

ACQ, Asthma Control Questionnaire; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SCS, systemic corticosteroid.

1. Papi A, et al. Article, supplementary appendix, and protocol. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163. 2. Chipps BE, et al. *BMJ Open Respir Res.* 2021;8:e001077. doi:10.1136/bmjresp-2021-001077. 3. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Data shown are for adults ≥18 years old

Baseline Patient Demographics

Patient Characteristic		Albuterol/budesonide 180/160 mcg as-needed n = 979	Albuterol 180 mcg as-needed n = 980
Age, y, mean (SD)		51.9 (13.7)	52 (14.2)
Age groups, n (%)	≥18 to <65 y	787 (80.4)	783 (79.9)
	≥65 y	192 (19.6)	197 (20.1)
Female, n (%)		631 (64.5)	662 (67.6)
Race, n (%)	White	800 (81.7)	824 (84.1)
	Black/African American	129 (13.2)	112 (11.4)
	Asian	26 (2.7)	20 (2.0)
	American Indian or Alaska Native	1 (0.1)	0
	Other	23 (2.3)	24 (2.4)
Ethnicity, n (%)	Hispanic or Latino	221 (22.6)	284 (29.0)
	Not Hispanic or Latino	758 (77.4)	696 (71.0)
Geographic region, n (%)	North America, Western Europe, South Africa	511 (52.2)	513 (52.3)
	Rest of world	468 (47.8)	467 (47.7)

Notes: Data shown for albuterol/budesonide 180/160 mcg and albuterol 180 mcg are for patients ≥18 years old.
SD, standard deviation.
Data on file. REF-174347, AZPLP.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Data shown are for adults ≥18 years old

Baseline Disease Characteristics

Disease Characteristic[1]		Albuterol/budesonide 180/160 mcg as-needed n = 979	Albuterol 180 mcg as-needed n = 980
Mean FEV_1 prebronchodilator[a] (SD), L		1.9 (0.6)	1.9 (0.6)
Mean FEV_1 prebronchodilator[a] (SD), % predicted normal		62.9 (12.5)	63.2 (12.6)
Mean reversibility[a,b] in FEV_1 (SD), %		27.5 (15.4)	27.9 (15.7)
Maintenance treatment[c] n (%)	Low-dose ICS-LABA or medium-dose ICS	301 (30.7)	284 (29.0)
	Medium-dose ICS-LABA or high-dose ICS	373 (38.1)	406 (41.4)
	High-dose ICS-LABA	289 (29.5)	272 (27.8)
Severe exacerbations within 12 mo prior to screening, n (%)	1	780 (79.7)	781 (79.7)
	>1	199 (20.3)	199 (20.3)
ACQ-5 score, mean		2.6 (0.7)	2.6 (0.6)
AQLQ+12 score,[d] mean		4.6 (1.0)	4.6 (1.0)

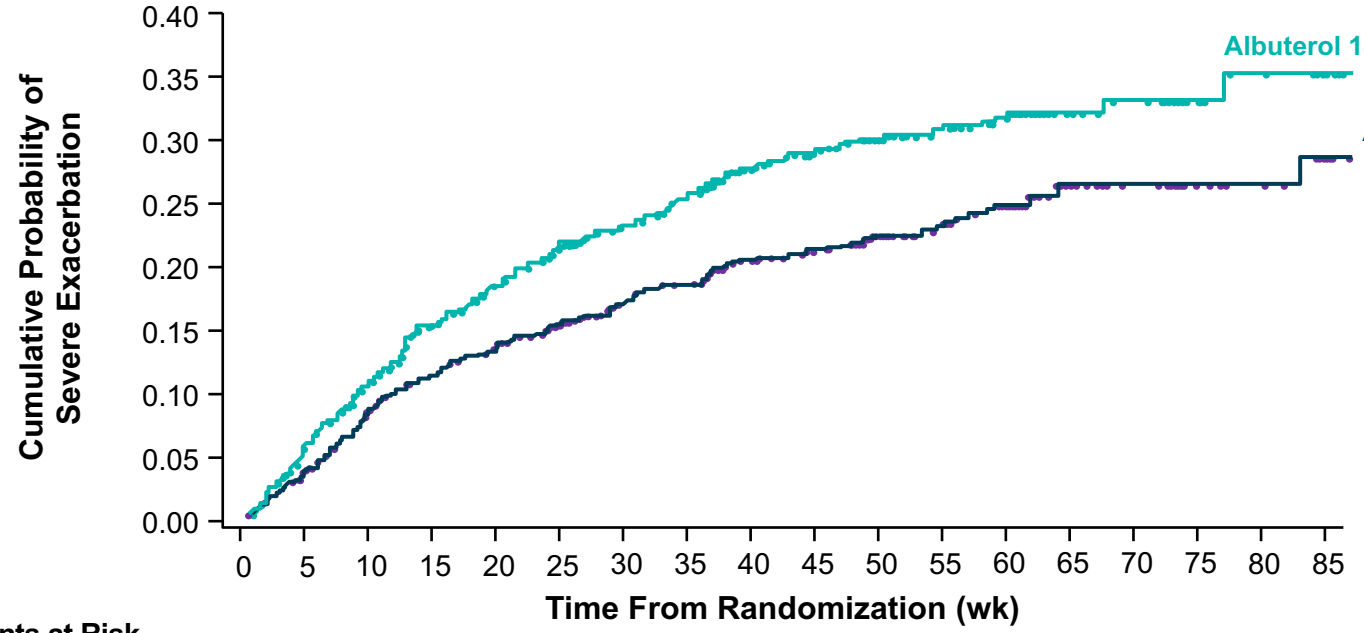
Note: Data shown for albuterol/budesonide 180/160 mcg and albuterol 180 mcg are for patients ≥18 years old.[1]
[a] Result from study entry visit 1 or visit 1a used to assess prebronchodilator FEV_1 eligibility criteria.[2] [b] Reversibility in FEV_1 (%) is [postbronchodilator FEV_1(L) - prebronchodilator FEV_1(L)]/prebronchodilator FEV_1 (L).[2] [c] Taken with or without LTRA, LAMA, or theophylline.[1] Changes to maintenance medication were allowed when clinically indicated.[2] [d] AQLQ+12 scores n=962 and n=960 for albuterol/budesonide 180/160 mcg and albuterol 180 mcg, respectively.[1]
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
1. Data on file. REF-174347, AZPLP. 2. Papi A, et al. *N Engl J Med*. 2022;386(22):2071-2083.

