Budesonide/Albuterol Sulfate Metered Dose Inhaler (BDA MDI)

U.S. Food & Drug Administration
Pulmonary-Allergy Drugs Advisory Committee

November 2022

Introduction

Ed Piper, MBBS

Global Franchise Head, Core Inhaled Products

AstraZeneca

Asthma Landscape in the US

- ~10 million asthma attacks each year in the US
  - ~1.6 million emergency department visits
  - Annual asthma deaths ranged between 3000-4000 over the last decade
  - Systemic corticosteroids used to treat attacks contribute to the burden of asthma

- Short-acting β2 agonists (SABA) are “standard of care” for asthma rescue but have no anti-inflammatory properties; SABA monotherapy is associated with an increased risk of asthma exacerbations

Asthma stats: asthma emergency department (ED) visits, 2010-2018; Data source: Emergency department visits: CDC/NCHS. National Hospital Ambulatory Medical Care Survey (NHAMCS): 2010-2018. https://www.cdc.gov/nchs/ahcd/about_ahcd.htm.

Budesonide/Albuterol Sulfate Metered Dose Inhaler (BDA MDI)

- First-in-class, fixed-dose albuterol/inhaled corticosteroid (ICS) combination in the US
- Asthma rescue treatment
  - Albuterol (short-acting β_2 agonist, SABA) provides rapid relief of symptoms
  - Budesonide (ICS) to treat airway inflammation
- Developed in partnership between Avillion and AstraZeneca

BDA MDI drug/device combination product

Clinical and Regulatory History of Budesonide and Albuterol

Budesonide

- First approved by FDA in 1998[1]
- Approved for
  - Treatment of asthma, chronic obstructive pulmonary disease and allergic rhinitis
  - Asthma maintenance treatment for patients 1 year of age and older

Albuterol Sulfate

- First approved by FDA in 1981; for adolescents and children in 1998 and 1999, respectively[2]
- Approved for
  - Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease
  - Prevention of exercise-induced bronchospasm
  - Patients 4 years of age and older (both indications)

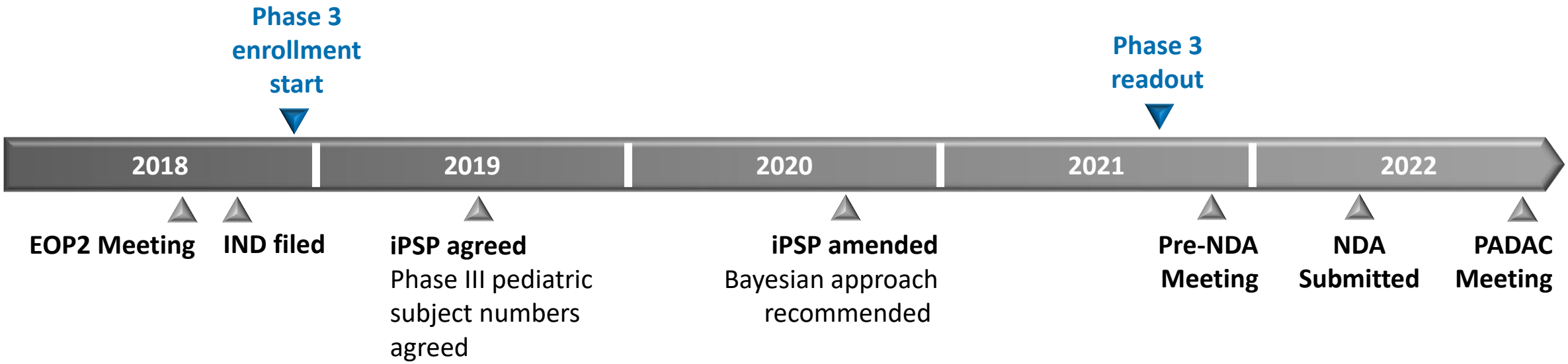
[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20441-S002_Pulmicort.cfm. Accessed October 1, 2022.
[2] Stein SW, et al. *J Aerosol Med Pulm Drug Del*. 2017;30(1):20-41.

BDA MDI Developed as a Novel Asthma Rescue Treatment to Address Burden of Asthma Exacerbations

- Complementary components
  - Albuterol to rapidly relieve symptoms
  - Budesonide to simultaneously treat airway inflammation
- BDA MDI rescue was expected to reduce the risk of asthma exacerbations vs albuterol rescue
- Built on ex-US experience of ICS/fast-acting bronchodilator combinations as rescue treatments
  - Licensed (eg, budesonide/formoterol since 2004)
  - Recommended in GINA and NAEPP guidelines

Global Initiative for Asthma. 2022. https://ginasthma.org/gina-reports/. Accessed September 13, 2022.
2020 Focused Updates to the Asthma Management Guidelines. 2020. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines. Accessed October 24, 2022.

Key Interactions With FDA



Pediatric and adolescent topics:

- Agency encouraged inclusion of children down to 4 years of age at End of Phase 2 (EOP2) Meeting
- Initial Pediatric Study Plan (iPSP)
  - MANDALA n~100 in 4-11 years and n~100 in 12-17 years
- Bayesian modeling recommended to support efficacy in pediatric populations

Clinical Development Program Supports the NDA

Phase I

LOGAN	ELBRUS	BLANC
N=91	N=67	N=12

Phase II

PT008001	ANTORA	ASPEN
N=147	N=86	N=46

Phase III

MANDALA (N=3132)

Evaluated BDA MDI as needed in moderate to severe asthma

Statistically significant and clinically meaningful 27% reduction in risk of severe exacerbation

DENALI (N=1001)

Evaluated contributions of albuterol and budesonide to BDA MDI lung function efficacy in mild to moderate asthma

Combination Rule met

TYREE (N=60)

Evaluated BDA MDI for the prevention of exercise-induced bronchoconstriction (EIB)

Effective in protecting against EIB vs placebo

Proposed Indication and Dose for BDA MDI Asthma Rescue

- **Proposed indication:** For the as-needed treatment and prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older
- **Proposed doses:**
  - **12 years of age and older:** BDA MDI 160/180 µg (2× inhalations 80/90)
  - **4-11 years of age:** BDA MDI 80/180 µg (2× inhalations 40/90)
- **Proposed maximum dose:** Use up to maximum of 6 times (12 inhalations) in 24 hours

Focus of PADAC Interaction

- BDA MDI is a first-in-class, fixed-dose albuterol/ICS combination rescue product that prevents severe asthma exacerbations with no new safety signals
- Important potential to address the continuing high rate of exacerbations for all severities of adult and pediatric asthma
- Key question is whether the totality of data is sufficient to support approval of BDA MDI in adolescents (12-17 years) and children (4-11 years)
- We view the benefit-risk assessment in both populations to be favorable
  - BDA MDI safety is consistent with the well-established safety profile of albuterol and budesonide
  - Clinical and pharmacologic rationale to extrapolate efficacy from overall population to adolescents and children
  - Supportive efficacy and safety data from ICS/fast-acting bronchodilator combinations in pediatric asthma

Agenda

Introduction	**Ed Piper, MBBS** AstraZeneca
Disease Background & Unmet Need	**Njira Lucia Lugogo, MD** University of Michigan
Clinical Development Program, Efficacy & Safety	**Mark Weinberg, MD, MBA** Avillion
MANDALA: Efficacy & Safety in Adolescents and Children	**Alison Church, MD** AstraZeneca
Clinical Context for BDA MDI in Pediatric Asthma	**Kevin R. Murphy, MD** Boys Town National Research Hospital
Conclusions	**Ed Piper, MBBS** AstraZeneca

Disease Background and Unmet Need

Njira Lugogo, MD
Clinical Professor, Department of Internal Medicine
Division of Pulmonary and Critical Care Medicine
University of Michigan
Director of Michigan Asthma Program
Ann Arbor, MI

The Burden of Asthma Is Significant

25,000,000 **Americans diagnosed with asthma**

1 *in* 10 **Children** diagnosed

13,800,000 Missed **school days** per year

14,200,000 Missed **workdays** per year

$80,000,000,000 Annual costs

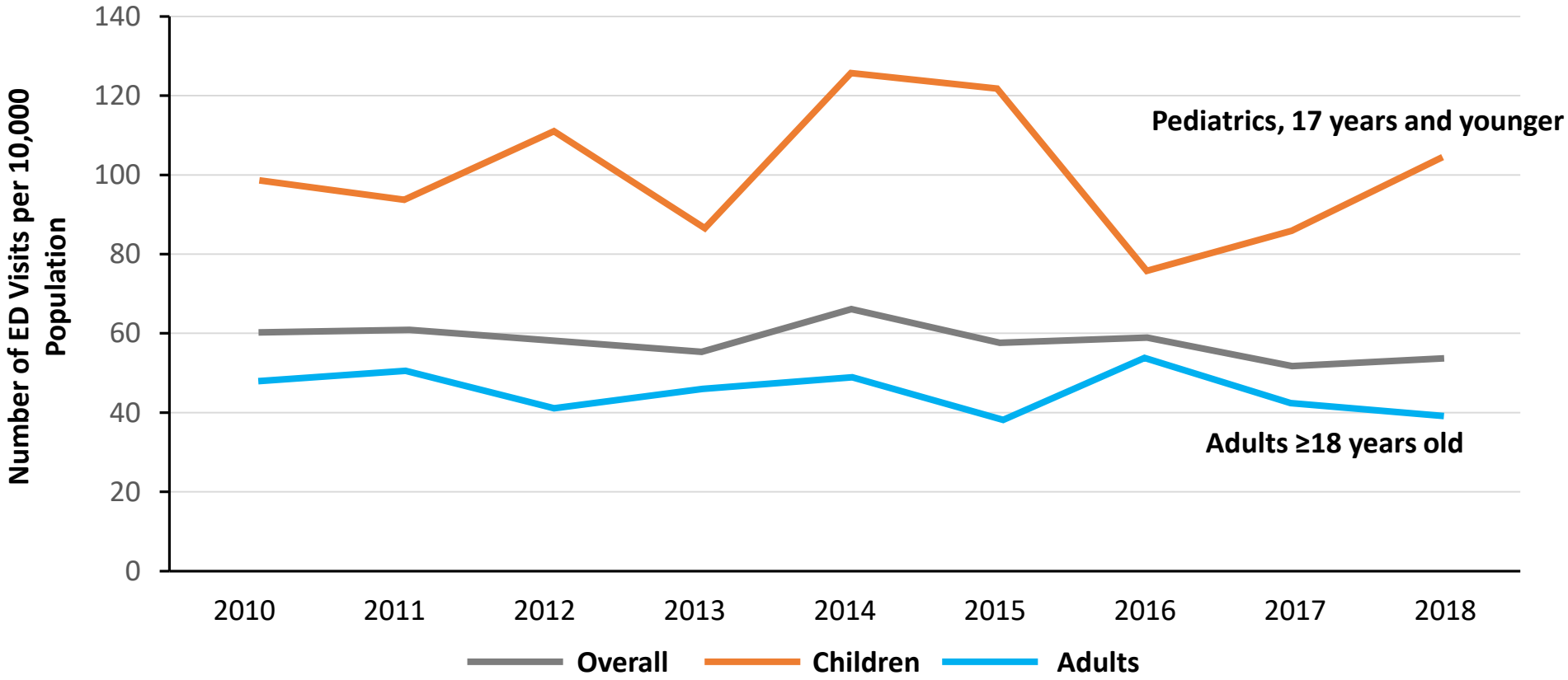
3 *in* 5 **Limit physical activity**

Data is from 2020.

Allergy & Asthma Network. https://allergyasthmanetwork.org/what-is-asthma/asthma-statistics. Accessed August 14, 2022.

Emergency Department Visits Have Not Declined

Asthma emergency department (ED) visit rate[a] (per 10,000 population) by age group[b] and year: United States 2010-2018

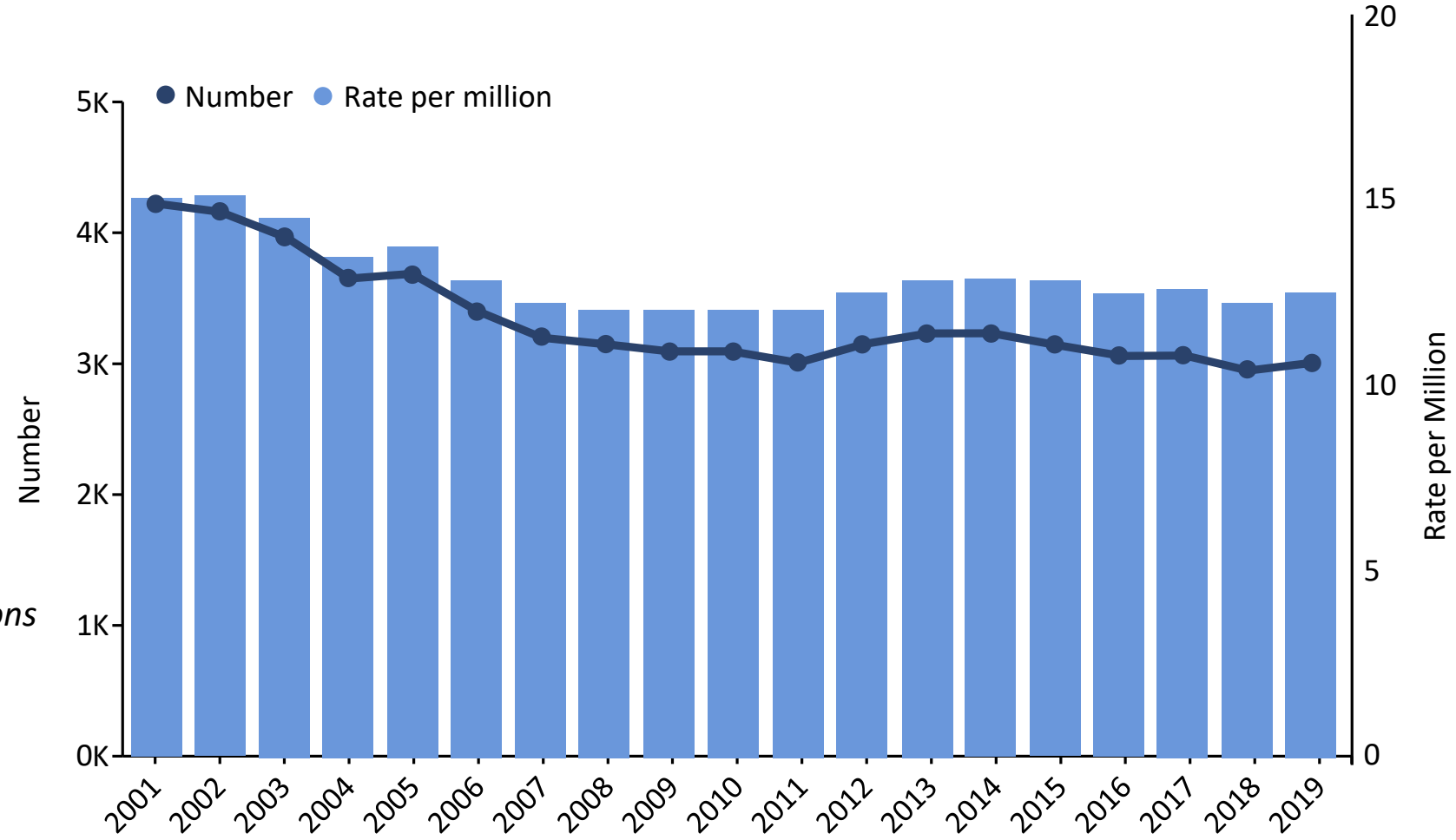


[a]Crude ED visits rate per 10,000 population.
[b]Child, persons aged 17 years and younger; Adult, persons aged 18 years and older.
Reprinted from Asthma stats: asthma emergency department (ED) visits, 2010-2018; Data source: Emergency department visits: CDC/NCHS. National Hospital Ambulatory Medical Care Survey (NHAMCS): 2010-2018. https://www.cdc.gov/nchs/ahcd/about_ahcd.htm; https://www.cdc.gov/asthma/asthma_stats/asthma-ed-visits_2010-2018.html. Accessed October 25, 2022.

Asthma Death Rates in the US Have Remained Constant Since 2007

4,145
DEATHS
annually in 2020[a]

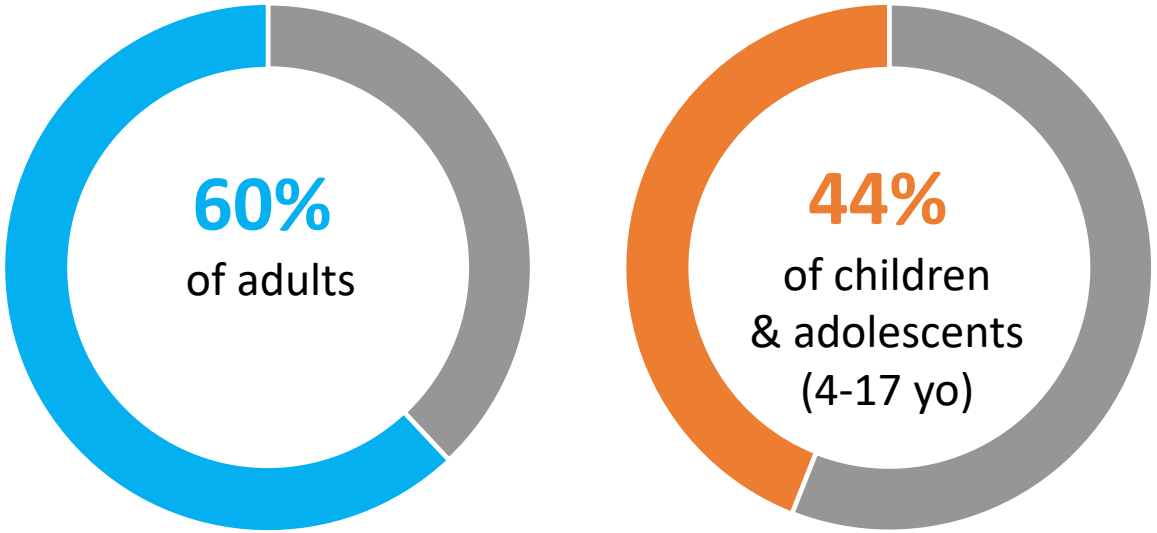
75% higher for Black persons than White persons[b]



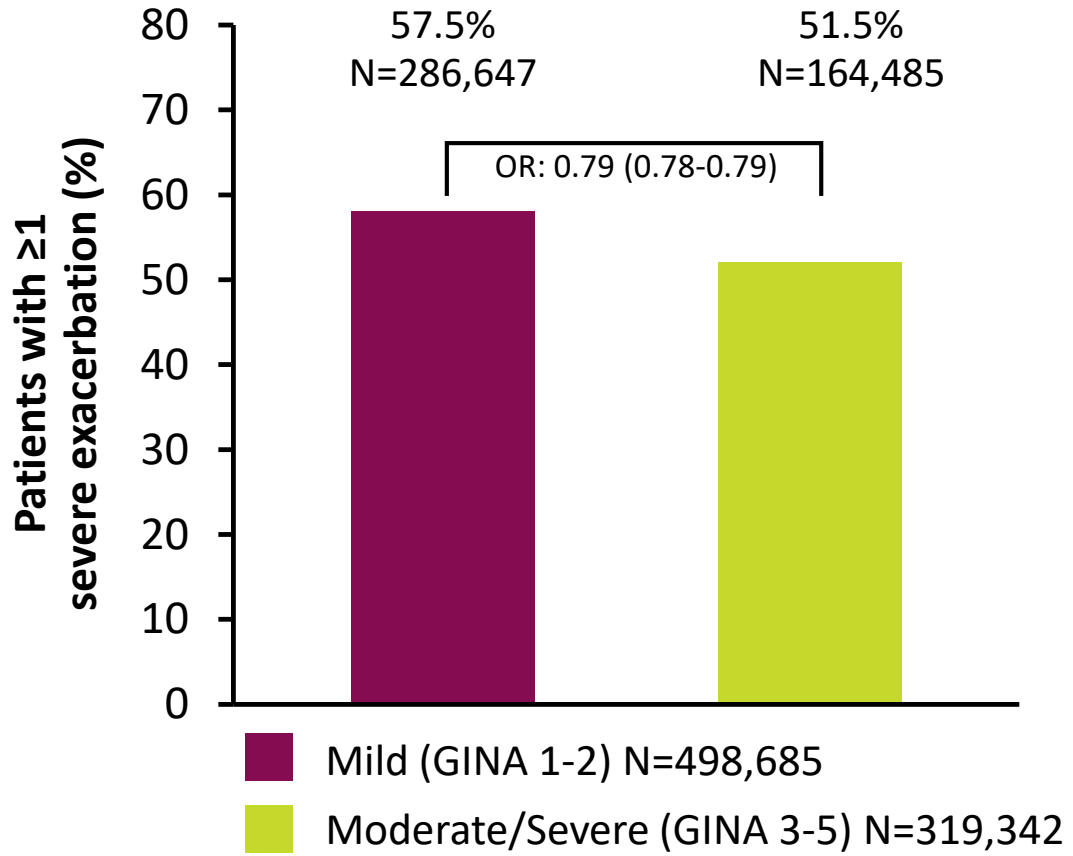
[a]CDC/National Center for Health Statistics. https://www.cdc.gov/nchs/fastats/asthma.htm; data are from 2020.
[b]Allergy & Asthma Network. https://allergyasthmanetwork.org/what-is-asthma/asthma-statistics. Accessed August 14, 2022.
CDC. https://www.cdc.gov/asthma/data-visualizations/default.htm. Accessed August 15, 2022.