AIRSUPRA™ (albuterol/budesonide) Inhalation Aerosol

Data shown are for adults ≥18 years old

As-needed Albuterol/budesonide Significantly Reduced the Risk of Severe Exacerbation in a Time-to-first-severe-exacerbation Analysis

Risk of Severe Exacerbation[a-c] with as-needed albuterol/budesonide 180/160 mcg vs albuterol 180 mcg[1]



28% Reduction

Albuterol/budesonide 180/160 mcg vs. albuterol 180 mcg
HR: 0.72, 95% CI: 0.60, 0.86;
p < 0.001

Number of Patients at Risk

Albuterol/budesonide 180/160 mcg	979	934	877	846	818	594	551	540	437	426	246	231	192	75	68	41	37	11
Albuterol 180 mcg	980	908	850	793	754	542	503	481	383	364	217	203	167	72	67	31	28	9

As-needed albuterol/budesonide demonstrated a significant reduction in the risk of severe asthma exacerbations compared with albuterol

[a] An asthma exacerbation was considered severe if it resulted in at least 1 of the following: a temporary bolus/burst of SCS for at least 3 consecutive days to treat symptoms of asthma worsening (a single depo-injectable dose of corticosteroids was considered equivalent), an ER or urgent care visit due to asthma that required SCS, or an in-patient hospitalization due to asthma.[2] [b] As measured by time to first severe exacerbation and adjusted for age group, region, and number of prior severe exacerbations in the 12 months before screening.[2] [c] Curve truncated when <1% of patient population remained at risk.[1]
Type I error was controlled for comparison of ALB/BUD 180/160 mcg dose with ALB with the Hochberg procedure.[2]
ALB, albuterol; BUD, budesonide; CI, confidence interval; ER, emergency room; HR, hazard ratio; SCS, systemic corticosteroid; wk, weeks.

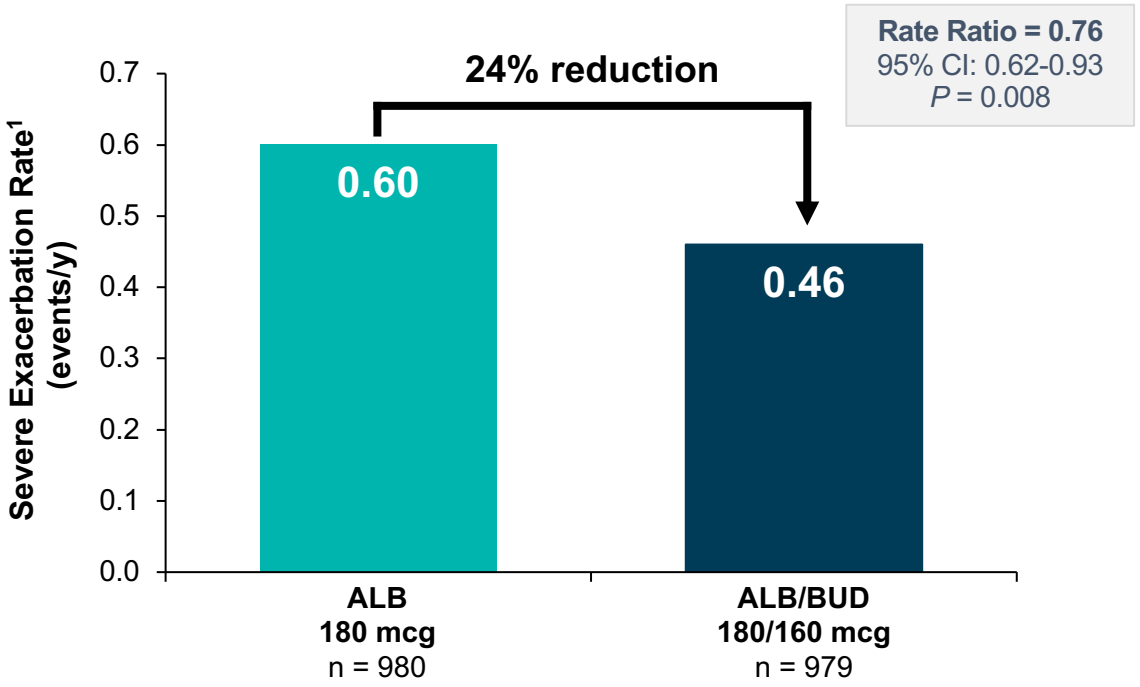
1. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. Papi A, et al. *N Engl J Med.* 2022;386(22):2071-2083.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