More Than 50% of Patients Have Uncontrolled Asthma and Exacerbations Are Present Across Ages and Disease Severities

Percentage of uncontrolled asthma in patients with current asthma[1]



Relationship between disease severity and ≥1 severe exacerbation[2]

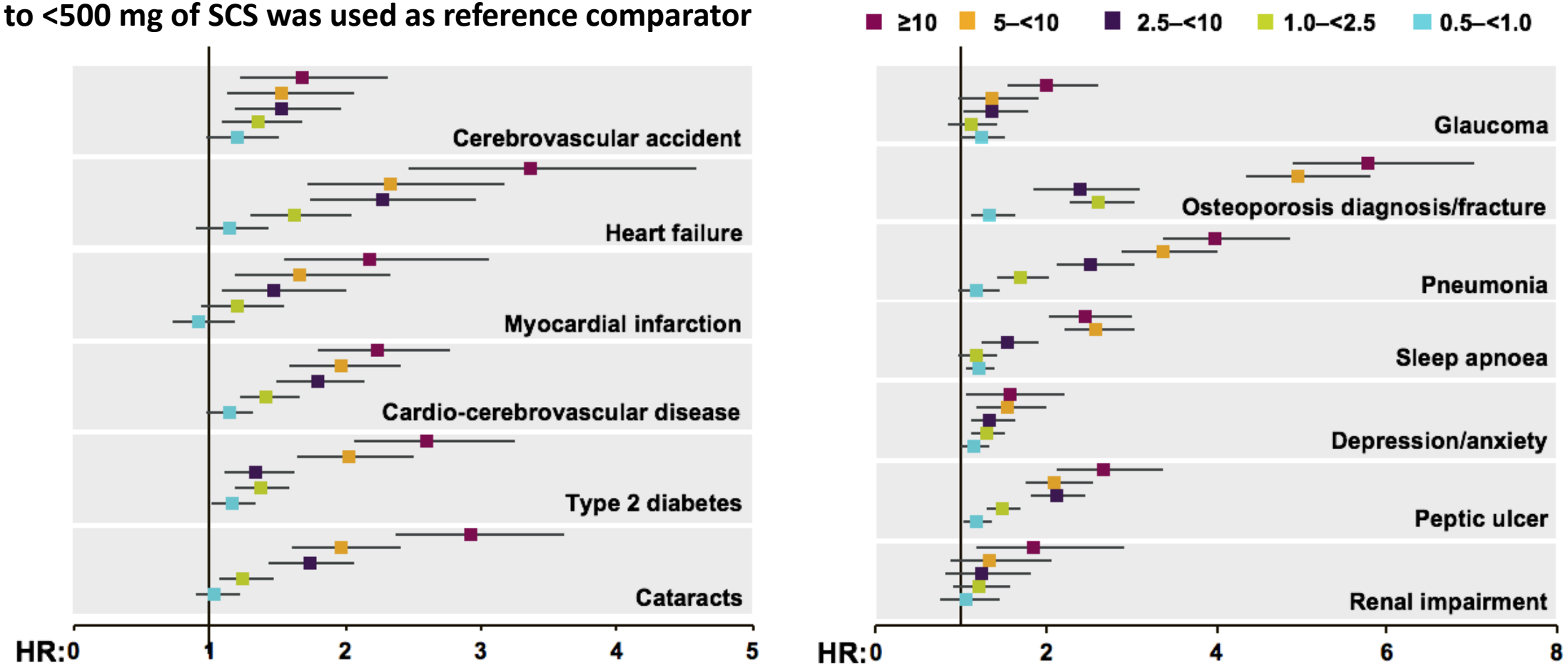


[1]CDC. https://www.cdc.gov/asthma/asthma_stats/. Accessed October 25, 2022; [2] Lugogo N, et al. *Ann Allergy Asthma Immunol*. 2020;125(5 suppl):S32.

Cumulative Lifetime Dose[a] of Systemic Corticosteroids Is Associated With Adverse Outcomes

Adults, ≥18 Years

>0 to <500 mg of SCS was used as reference comparator



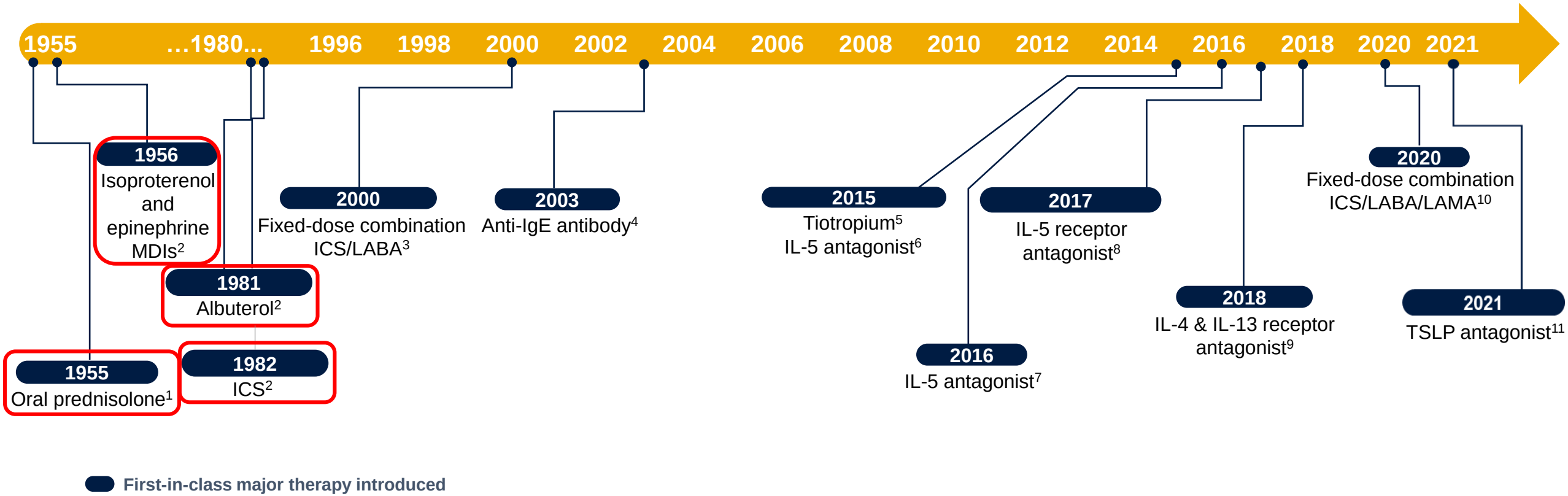
500 mg is equivalent to 2 short courses of SCS

[a] In grams, unless otherwise noted.

HR = hazard ratio; SCS = systemic corticosteroids

Adapted from Price DB, et al. *J Asthma Allergy*. 2018;11:193-204. Originally published by and used with permission from Dove Medical Press Ltd.

Exacerbations Are Present Despite Asthma Therapy Advances Over the Years



ICS = inhaled corticosteroid; IL = interleukin; LABA = long acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LM/LTRA = leukotriene modifier/leukotriene receptor antagonist; OCS = oral corticosteroid.

1. https://pubchem.ncbi.nlm.nih.gov/compound/Prednisolone. Accessed August 15, 2022; 2. Stein SW, et al. *J Aerosol Med Pulm Drug Deliv*. 2017;30(1):20-41; 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021077s029lbl.pdf. Accessed May 3, 2020; 4. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. Accessed April 13, 2020; 5. https://www.drugs.com/newdrugs/fda-approves-spiriva-respimat-tiotropium-maintenance-asthma-adults-adolescents-4263.html Accessed October 23, 2022. 6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed April 13, 2020; 7. https://www.accessdata.fda.gov/ drugsatfda_docs/label/2016/761033lbl.pdf. Accessed April 13, 2020; 8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761070s005lbl.pdf. Accessed May 21, 2020; 9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed April 12, 2020; 10. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/ US/en/Prescribing_Information/Trelegy/pdf/TRELEGY-ELLIPTA-PI-PIL-IFU.PDF. Accessed September 10, 2020; 11. Parnes JR, et al. *J Asthma Allergy*. 2022;15:749-765.

Significant Shift in Asthma Care

A fundamental change occurred in GINA (Global Initiative in Asthma) Strategy in 2019, and the treatment of asthma with **short-acting bronchodilators alone was no longer** recommended for adults and adolescents with asthma

Reddel HK, et al. *Eur Respir J*. 2019;53(6):1901046.

Published Data Informed GINA and NAEPP to Recommend Treating Symptoms and Inflammation Concomitantly

GINA 2022[1]
Adults & adolescents 12+ years

Track 1	**Steps 1-2** As-needed low-dose ICS-formoterol[a]
Plus as-needed low-dose ICS-formoterol[a]	**Step 3** Low-dose maintenance & reliever ICS-formoterol
	Step 4 Medium-dose maintenance & reliever ICS-formoterol
	Step 5 Add on LAMA. Refer for phenotypic assessment ± anti-IgE, anti–IL-5/-5R, anti–IL-4R, anti-TSLP. Consider high-dose ICS-formoterol

NAEPP Focused Updates 2020[2]
Adults & adolescents 12+ years

2020 FOCUSED UPDATES TO THE Asthma Management Guidelines

Preferred	**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
	Step 4 Daily and PRN combination medium-dose ICS-formoterol
	Step 5 Daily medium-/high-dose ICS/LABA + LAMA and PRN SABA
	Step 6 Daily high-dose ICS/LABA + OCS + PRN SABA

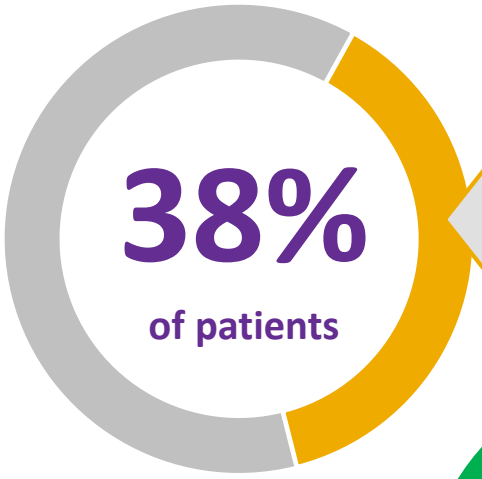
The use of ICS-formoterol is not approved for maintenance and rescue therapy in the United States. The recommendations for ICS-formoterol are based on clinical data evaluating the use of ICS-formoterol formulations and strengths not approved and not available in the United States.

[a]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 is SABA.

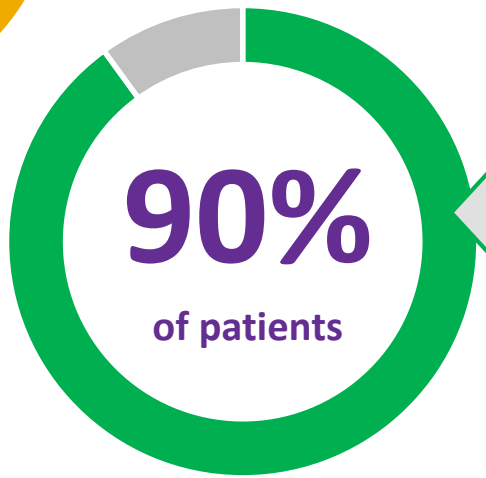
GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic agonist; NAEPP = National Asthma Education and Prevention Program; OCS = oral corticosteroid; PRN = as needed; SABA = short-acting β_2-agonist.

[1]Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org. Accessed October 25, 2022; [2]National Asthma Education and Prevention Program. 2020 Focused Updates to the Asthma Management Guidelines. Bethesda, Maryland: National Heart, Lung, and Blood Institute, National Institutes of Health. December 2020. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines. Accessed October 25, 2022.

Patient Beliefs About Inhalers Drive Important Behavior



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



Wanted treatments that provide **immediate relief**

INSPIRE Study[a] (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.

We Need to Meet Patients Where They Are

- Leverage patient behavior to improve outcomes
- Follow the science concurrently targeting the key factors driving exacerbations: inflammation and bronchoconstriction
- Align with current treatment and guideline-based recommendations by incorporating a simple and easy-to-implement switch in rescue therapy

Clinical Development Program Efficacy & Safety

Mark Weinberg, MD, MBA

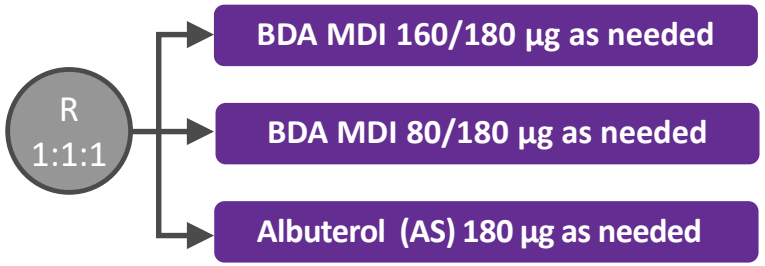
Chief Medical Officer & President, Avillion US Inc

Avillion

Phase 3 Studies in the Clinical Development Program

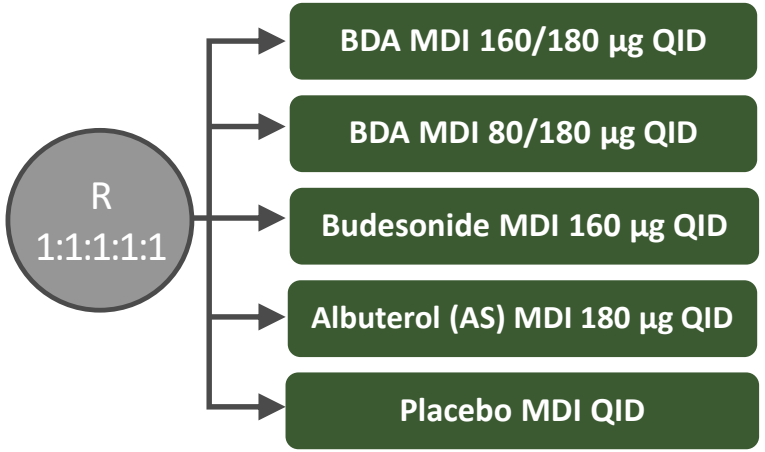
MANDALA (N=3132)

- Evaluated as-needed BDA MDI for reduction of severe exacerbation events
- 27% reduction (BDA MDI 160/180)



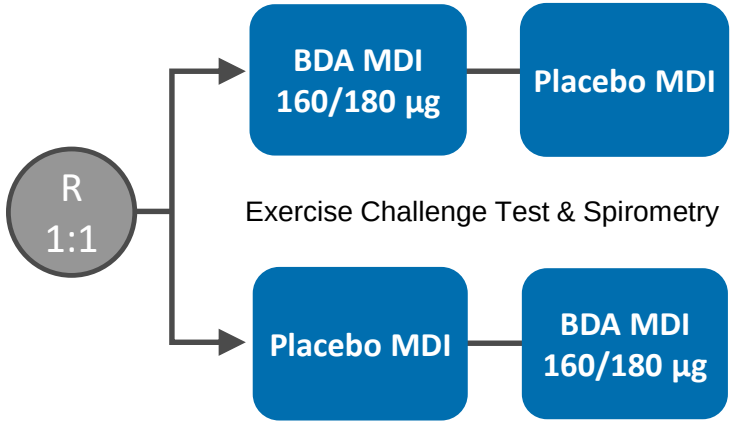
DENALI (N=1001)

- Evaluated QID scheduled dosing to assess contributions of albuterol and budesonide in BDA MDI
- FDA combination rule met

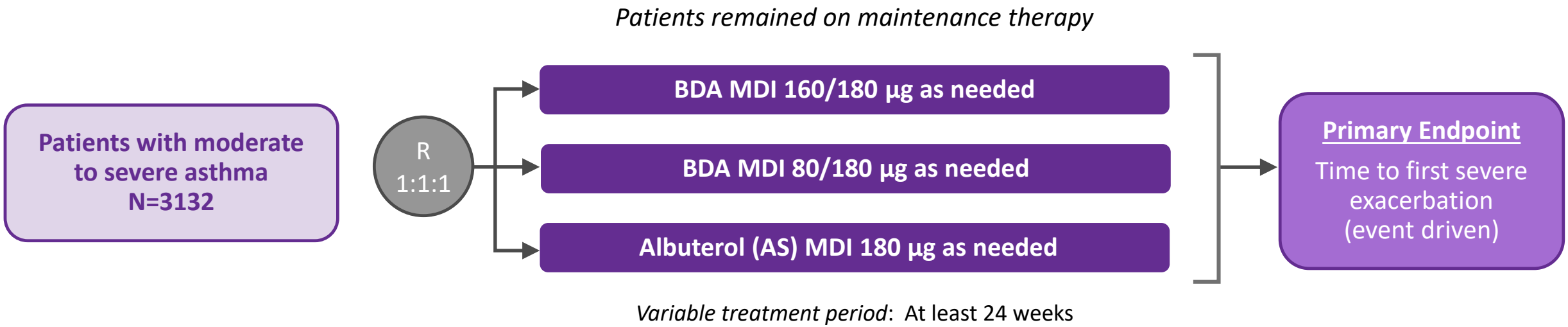


TYREE (N=60)

- Evaluated single dose in asthmatics with exercise-induced bronchoconstriction (EIB)
- BDA MDI prevented EIB



MANDALA Evaluated As-Needed BDA MDI vs Albuterol



Study Design

- Randomized, double-blind, active-controlled, parallel-group, multicenter, event-driven, Phase 3 exacerbation study at 296 sites globally

Patient Population

- ≥12 years randomized 1:1:1 and patients aged 4 to 11 years randomized to BDA MDI 80/180 or albuterol (1:1)
- History of ≥1 exacerbation in the past year and were on background maintenance medication including ICS +/- LABA with or without one additional therapy
- 92.9% of patients remained in the study for at least 24 weeks

Demographic and Baseline Disease Characteristics Were Balanced Across Treatment Arms

MANDALA

Demographic Characteristic		Number of Patients (%)			
		BDA MDI 160/180 N=1013	BDA MDI 80/180 N=1054	AS MDI 180 N=1056	Total N=3123
Age (years), mean (SD)		50.6 (15.1)	48.5 (16.7)	49.1 (17.2)	49.4 (16.4)
n (%)	≥4-<12	N/A	41 (3.9)	42 (4.0)	83 (2.7)
	≥12-<18	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
	≥18-<65	787 (77.7)	804 (76.3)	783 (74.1)	2374 (76.0)
	≥65	192 (19.0)	177 (16.8)	197 (18.7)	566 (18.1)
Sex, n (%)	Male	368 (36.3)	369 (35.0)	362 (34.3)	1099 (35.2)
Race, n (%)	White	818 (80.8)	847 (80.4)	868 (82.2)	2533 (81.1)
	Black or African American	139 (13.7)	141 (13.4)	137 (13.0)	417 (13.4)
	Asian	29 (2.9)	33 (3.1)	23 (2.2)	85 (2.7)
	Other	27 (2.7)	33 (3.1)	28 (2.7)	88 (2.9)
Ethnicity, n (%) Hispanic or Latinx		233 (23.0)	260 (24.7)	315 (29.8)	808 (25.9)
Lung function at baseline					
FEV_1 prebronchodilator (L), mean (SD)		2.0 (0.71)	2.0 (0.69)	2.0 (0.72)	2.0 (0.71)
FEV_1 prebronchodilator % predicted, mean (SD)		68.2 (16.0)	68.3 (16.5)	69.4 (16.0)	68.6 (16.2)

Statistical Testing Procedure

MANDALA

Test *primary endpoint:* time to first severe exacerbation[a]

→

Are *both* BDA MDI doses statistically significant at α = 0.05 vs. albuterol?

YES

Test *secondary endpoints* in sequential order (BDA MDI 160/180 then 80/180)[b]

1. Annualized severe exacerbation rate
2. Total systemic corticosteroid dose (annualized)[c]
3. ACQ-5 % responders at Week 24
4. AQLQ % responders at Week 24

Stop testing at first *P*>0.05

[a]Severe exacerbation defined as deterioration of asthma requiring use of SCS for ≥3 days or inpatient hospitalization or emergency room visit that required SCS.
[b]Hochberg step-up procedure; type 1 error no longer controlled at first *P*>0.05.
[c]Calculated as annualized total systemic corticosteroid dose (mg/year).
ACQ-5 is scored on a scale from 0 to 6 (lower numbers indicating better asthma control; MCID, 0.5 points); AQLQ+12 is scored on a scale from 1 to 7 (higher scores indicating better asthma-related quality of life; MCID, 0.5 points). Responders were defined as patients with a decrease (ACQ-5) or increase (AQLQ+12/PAQLQ) of ≥0.5 from baseline score.
ACQ-5 = Asthma Control Questionnaire 5-item; AE = adverse event; AQLQ+12 = Asthma Quality of Life Questionnaire for 12 years and older; MCID = minimal clinically important difference; SCS = systemic corticosteroid.

Risk of a Severe Exacerbation Reduced: 27% and 17%

MANDALA

Treatment Group	N	Number (%) of Patients With a Severe Exacerbation[a,b]	Hazard Ratio	95% CI	*P* Value (2-sided)
BDA MDI 160/180 (≥12 y)	1013	207 (20.4)	0.733	(0.611, 0.879)	<0.001
AS MDI 180 (≥12 y)	1014	266 (26.2)			

Treatment Group	N	Number (%) of Patients With a Severe Exacerbation[a,b]	Hazard Ratio	95% CI	*P* Value (2-sided)
BDA MDI 80/180 (all ages)	1054	241 (22.9)	0.835	(0.702, 0.992)	0.041
AS MDI 180 (all ages)	1056	276 (26.1)			

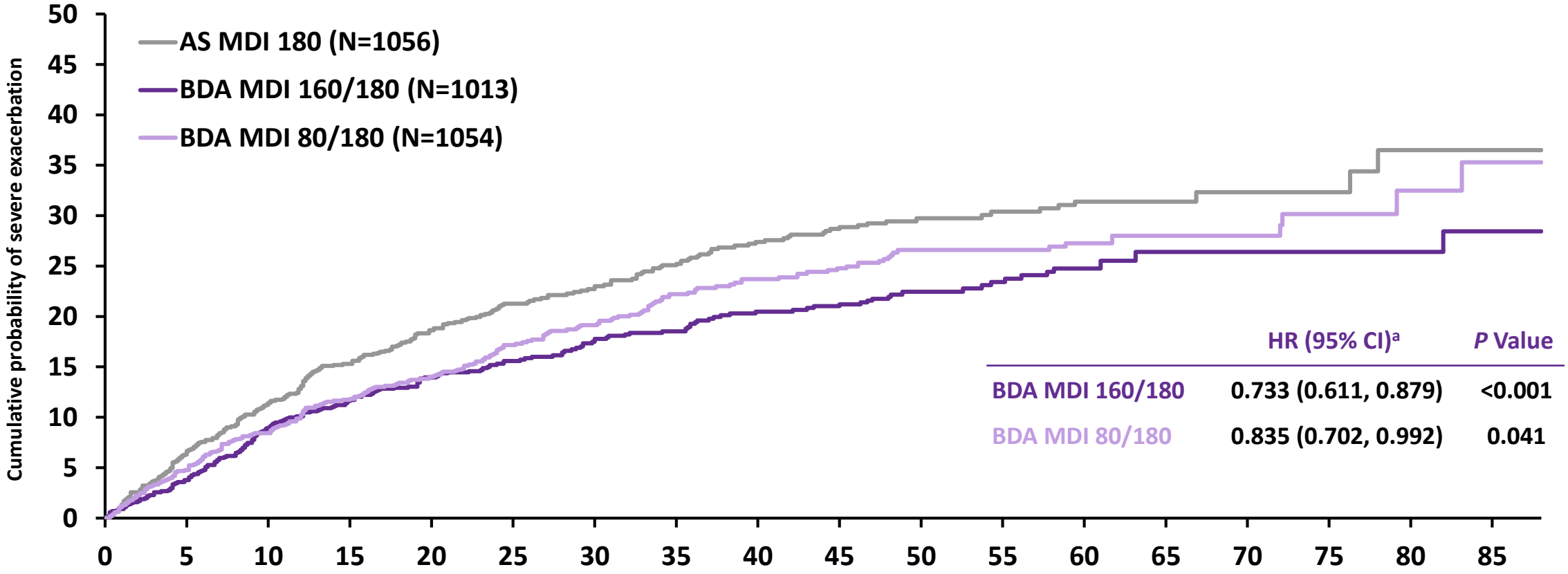
Note: Hazard ratios, 95% CIs for hazard ratios, and *P* values are estimated using a Cox regression model with treatment group, age group, region, and number of severe exacerbations in the last 12 months prior to randomization as factors. A hazard ratio less than 1 favors BDA MDI treatment groups.