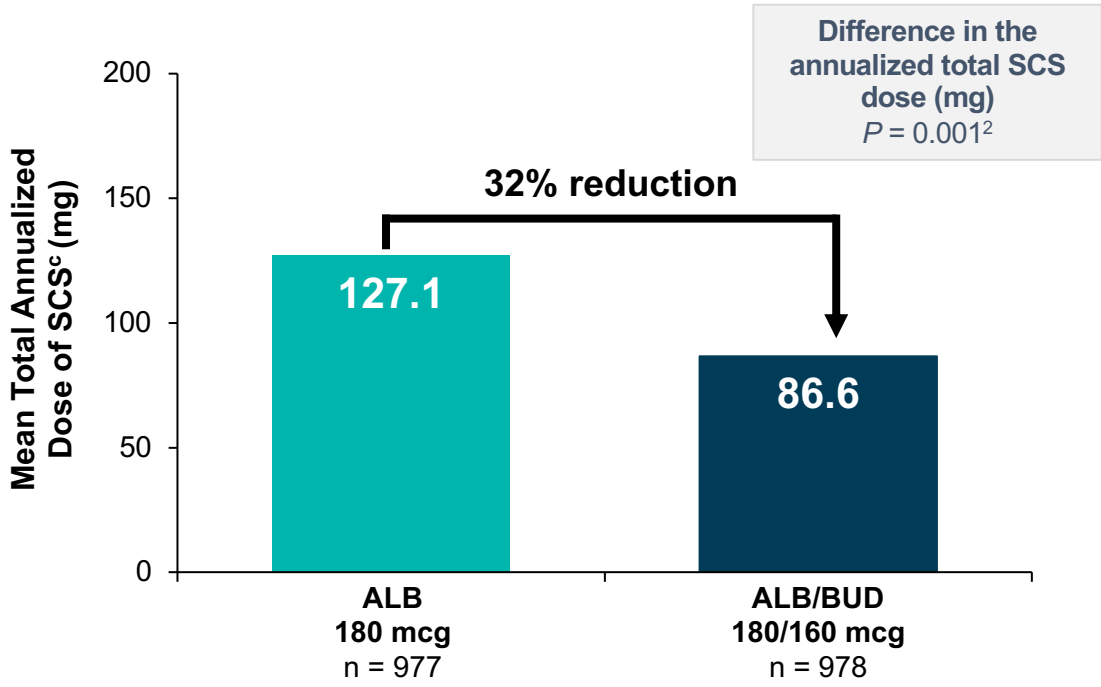
Data shown are for adults ≥18 years old

Key Secondary Endpoints

Annualized Severe[a] Exacerbation Rate[1,b]



Annualized Systemic Corticosteroid Dose[1,2,c,d]



There was a significant reduction in the annualized rate of severe exacerbations and a significant difference in the annualized total SCS dose with as-needed albuterol/budesonide 180/160 mcg vs albuterol

Notes: Data shown for albuterol/budesonide 180/160 mcg and albuterol 180 mcg are for patients ≥18 years old.[1] Data are from the preplanned on-treatment efficacy analysis and included data collected while on randomized treatment prior to treatment discontinuation or change in maintenance therapy, with censoring of data at the time of discontinuation or change in therapy.[3] Secondary end points were controlled using a hierarchical testing sequence between all treatment comparisons, grouped by end point.[3]

[a]An asthma exacerbation was considered severe if it resulted in at least 1 of the following: a temporary bolus/burst of SCS for at least 3 consecutive days to treat symptoms of asthma worsening (a single depo-injectable dose of corticosteroids was considered equivalent), an ER or urgent care visit due to asthma that required SCS, or an in-patient hospitalization due to asthma.[3] [b]Annualized severe asthma exacerbation rates were adjusted for age, region, and number of severe exacerbations in the 12 months before screening and time at risk.[3] There were 324 severe exacerbations for ALB/BUD and 403 for ALB.[1] [c]Prednisone equivalent.[3] [d]Mean annualized doses of SCS were rounded to the nearest whole number in the AIRSUPRA Prescribing Information.[1]

ALB, albuterol; BUD, budesonide; CI, confidence interval; ER, emergency room; SCS, systemic corticosteroid.

1. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. Data on File. REF-197604, AZPLP. 3. Papi A, et al. *N Engl J Med*. 2022;386(22):2071-2083.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Data shown are for adults and adolescents ≥12 years old

Summary of Adverse Reactions Reported in ≥1% of Patients Who Used Albuterol/budesonide 180/160 mcg

	MANDALA	
	Albuterol/budesonide 180/160 mcg n = 1015 **n (%)**	**Albuterol 180 mcg** n = 1015 **n (%)**
Headache	44 (4.3)	50 (4.9)
Oral candidiasis[a]	13 (1.3)	5 (0.5)
Cough	10 (1.0)	11 (1.1)

The safety profile of albuterol/budesonide 180/160 mcg in MANDALA was similar across the 2 treatment groups irrespective of background ICS dose

Data shown for albuterol/budesonide 180/160 mcg and albuterol 180 mcg are for patients ≥12 years old. AIRSUPRA is not approved for patients 12 to 17 years of age.

[a] Oral candidiasis also includes those reactions reported under the preferred term *oropharyngeal candidiasis*.
ICS, inhaled corticosteroid.
AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

MANDALA:
Exploratory Analysis

Asthma Deteriorations and Severe Exacerbations

- This exploratory efficacy analysis evaluated as-needed albuterol/budesonide 180/160 mcg versus albuterol 180 mcg on the time to first asthma deterioration and the time to first progression from an asthma deterioration to a severe exacerbation in patients ≥18 years
- The first asthma deterioration post-randomization was evaluated for progression to a severe exacerbation within the subsequent 21 days

Asthma deterioration

≥1 of the following for ≥2 consecutive days:

- **PEF decline** ≥20% from baseline
- **Study medication use** >4 inhalations[a]/day and ≥2x baseline
- **Symptom score increase**[b]
  - Nighttime score > baseline and ≥2
    OR
  - Daytime score > baseline and =3

Severe asthma exacerbation

An asthma worsening leading to ≥1 of the following:

- **≥3-day course of SCS** or corresponding single injectable dose
- **ER or UC visit** due to asthma that required **SCS**
- **Hospitalization** due to asthma
- **Death** due to asthma

[a]1 dose = 2 inhalations. [b]Asthma symptom score was assessed on a 4-point scale (0 to 3), with higher values indicating more severe asthma symptoms.
ER, emergency room; PEF, peak expiratory flow; SCS, systemic corticosteroids; UC, urgent care.

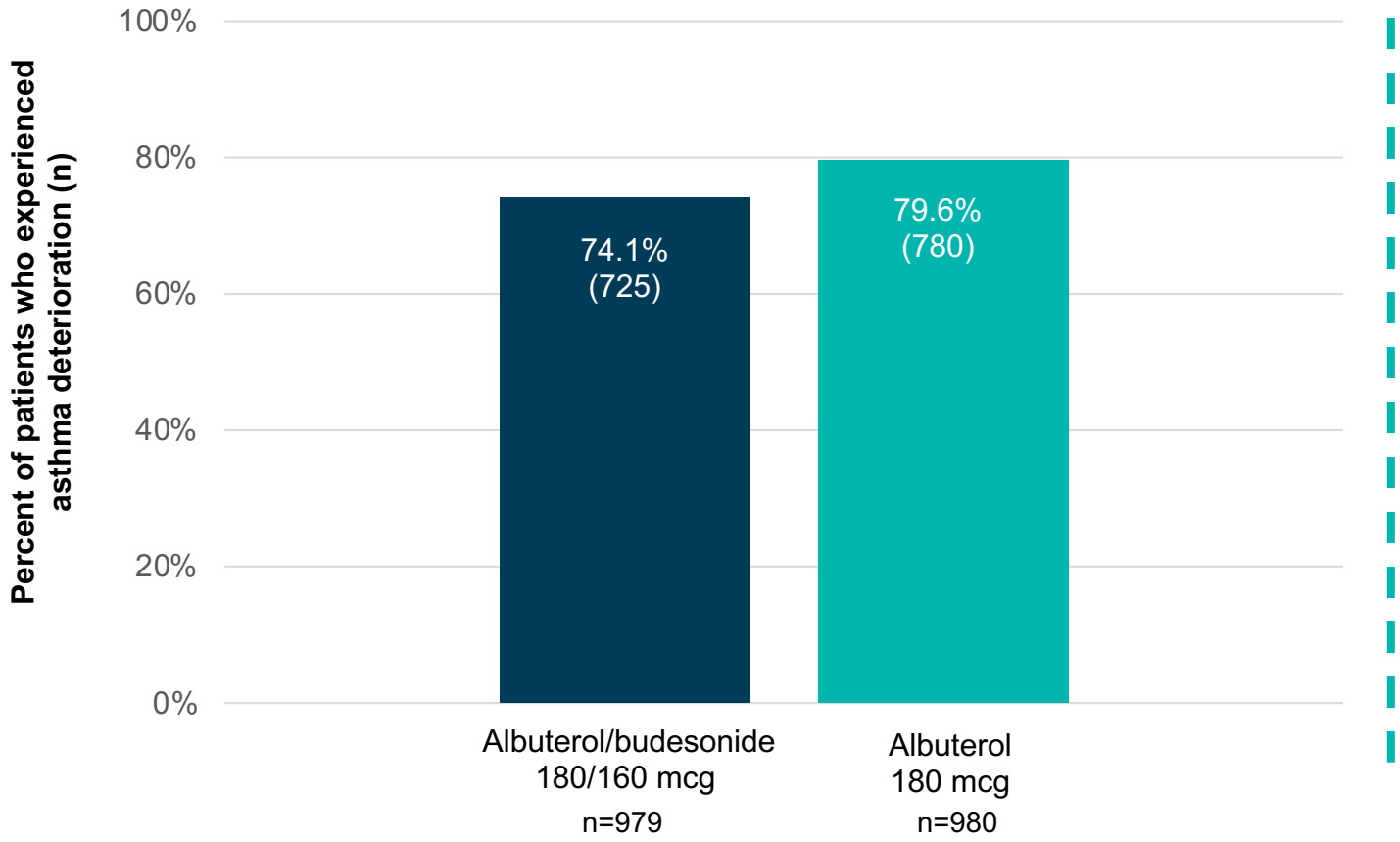
Chipps BE, et al. Poster presented at: The Association of Asthma Educators (AAE) Annual Meeting; August 2023; Big Sky, Montana.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Data shown are for adults ≥18 years old