[a]Deterioration of asthma requiring use of SCS for at least 3 days or inpatient hospitalization or emergency department visit that required SCSs.

[b]Before discontinuation of randomized treatment or change in maintenance therapy.

BDA MDI Demonstrated a Statistically Significant and Clinically Meaningful Reduction in Risk of a Severe Asthma Exacerbation

MANDALA



	HR (95% CI)[a]	*P* Value
BDA MDI 160/180	0.733 (0.611, 0.879)	<0.001
BDA MDI 80/180	0.835 (0.702, 0.992)	0.041

Number of patients at risk[b,c]

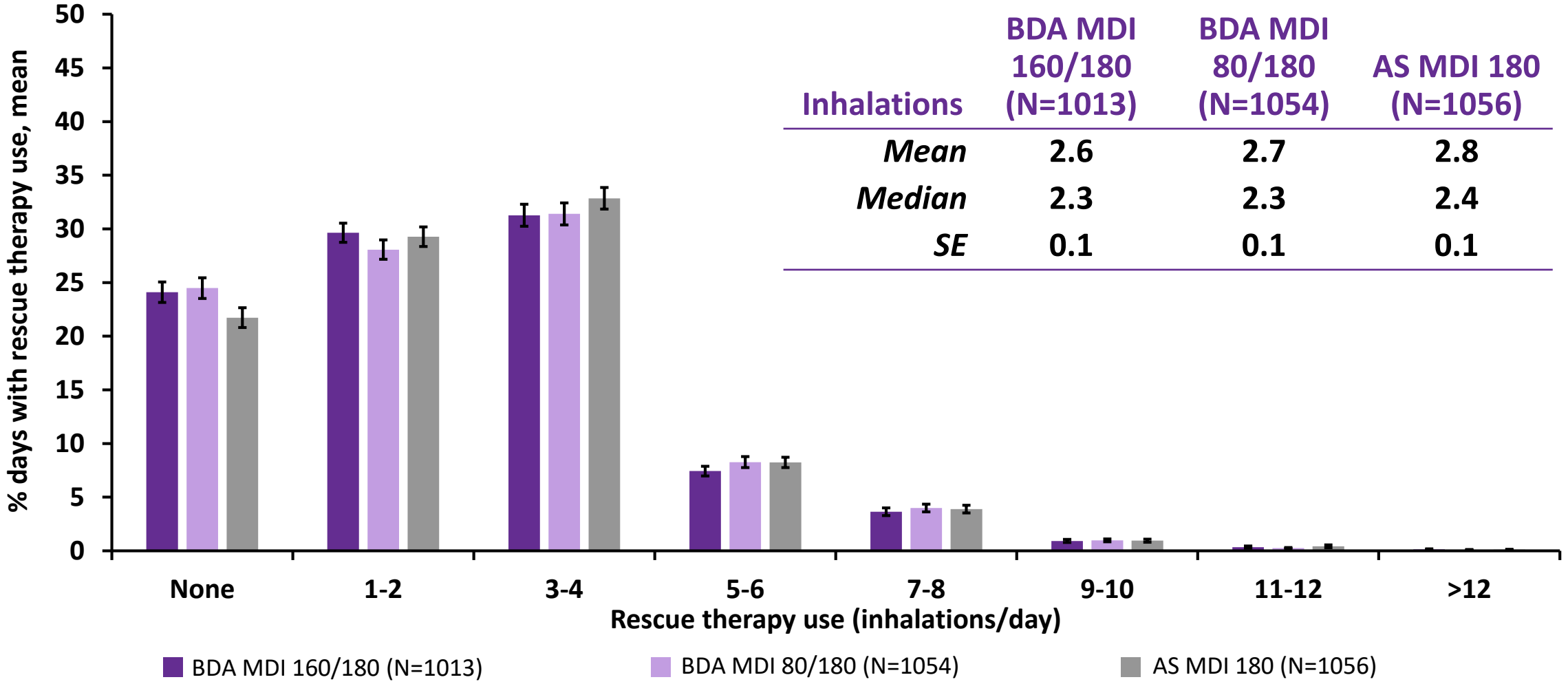
AS MDI 180	1056	973	906	845	799	571	528	504	401	381	229	215	177	76	71	33	29	9
BDA MDI 160/180	1013	963	903	870	839	601	557	546	442	431	248	233	194	75	68	41	37	11
BDA MDI 80/180	1054	993	942	896	861	610	558	528	433	415	249	229	194	84	78	35	28	4

[a]Comparison for BDA 160/180 vs AS MDI 180 µg is in patients 12 years and older.

[b]Kaplan-Meier plot truncated at 88 weeks, when <1% of patients remained in the study. Cox proportional hazards regression model adjusted for age group, region, and number of severe exacerbations in the 12 months before screening. Data are for all patients. [c]The number of patients at risk includes all ages, 4 years of age and older.

Mean Daily As-Needed Use Was <3 Inhalations (<1.5 Doses)

MANDALA



Inhalations	BDA MDI 160/180 (N=1013)	BDA MDI 80/180 (N=1054)	AS MDI 180 (N=1056)
Mean	2.6	2.7	2.8
Median	2.3	2.3	2.4
SE	0.1	0.1	0.1

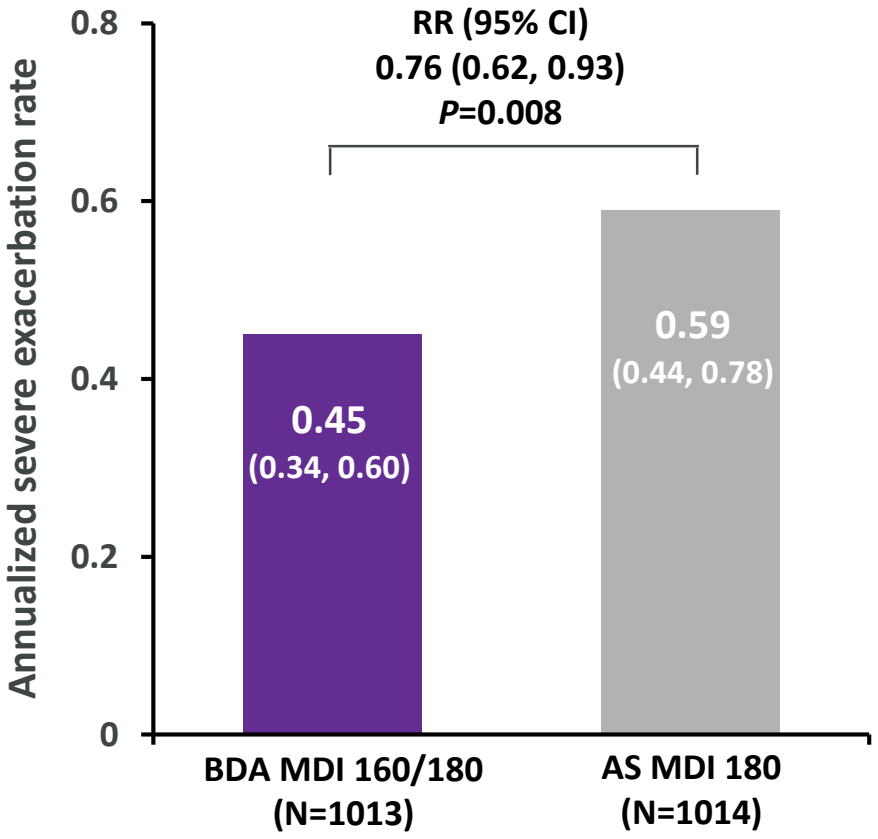
Error bars represent standard error (SE).

Decreased Annualized Severe Exacerbation Rate

MANDALA

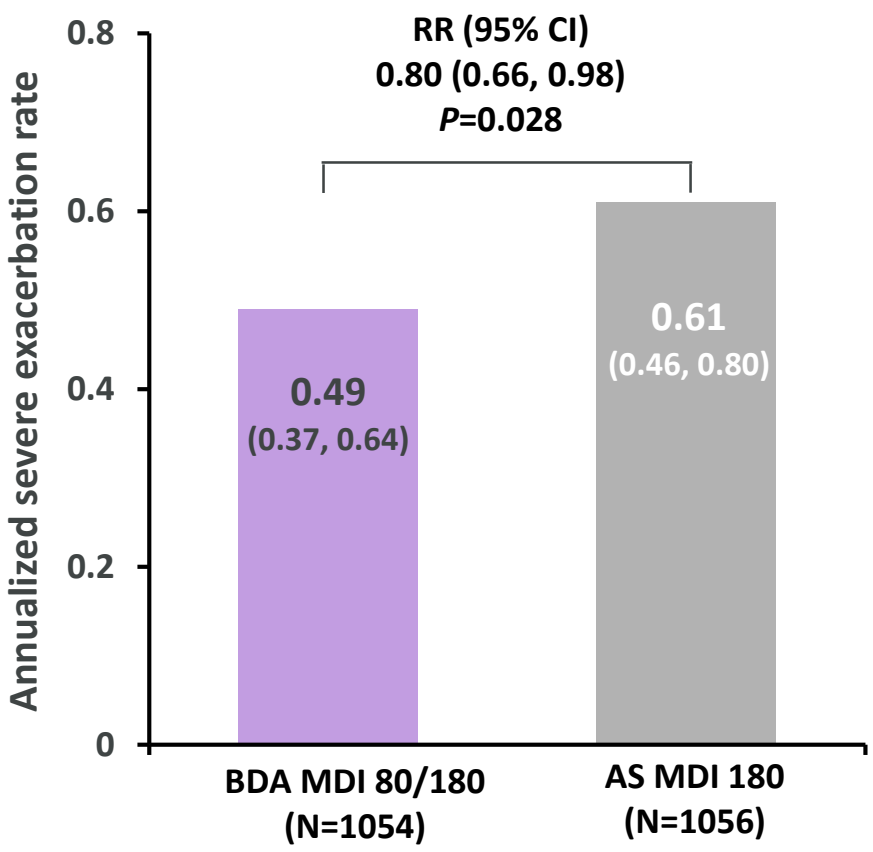
BDA MDI 160/180 vs AS MDI 180

24% reduction



BDA MDI 80/180 vs AS MDI 180

20% reduction



Additional Secondary Endpoints Demonstrated Meaningful Benefits of BDA MDI

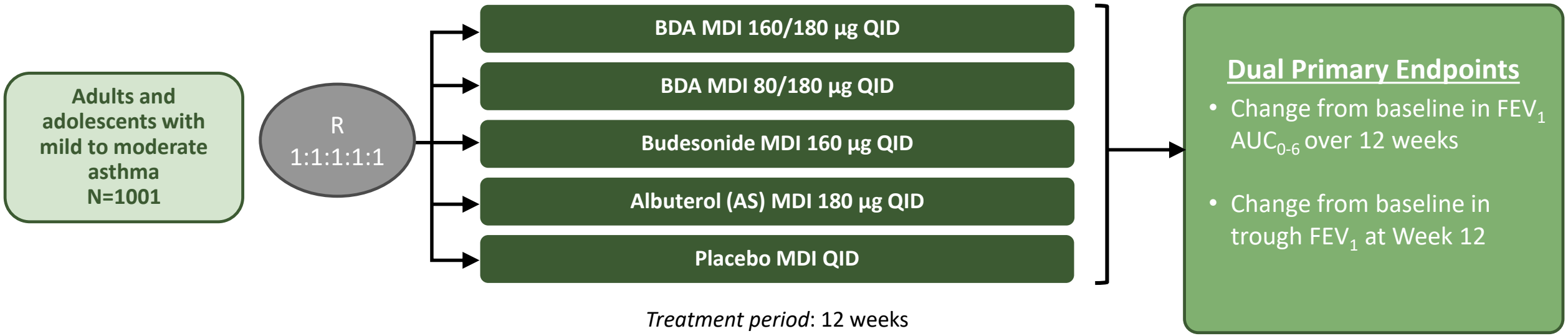
MANDALA

Secondary Endpoint	BDA MDI 160/180 (N=1013) vs AS MDI 180 (N=1014)		BDA MDI 80/180 (N=1054) vs AS MDI 180 (N=1056)	
	Treatment Comparison	*P* Value	Treatment Comparison	*P* Value
Annualized total SCS dose (% difference)[a]	-33%	0.002	-25%	0.060