Asthma Deteriorations

Occurrence of Asthma Deterioration (% of analysis population)



Time to First Asthma Deterioration

In a time to first asthma deterioration analysis:
albuterol/budesonide 180/160 mcg (n=979)
vs
albuterol 180 mcg (n=980)
Hazard Ratio = 0.83,
95% CI: 0.75, 0.92

CI, Confidence interval; HR, hazard ratio.

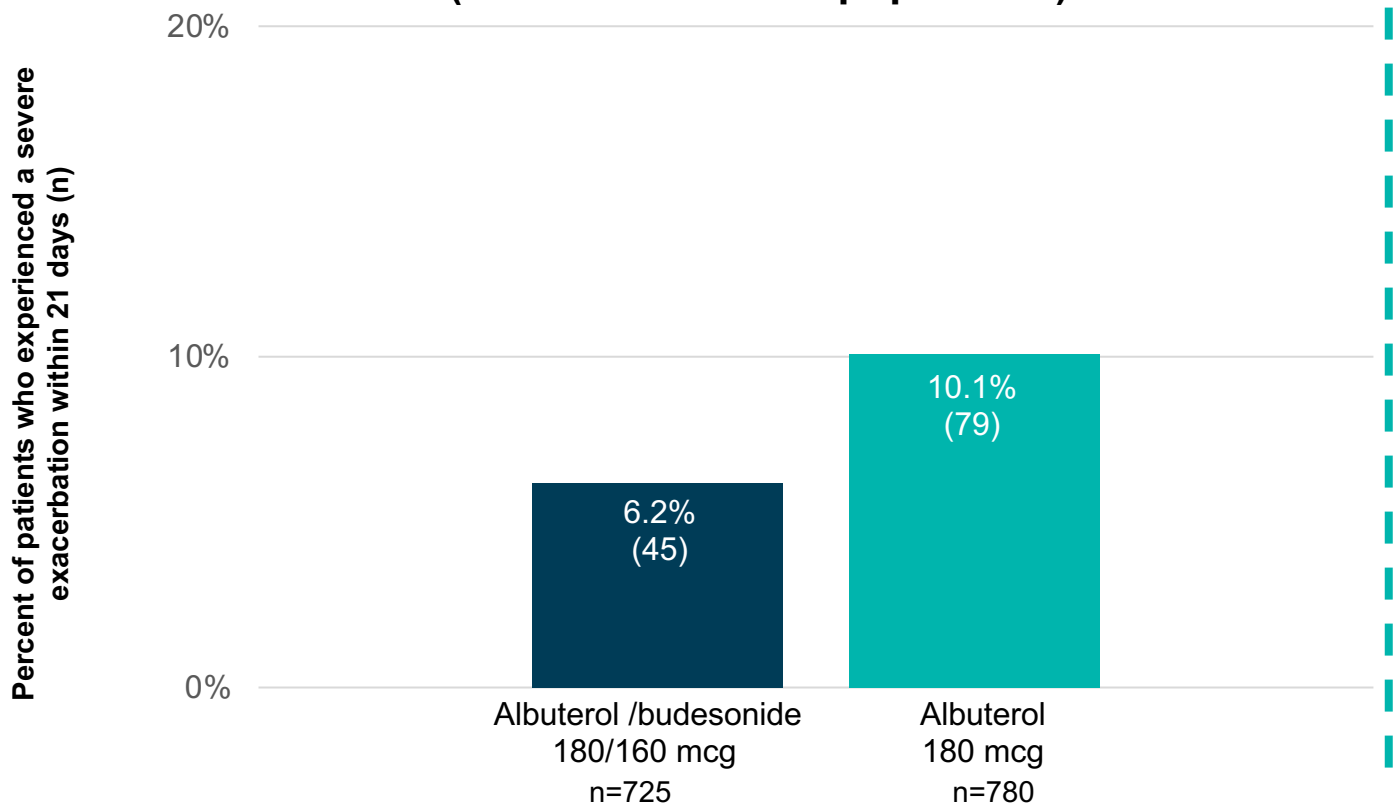
Chipps BE, et al. Poster presentation at The Association of Asthma Educators (AAE). August 2023. Big Sky, Montana.