Secondary Endpoint (Week 24)	BDA MDI 160/180 (N=1013) vs AS MDI 180 (N=1014)				BDA MDI 80/180 (N=1054)[b] vs AS MDI 180 (N=1056)			
	BDA MDI Estimate (nR/n)	AS MDI Estimate (nR/n)	Odds Ratio (95% CI)	Nominal *P* Value	BDA MDI Estimate (nR/n)	AS MDI Estimate (nR/n)	Odds Ratio (95% CI)	Nominal *P* Value
ACQ-5 MCID responder analysis	66.8% (677/1013)	62.1% (630/1014)	1.22 (1.02, 1.47)	0.033	64.7% (681/1052)	61.6% (650/1055)	1.13 (0.95, 1.35)	0.175
AQLQ+12 MCID responder analysis[c]	51.1% (508/994)	46.4% (461/993)	1.23 (1.02, 1.48)	0.028	49.5% (489/987)	46.4% (461/993)	1.11 (0.93, 1.34)	0.260

[a]% difference in arithmetic means, *P* values are from Wilcoxon rank sum derived from total mg per patient per year.
[b]ACQ-5 is in the FAS ≥6 years population.
[c]AQLQ+12 is in the FAS ≥ 12 years population.
ACQ-5 = Asthma Control Questionnaire 5-item; AQLQ+12 = Asthma Quality of Life Questionnaire; MCID = minimal clinically important difference; n= number patients in the analysis; nR=number of responders.

Scheduled Dosing in DENALI Evaluated the Contribution of the Individual Components of BDA on Lung Function



Treatment period: 12 weeks

Study Design

- Randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 lung function study
- 110 study sites in US, Europe, and South America

Patient Population

- ≥4 years with mild to moderate asthma as defined by GINA (2018)
- Currently treated with PRN SABA or low-dose ICS in addition to PRN SABA
- FEV_1 ≥50 to <85% predicted normal value for adults with in-clinic reversibility of FEV_1 ≥15%
- 92.7% of patients completed randomized treatment

Contribution of Albuterol in BDA MDI: Improvement in FEV_1 AUC_{0-6}

DENALI, Dual Primary Endpoint

- **BDA MDI 160/180 µg QID**
- BDA MDI 80/180 µg QID
- **Budesonide MDI 160 µg QID**
- Albuterol (AS) MDI 180 µg QID
- Placebo MDI QID

Change from baseline in FEV_1 AUC_{0-6} over 12 weeks

Visit	Comparison	n	Least-Squares Mean (mL)	Treatment Comparison: Difference in Least-Squares Means (mL)	Treatment Comparison: 95% CI	Treatment Comparison: *P* Value (2-sided)
Average over 12 weeks	BDA MDI 160/180 vs BD MDI 160	197 199	259 178	81	(28, 133)	0.003

AUC_{0-6} = area under the curve from 0 to 6 hours; FEV_1 = forced expiratory volume in 1 second; n = number of patients in analysis.

Contribution of Budesonide in BDA MDI: Improvement in Trough FEV_1

DENALI, Dual Primary Endpoint

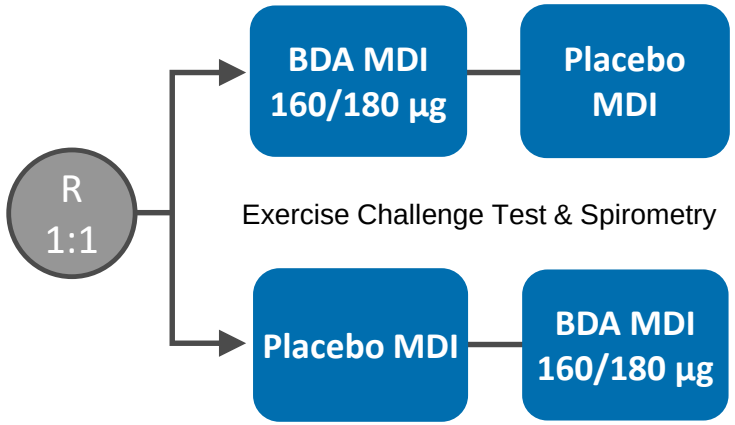
- BDA MDI 160/180 µg QID
- BDA MDI 80/180 µg QID
- Budesonide MDI 160 µg QID
- Albuterol (AS) MDI 180 µg QID
- Placebo MDI QID

Change from baseline in trough FEV_1 at Week 12

			Comparison Between Groups		
Comparison	n	Least-Squares Mean (mL)	Difference in Least-Squares Means (mL)	95% CI	*P* Value (2-sided)
BDA MDI 160/180 vs AS MDI 180	186 172	136 3	133	(64, 202)	<.001
BDA MDI 80/180 vs AS MDI 180	184 172	124 3	121	(52, 190)	<.001

$AUC_{0\text{-}6}$ = area under the curve from 0 to 6 hours; FEV_1 = forced expiratory volume in 1 second; n = number of patients in analysis.

TYREE With Pre-Exercise Dosing Demonstrated BDA MDI Protected Patients From EIB



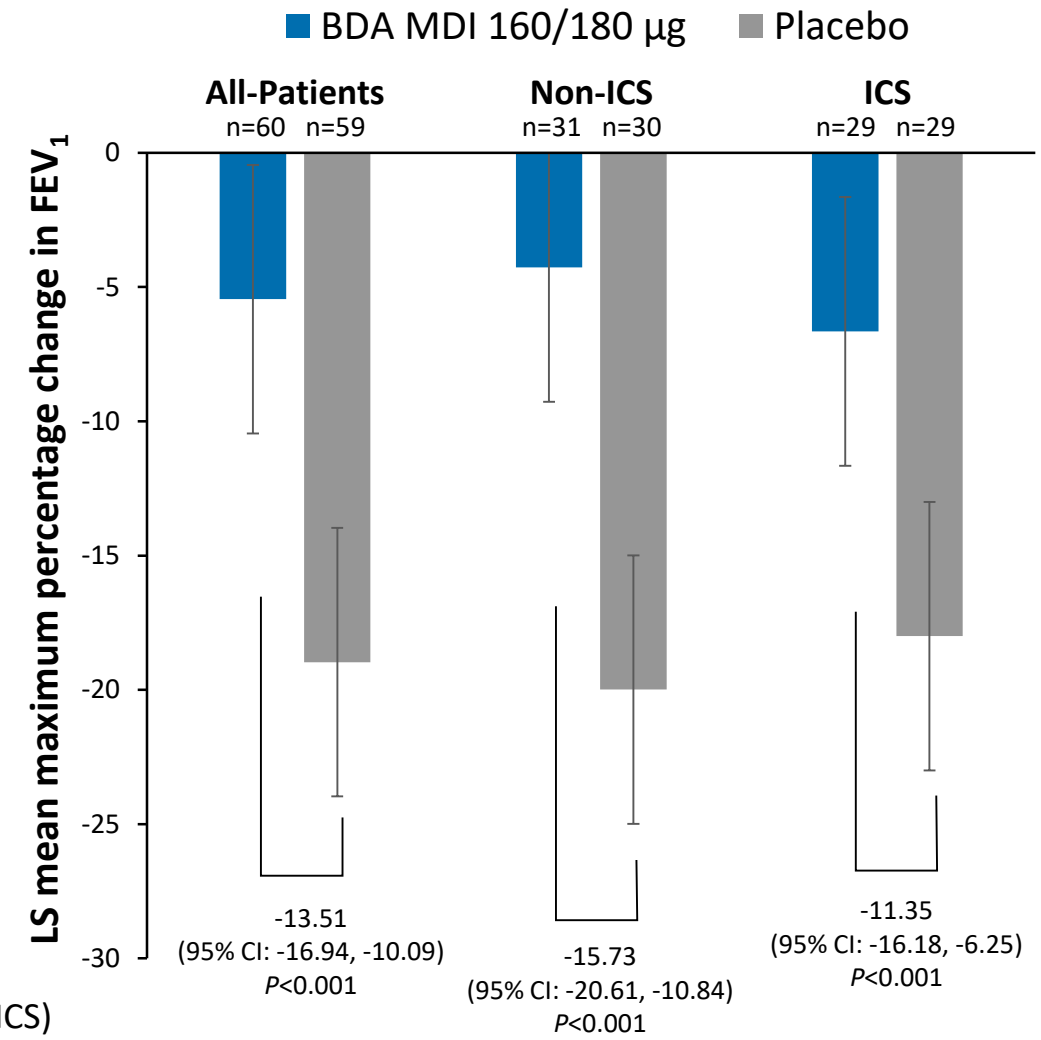
Primary endpoint:
Maximum % reduction from *post-dose, pre-exercise* baseline in FEV_1 observed up to 60 minutes post-ECT

Study Design

- Crossover study
- 3 to 7 day washout out between Visits 3 and 4
- Patients underwent treadmill ECTs on 2 separate visits

Patient Population

- ≥12 years
- Enrolled 60 patients with asthma and EIB:
  - 30 receiving only short-acting β2 agonists (SABA) PRN (non-ICS)
  - 30 receiving low to medium doses of inhaled corticosteroids plus SABA PRN (ICS)



BDA = budesonide/albuterol; ECT = exercise challenge test; EIB = exercise-induced bronchoconstriction; R = randomization.

Safety of Budesonide and Albuterol Are Well Understood

- Safety profile of budesonide and albuterol as monotherapy is well known
- Both budesonide and albuterol have been in use for >25 years
- No new safety signals in the BDA MDI program

MANDALA	DENALI
Intended as-needed use of BDA MDI and how patients will be using the product in the real world	Chronic, regular QID use of BDA MDI over 12 weeks at a substantially higher than anticipated as-needed use

Safety Overview, AEs and SAEs Were Similar Across Treatment Groups

MANDALA, Overall Population

Category	Patients, n (%)		
	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Any AE	**469 (46.2)**	**497 (47.1)**	**490 (46.4)**
AE causally related to randomized treatment	21 (2.1)	20 (1.9)	16 (1.5)
AE leading to discontinuation of randomized treatment	10 (1.0)	9 (0.9)	9 (0.9)
SAE	53 (5.2)	40 (3.8)	48 (4.5)
AE with an outcome of death	4 (0.4)	2 (0.2)	1 (0.1)

Causes of death:

- BDA MDI 160/180: 2× COVID-19; elevated glucose (reported term, no additional information); cardiac arrest
- BDA MDI 80/180: COVID-19 pneumonia; lung metastases (pneumothorax)
- AS MDI 180: COVID-19

AE = adverse event; SAE = serious adverse event.

Most Common Adverse Events by PT (≥2%) Were Similar Across Treatment Groups

MANDALA, Overall Population

Preferred Term (PT)	Patients, n (%)		
	BDA MDI 160/180[a] (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Patients with any AE	**469 (46.2)**	**497 (47.1)**	**490 (46.4)**
Nasopharyngitis	76 (7.5)	61 (5.8)	54 (5.1)
Headache	44 (4.3)	50 (4.7)	50 (4.7)
COVID-19	43 (4.2)	52 (4.9)	46 (4.4)
Back pain	27 (2.7)	23 (2.2)	20 (1.9)
Upper respiratory tract infection	26 (2.6)	31 (2.9)	26 (2.5)
Bronchitis	25 (2.5)	27 (2.6)	28 (2.6)
Hypertension	22 (2.2)	27 (2.6)	26 (2.5)
Influenza	21 (2.1)	23 (2.2)	14 (1.3)
Asthma	18 (1.8)	20 (1.9)	35 (3.3)
Sinusitis	15 (1.5)	17 (1.6)	24 (2.3)

[a]With AEs, sorted in decreasing total frequency for preferred term per BDA MDI 160/180. Patients with multiple events in the same preferred term were counted only once in that preferred term (PT).

Low Number of Systemic/Local Inhaled Corticosteroid (ICS)-Associated AEs

MANDALA, Overall Population

Groups With Selected Preferred Terms	Patients, n (%)		
	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Patients with any systemic ICS-associated AE	**33 (3.3)**	**34 (3.2)**	**40 (3.8)**
Adrenal disorders	0	7 (0.7)	2 (0.2)
Diabetes and glucose disorders	11 (1.1)	5 (0.5)	11 (1.0)
Ocular disorders	2 (0.2)	0	2 (0.2)
Skeletal disorders	5 (0.5)	8 (0.8)	12 (1.1)
Patients with any local ICS-associated AE	**20 (2.0)**	**19 (1.8)**	**14 (1.3)**
Local candidiasis infection	14 (1.4)	13 (1.2)	7 (0.7)
Aphonia/dysphonia	5 (0.5)	6 (0.6)	4 (0.4)

Patients may be counted in one or more PT categories:
Adrenal disorders include adrenocortical insufficiency acute, cortisol decreased, and secondary adrenocortical insufficiency.
Diabetes and glucose disorders include blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, diabetic metabolic decompensation, hyperglycemia, and type 2 diabetes mellitus.
Ocular disorders include cataracts and glaucoma.
Skeletal disorders also include one report of osteopenia in the BDA MDI 160/180 group.
Local candidiasis infection includes candida infection, esophageal candidiasis, oral candidiasis, and oropharyngeal candidiasis.

BDA MDI Has a Positive Benefit-Risk Ratio

- Both doses of BDA MDI used as needed resulted in statistically significant and clinically meaningful reductions in severe exacerbation risk
- As-needed BDA MDI 160/180 resulted in
  - Reductions in annualized exacerbations and mean total SCS exposure
  - Higher odds of clinically relevant improvements in asthma control and quality-of-life measures
- Both mono-components contributed to the efficacy of BDA MDI
- BDA MDI was effective in protecting patients with asthma and EIB from exercise-induced bronchoconstriction
- No new safety signals were observed
- BDA MDI 160/180 taken as needed by patients receiving a wide range of ICS-containing maintenance therapies had a superior benefit-risk ratio compared with albuterol

MANDALA: Efficacy & Safety in Adolescents and Children

Alison Church, MD

Pediatric Allergist/Immunologist

VP Late Phase Respiratory Clinical Development AZ

Unmet Need Still Exists in Adolescents and Children for New Treatments to Prevent Severe Asthma Exacerbations and Systemic Corticosteroid Use

- Approximately 50% of children with mild to moderate asthma and 2/3 children with severe asthma receiving maintenance therapy suffer from ≥1 asthma exacerbation/year[1]
- Systemic corticosteroids are the main treatment for severe asthma exacerbations
- Courses of systemic corticosteroids are associated with adverse effects in both children and adolescents
  - A recent retrospective population study evaluating patients <18 years found that 1 course of SCS used for up to 14 days was associated with a 1.4- to 2.2-fold increased risk of significant AEs within the first month after dosing[2]
  - In a meta-analysis of oral corticosteroid use in children, vomiting, mood swings/behavioral issues, and sleep disturbance were the most common ADRs after short-course SCS[3]

[1]Lanz MJ, et al. *Am J Respir Crit Care Med*. 2020;201:A1819. https://doi.org/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A1819; [2]Yao T-C, et al. *JAMA Pediatr*. 2021;175(7):723-729. doi: 10.1001/jamapediatrics.2021.0433; Published online April 19, 2021. Corrected on July 6, 2021; [3]Aljebab F, et al. *Arch Dis Child.* 2016;101(4):365-370.

ICS/Fast-Acting Bronchodilator as Rescue in Asthma: A Proven Treatment Approach for Adolescents and Children

- Studies of ICS/fast-acting bronchodilator combinations used as rescue in children and adolescents demonstrated decreased risk of severe asthma exacerbations compared with fast-acting bronchodilators alone[1,2]
- Based on these and other published data, GINA[3] and NAEPP[4] treatment guidelines recommend ICS/fast-acting bronchodilators as rescue for children, adolescents, and adults with asthma
- No treatments are approved for this use in the US
- BDA MDI was developed to fill this unmet need

[1]Bisgaard H, et al. *CHEST*. 2006;130(6):1733-1743; [2]Jorup C, et al. *Eur Respir J*. 2018;51(1):1701688; [3]Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org; [4]National Asthma Education and Prevention Program. 2020 Focused Updates to the Asthma Management Guidelines. Bethesda, Maryland: National Heart, Lung, and Blood Institute, National Institutes of Health. December 2020. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines.

Budesonide and Albuterol: Effective and Well Tolerated in Children and Adolescents With Asthma

- Budesonide (Pulmicort Turbuhaler) FDA approved in 1997 for asthma in patients ≥12 years of age
  - Currently approved in patients with asthma ≥12 months to 8 years of age (Pulmicort Respules) and ≥6 years of age (Pulmicort Flexhaler)
- Albuterol was FDA approved in 1981 for adults, followed by approvals for adolescents and children in 1998 and 1999, respectively
- Both albuterol and budesonide are commonly prescribed to children and adolescents with asthma
  - Bronchodilators were the most commonly used drug class for ages 0-11 years and the second most common drug class in adolescents in a CDC study[1]

[1]Martin CB, et al. Prescription drug use in the United States, 2015–2016. NCHS Data Brief, no 334. Hyattsville, MD: National Center for Health Statistics. 2019. https://www.cdc.gov/nchs/products/databriefs/db334.htm.

BDA MDI Pediatric Regulatory Background

- Pre-IND meeting (2015): FDA recommended to include children in addition to patients ≥12 years
- EOP2 meeting (2018): FDA advised inclusion of children ≥4 years in the Phase 3 Program
- Initial Pediatric Study Plan
  - Waiver for treatment of patients <4 years
  - MANDALA: Target approximately 100 adolescents and 100 children ≥4 years
- Requirements of Pediatric Research Equity Act (PREA) met
- Given the small number of adolescents and children in the Phase 3 program, FDA suggested Bayesian analyses would be useful based on the scientific rationale for extrapolation

EOP2 = End of Phase 2.

Clinical and Pharmacologic Rationale for Extrapolation of Benefit Across Age Groups[1]

MANDALA

- FDA guidance: When adult data are available in conditions existing in both adults and children, evidence of clinical benefit from the drug in adults can provide support for the prospect of direct benefit in children[2]
- Across adults, adolescents, and children
  - *Similar* airway inflammation and bronchoconstriction during exacerbations[3]
  - Guidelines use the same principles for diagnosis, assessment, and treatment strategies[4]
  - Treatment of severe exacerbations is the same
  - Similar treatment effects of rescue ICS/fast-acting bronchodilators on severe exacerbations
  - The same endpoints in clinical trials are used to measure efficacy
- A recent study shows that adolescents and adults with asthma have comparable inflammatory biomarker profiles [5]

[1]Committee for Medicinal Products for Human Use. ICH Harmonised Guideline Pediatric Extrapolation: E11A, Step 2b. April 4, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf; [2]Ethical Considerations for Clinical Investigations of Medical Products Involving Children. Draft Guidance for Industry, Sponsors, and IRBs. September 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children; [3]Chedevergne F, et al. *Arch Dis Child.* 2000;82(suppl II):ii6-ii9; [4]Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org; [5]Beuther DA, et al. *J Allergy Clin Immunol Pract*. 2022;S2213-2198(22)00822-4.

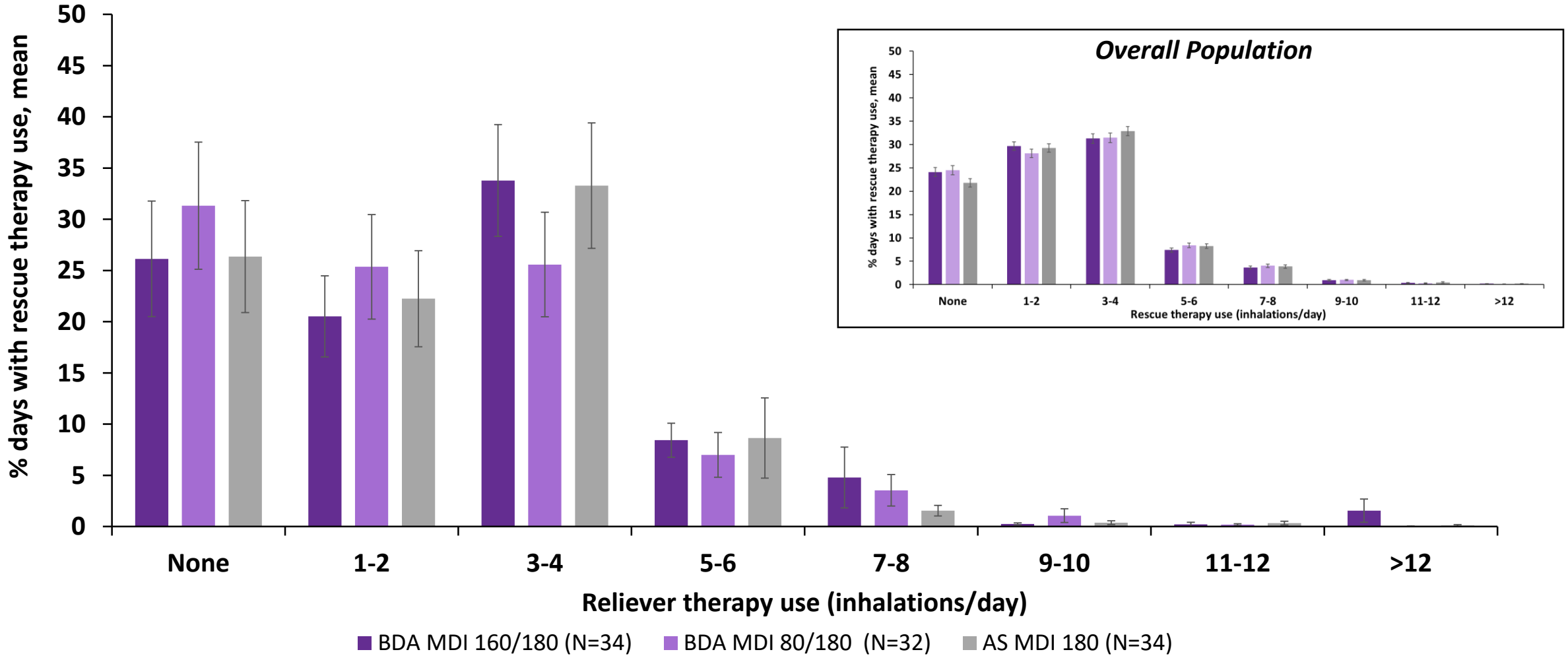
Adolescents: Demographic and Baseline Disease Characteristics Were Generally Balanced Across Treatment Arms