AIRSUPRA™ (albuterol/budesonide) Inhalation Aerosol

Data shown are for adults ≥18 years old

Asthma Deteriorations that Progressed to a Severe Exacerbation

Occurrence of a Severe Exacerbation Following an Asthma Deterioration (% of deterioration population)



Time to First Severe Exacerbation Following an Asthma Deterioration[a]

In a time to first severe exacerbation following an asthma deterioration analysis:

albuterol/budesonide 180/160 mcg (n=725)

vs

albuterol 180 mcg (n=780)

Hazard Ratio = 0.60,

95% CI: 0.42, 0.87

[a]First deterioration following randomization was analyzed to evaluate progression to severe exacerbation within the subsequent 21 days.
CI, Confidence interval; HR, hazard ratio.
Chipps BE, et al. Poster presentation at The Association of Asthma Educators (AAE). August 2023. Big Sky, Montana

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Exploratory Analysis Study Limitations

- Other indicators of a deterioration may exist that were not captured in the definition used here
- These data were from patients with moderate-to-severe asthma who remained highly adherent (median, 85.1% of study days) to their ICS-containing maintenance medication
- Results may differ for patients taking lower levels of, or no, maintenance therapy, and those with lower levels of maintenance adherence
- The time-to-event analyses were based on the subgroup of patients who experienced an asthma deterioration post-randomization

ICS, inhaled corticosteroid.

Chipps BE, et al. Poster presented at: The Association of Asthma Educators (AAE) Annual Meeting; August 2023; Big Sky, Montana.

DENALI Clinical Trial

DENALI: Study Design

Phase 3 study that evaluated the efficacy and safety of albuterol/budesonide pMDI compared to albuterol pMDI and budesonide pMDI administered QID on improvement in lung function (N=989)[1-3]

- Patients ≥12 years of age with mild to moderate asthma
- Previously treated with as-needed SABA alone or low-dose maintenance ICS plus as-needed SABA

R

1:1:1:1:1

Treatment phase[a] – 12 weeks

- Albuterol/budesonide 180/160 mcg QID[b]
- Albuterol/budesonide 180/80 mcg QID[b]
- Albuterol 180 mcg QID[b]
- Budesonide 160 mcg QID[b]
- Placebo QID

While patients 12 to 17 years were included in DENALI, AIRSUPRA is not approved in this age group; therefore, efficacy results are presented only for adults ≥18 years of age. Because albuterol/budesonide 180/80 mcg is not an approved dose, this presentation will not include results for this arm of the study. AIRSUPRA is not indicated or approved for maintenance use.

[a]Sponsor provided SABA (Ventolin®) to all patients for as-needed use in response to asthma symptoms during run-in and treatment phase.[1] [b]Study medication administered as 2 actuations of albuterol/budesonide 90/80 mcg or 90/40 mcg, albuterol 90 mcg, and budesonide 80 mcg.[1]

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; pMDI, pressurized metered-dose inhaler; QID, 4 times daily; R, randomization; SABA, short-acting β_2-agonist.

1. Chipps BE, et al. *Chest.* 2023;164(3):585-595. 2. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023; 3. Data on File. REF-174347, AZPLP.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

DENALI: Select Inclusion and Exclusion Criteria

Inclusion criteria

- Physician diagnosis and documented 6-month history of asthma
- Receiving 1 of the following inhaled asthma medications with stable dosing for at least 30 days prior to Visit 1:
  - Only SABA used as needed
  - Stable low-dose ICS in addition to as-needed use of SABA
- Prebronchodilator FEV_1 of ≥50 to <85% predicted normal (adults), or ≥50% predicted normal value (ages 12 to <18 years)
- Reversibility of airflow limitation (≥15% increase in FEV_1 relative to baseline after sponsor-provided SABA [Ventolin®])
- Use of SABA (Ventolin®) on ≥2 days out of 7 days prior to Visit 2

Exclusion criteria

- COPD or other significant lung disease
- SCS use within 3 months before Visit 1
- Investigational biologic within 3 months or 5 half-lives before Visit 1
- ≥12 actuations per day of sponsor-provided SABA (Ventolin®) during the run-in period prior to Visit 2[a]

While patients 12 to 17 years were included in DENALI, AIRSUPRA is not approved in this age group; therefore, efficacy results are presented only for adults ≥18 years of age.

[a]≥2 days out of 14 days, or ≥3 days out of 15 to 21 days, or ≥4 days out of 22 or more days.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SABA, short-acting $beta_2$-agonist; SCS, systemic corticosteroids.
ClinicalTrials.gov website. Identifier NCT03847896. Accessed November 2, 2023.

Data shown are for adults ≥18 years old

DENALI Baseline Patient Demographics

Patient Characteristic	DENALI[1]			
	Albuterol/budesonide 180/160 mcg QID (n = 193)	Albuterol 180 mcg QID (n = 191)	Budesonide 160 mcg QID (n = 194)	Placebo QID (n = 192)
Age, years, mean (SD)	50.7 (15.1)	48.6 (15.4)	49.2 (15.0)	49.9 (14.4)
Female, n (%)	123 (63.7)	118 (61.8)	118 (60.8)	122 (63.5)
Prebronchodilator FEV_1, mean (SD), L	2 (0.6)	2.1 (0.6)	2.1 (0.6)	2 (0.6)
Prebronchodilator FEV_1, mean (SD), % predicted normal	65.5 (9.1)	65.5 (9.0)	65.8 (9.5)	64.7 (8.9)
Reversibility[a] in FEV_1, mean (SD), %	28.2 (13.6)	27.4 (13.3)	28.5 (14.5)	28.9 (14.3)
Pre-study background ICS therapy, n (%)	93 (48.2)	93 (48.7)	94 (48.5)	93 (48.4)

AIRSUPRA is not indicated or approved for maintenance use.

Note: Data shown for albuterol/budesonide 180/160 mcg and albuterol 180 mcg are for patients ≥18 years old.[1]
[a]Reversibility determined at screening visit; all other values in the table were determined at the baseline visit.[2]
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SD, standard deviation.
1. Data on File. REF-174347, AZPLP. 2. Chipps BE, et al. *Chest.* 2023;S0012-3692(23)00463-4.

Data shown are for adults ≥18 years old

DENALI: Primary and Key Secondary End Points

1

Dual primary end points:[1]

- Change from baseline in FEV_1 $AUC_{0\text{-}6hr}$ over 12 weeks
- Change from baseline in trough FEV_1 at Week 12

Both primary endpoints met statistical significance demonstrating the contribution of the mono-components to the efficacy of the fixed-dose combination[2]

FEV_1 $AUC_{0\text{-}6hr}$ over 12 weeks	✓ Difference in LSM change (mL) between albuterol/budesonide 180/160 mcg and budesonide 160 mcg was 77.2 (95% CI: 24.8, 129.6)[2,a]
Trough FEV_1 at Week 12	✓ Difference in LSM change (mL) between albuterol/budesonide 180/160 mcg and albuterol 180 mcg was 129.0 (95% CI: 59.6, 198.5)[2,a]

2

Key secondary end points:[1,3]

- Time to onset
- Duration of bronchodilation

Onset of bronchodilation was defined as a ≥15% increase in FEV_1 post-dose within 30 minutes on Day 1[1,3]

[a] Repeated-measures linear model analysis.[1]

AUC, area under the curve; BL, baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LSM, least squares mean.

1. Chipps BE, et al. *Chest.* 2023;164(3):585-595. 2. Data on File. REF-202630, AZPLP. 3. AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Data shown are for adults ≥18 years old

DENALI Key Secondary Analysis: Onset And Duration of Bronchodilation

Day 1 Responders[1,a]

51%
Of those receiving albuterol/budesonide 180/160 mcg

- **Time to onset (median)[b]**: **7.5** min
- **Duration of bronchodilation (mean)[c]**: **186.9** min

43%
Of those receiving albuterol 180 mcg

- **Time to onset (median)[b]**: **10.0** min
- **Duration of bronchodilation (mean)[c]**: **167.9** min

Data were not evaluated for statistical significance. Results are descriptive only.

[a]Onset of bronchodilation defined as a ≥15% increase in FEV_1 postdose within 30 minutes.[1] [b]Time to onset was defined as the time from dose to the first instance where a response (≥15% increase in FEV_1 post-dose within 30 minutes on Day 1) was observed.[2]
[c]Duration was defined as the continual period in which the response (≥15% increase in FEV_1 post-dose within 30 minutes on Day 1) was observed.[2]

1. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023 2. ClinicalTrials.gov website. Identifier NCT03847896. Accessed November 2, 2023.

Data shown are for adults and adolescents ≥12 years old

DENALI Summary of Adverse Reactions[a] Reported in ≥1% of Patients Who Used Albuterol/Budesonide 180/160 mcg

	DENALI[1,2]	
	Albuterol/budesonide 180/160 mcg (n = 197) n (%)	**Placebo** (n = 196) n (%)
Headache	10 (5.1)	14 (7.1)
Dysphonia	4 (2.0)	0
Oral/oropharyngeal candidiasis	3 (1.5)	0

Data shown for albuterol/budesonide 180/160 mcg and placebo are for patients ≥12 years old. AIRSUPRA is not approved for patients 12 to 17 years of age. AIRSUPRA is not indicated or approved for maintenance use.

[a]Adverse reactions for albuterol/budesonide 180/160 mcg with an incidence ≥1% that exceeded the incidence in MANDALA.[1]

1. AIRSUPRA™ (albuterol/ budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. Data on File. REF-174347, AZPLP.

AIRSUPRA™
(albuterol 90 mcg/budesonide 80 mcg)
Inhalation Aerosol

Important Safety Information (cont'd)

- **Do Not Exceed Recommended Dose:** Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs
- **Hypersensitivity Reactions, Including Anaphylaxis:** Can occur after administration of albuterol sulfate and budesonide, components of AIRSUPRA, as demonstrated by cases of anaphylaxis, angioedema, bronchospasm, oropharyngeal edema, rash, and urticaria. Discontinue AIRSUPRA if such reactions occur
- **Risk of Sympathomimetic Amines with Certain Coexisting Conditions:** AIRSUPRA, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines
- **Hypokalemia:** Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients. The decrease in serum potassium is usually transient, not requiring supplementation
- **Immunosuppression and Risk of Infections:** Due to possible immunosuppression from the use of inhaled corticosteroids (ICS), potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients

Please see additional Important Safety Information at the end of this presentation and please see the full Prescribing Information, including Patient Information at this presentation.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.

Important Safety Information (cont'd)

- **Oropharyngeal Candidiasis:** Has occurred in patients treated with ICS agents. Monitor patients periodically. Advise patients to rinse his/her mouth with water, if available, without swallowing after inhalation
- **Hypercorticism and Adrenal Suppression:** May occur with very high doses in susceptible individuals. If such changes occur, consider appropriate therapy
- **Reduction in Bone Mineral Density:** Decreases in bone mineral density have been observed with long-term administration of ICS. For patients at high risk for decreased bone mineral density, assess initially and periodically thereafter
- **Glaucoma and Cataracts:** Have been reported following the long-term administration of ICS, including budesonide, a component of AIRSUPRA
- **Effects on Growth:** Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. The safety and effectiveness of AIRSUPRA have not been established in pediatric patients, and AIRSUPRA is not indicated for use in this population

Please see additional Important Safety Information at the end of this presentation and please see the full Prescribing Information, including Patient Information at this presentation.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.

Important Safety Information (cont'd)

- **Most common adverse reactions** (incidence ≥ 1%) are headache, oral candidiasis, cough, and dysphonia
- **Drug Interactions:** AIRSUPRA should be administered with caution to patients being treated with:
  - Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
  - Short-acting bronchodilators (concomitant use of additional beta-agonists with AIRSUPRA should be used judiciously to prevent beta-agonist overdose)
  - Beta-blockers (may block pulmonary effects of beta-agonists and produce severe bronchospasm)
  - Diuretics or non-potassium-sparing diuretics (may potentiate hypokalemia or ECG changes). Consider monitoring potassium levels
  - Digoxin (may decrease serum digoxin levels). Consider monitoring digoxin levels
  - Monoamine oxidase inhibitors (MAOI) or tricyclic antidepressants (Use AIRSUPRA with extreme caution; may potentiate effect of albuterol on the cardiovascular system)
- Use AIRSUPRA with caution in patients with hepatic impairment, as budesonide systemic exposure may increase. Monitor patients with hepatic disease

Please see additional Important Safety Information at the end of this presentation and please see the full Prescribing Information, including Patient Information at this presentation.

ECG, electrocardiogram.

AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

Conclusions

- AIRSUPRA is the first and only rescue medication approved in the United States for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older[1]
- In the MANDALA trial, AIRSUPRA significantly reduced the risk of severe exacerbations by 28% and the annualized rate of severe exacerbations by 24% compared to albuterol[1]
- There was a significant difference in the annualized total SCS dose with AIRSUPRA vs albuterol, with a 32% reduction in mean annualized dose per patient[2]
- Most common adverse reactions are headache, oral candidiasis, cough, and dysphonia[1]
- When looking to reframe rescue therapy to help prevent asthma exacerbations, consider AIRSUPRA, a rescue treatment designed to address asthma symptoms and airway inflammation concomitantly[1]

Please see the full Prescribing Information, including Patient Information, at this presentation.

AIRSUPRA™
(albuterol/budesonide)
Inhalation Aerosol

SCS, systemic corticosteroid.

1. AIRSUPRA™ (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. In House Data, AstraZeneca. DoF REF-197604, AZPLP.

AstraZeneca is committed to conducting business with the highest standards of integrity and professionalism

If you have any comments about this presentation, please contact AstraZeneca at 1-800-236-9933

For medical information requests and access to other AstraZeneca resources, please visit AZmedical.com

You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088

Thank you for your participation today.
This concludes today's program.

Questions