MANDALA, Adolescents ≥12 to <18 Years

Characteristic		Number of Patients (%)		
		BDA MDI 160/180 N=34	BDA MDI 80/180 N=32	AS MDI 180 N=34
Age (years), mean (SD)		14.3 (1.9)	13.3 (1.3)	14.3 (1.8)
Sex n (%)	Male	20 (58.8)	16 (50.0)	15 (44.1)
Race n (%)	White	18 (52.9)	19 (59.4)	19 (55.9)
	Black or African American	10 (29.4)	7 (21.9)	13 (38.2)
	Asian	3 (8.8)	4 (12.5)	1 (2.9)
	Other	3 (8.8)	2 (6.3)	1 (2.9)
Ethnicity, n (%)	Hispanic or Latinx	12 (35.3)	12 (37.5)	9 (26.5)
Lung function at baseline (L)				
FEV_1 prebronchodilator, mean (SD)		2.6 (0.84)	2.2 (0.52)	2.5 (0.82)
FEV_1 prebronchodilator % predicted, mean (SD)		81.8 (12.9)	80.6 (18.1)	82.7 (15.4)

Patterns of Use: BDA MDI and Albuterol Use Is Similar and Use in Adolescents Is Similar to Overall Population

MANDALA, Adolescents ≥12 to <18 Years

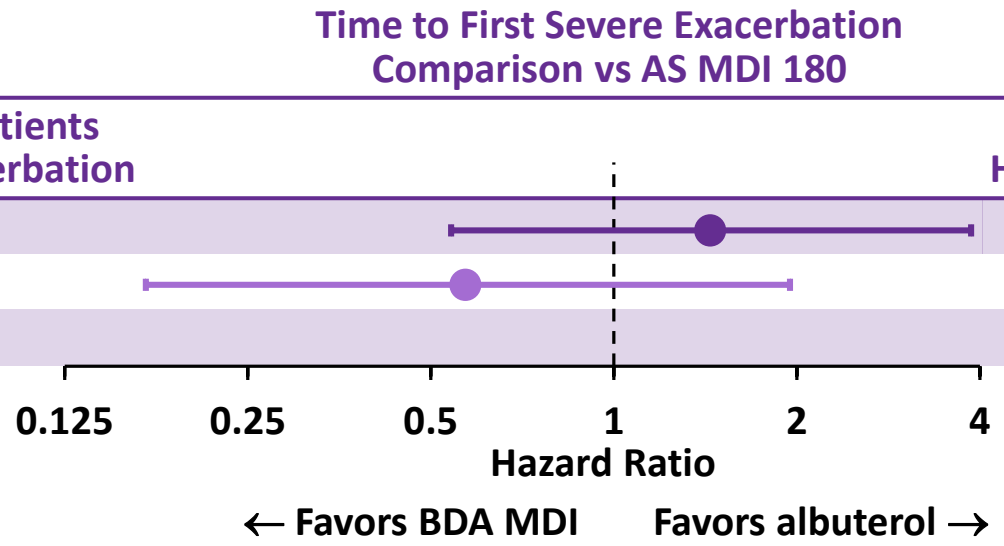


Error bars represent standard error (SE).

Adolescents Primary Endpoint: Time to First Severe Asthma Exacerbation

MANDALA, Adolescents ≥12 to <18 Years

Treatment Group	Number (%) of Patients With a Severe Exacerbation	Hazard Ratio (95% CI)	*P* Value (2-sided)
BDA MDI 160/180 (N=34)	9 (26.5)	1.441 (0.54, 3.87)	0.469
BDA MDI 80/180 (N=32)	4 (12.5)	0.570 (0.17, 1.95)	0.369
AS MDI 180 (N=34)	7 (20.6)		

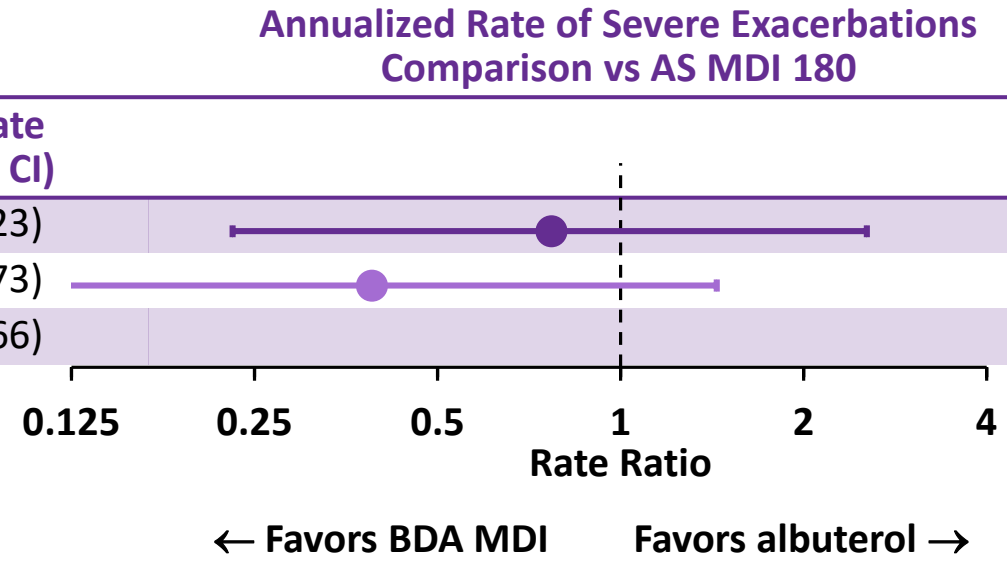


Treatment by age group interaction, *P*=0.235.

Adolescents Secondary Endpoint: Annualized Rate of Severe Exacerbations

MANDALA, Adolescents ≥12 to <18 Years

Treatment Group	Annualized Rate Estimate (95% CI)	Rate Ratio (95% CI)	*P* Value (2-sided)
BDA MDI 160/180 (N=34)	0.54 (0.23, 1.23)	0.77 (0.23, 2.54)	0.664
BDA MDI 80/180 (N=32)	0.27 (0.10, 0.73)	0.39 (0.10, 1.44)	0.157
AS MDI 180 (N=34)	0.70 (0.29, 1.66)		



Adolescents: Secondary Endpoint Results

MANDALA, Adolescents ≥12 to <18 Years

Secondary Endpoint (BDA vs AS MDI 180)	Treatment Group	Annualized Total SCS Dose, mg/subject (n)	Treatment Comparison (95% CI)	*P* Value
Annualized total SCS dose, % difference in means[a]	BDA MDI 160/180	73.6 mg (34)	-62.0%	0.723
	BDA MDI 80/180	29.4 mg (32)	-84.8%	0.498
	AS MDI 180	193.6 mg (34)		

Secondary Endpoint (BDA vs AS MDI 180)	Treatment Group	Percentage of Responders, (n)	Odds Ratio, Treatment Comparison (95% CI)	*P* Value
ACQ-5 MCID at Week 24, % responders (odds ratio)	BDA MDI 160/180	50.0% (34)	1.47 (0.56, 3.86)	0.436
	BDA MDI 80/180	65.6% (32)	2.90 (1.06, 7.94)	0.039
	AS MDI 180	41.2% (34)		
AQLQ+12 MCID at Week 24, % responders (odds ratio)	BDA MDI 160/180	37.5% (32)	1.54 (0.52, 4.54)	0.436
	BDA MDI 80/180	46.9% (32)	2.36 (0.81, 6.87)	0.116
	AS MDI 180	27.3% (33)		

[a]Percentage difference in arithmetic means.

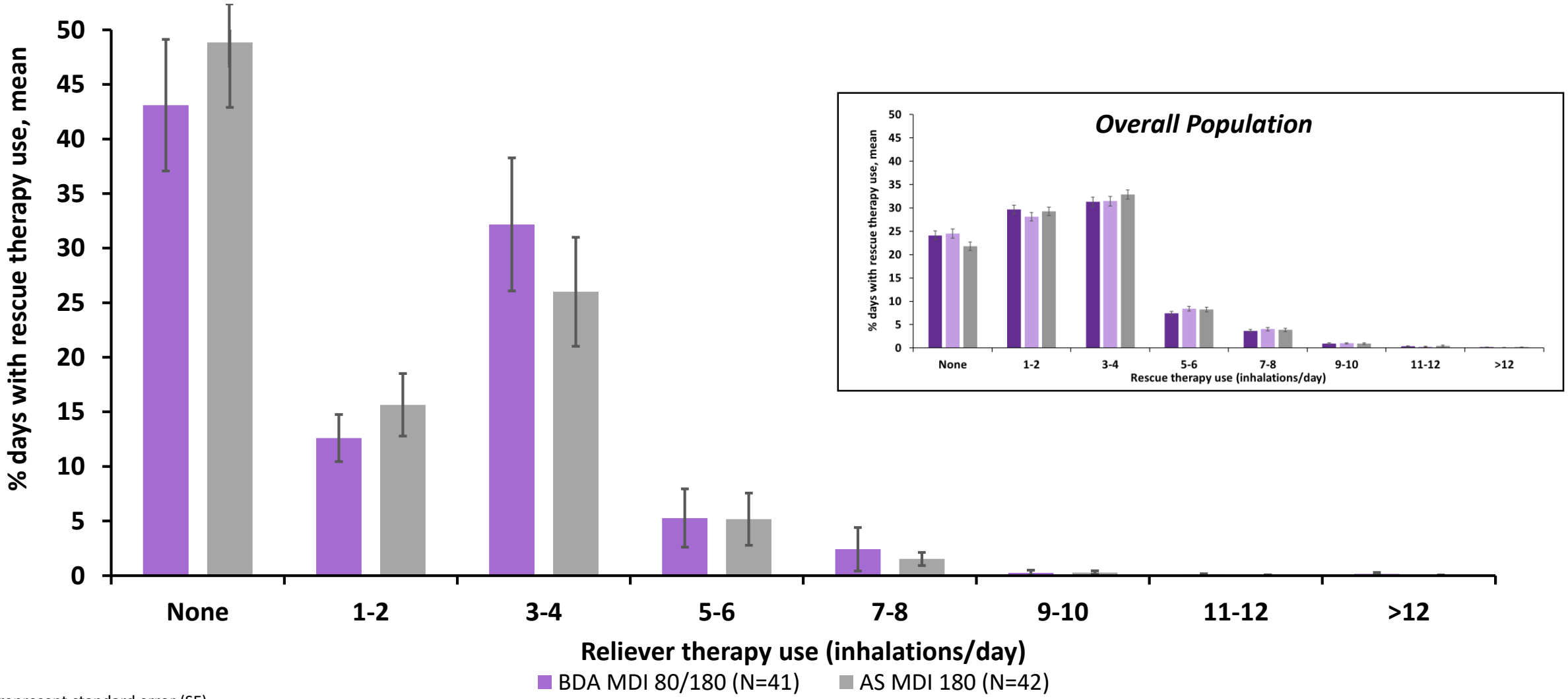
Children: Demographic and Baseline Disease Characteristics Were Balanced Across Treatment Arms

MANDALA, Children ≥4 to <12 Years

Demographic Characteristic		Number of Patients (%) BDA MDI 80/180 N=41	Number of Patients (%) AS MDI 180 N=42
Age (years), mean (SD)		9.2 (1.8)	9.1 (1.8)
Sex n (%)	Male	27 (65.9)	29 (69.0)
Race n (%)	White	28 (68.3)	25 (59.5)
	Black or African American	10 (24.4)	12 (28.6)
	Asian	1 (2.4)	2 (4.8)
	Other	2 (4.9)	3 (7.1)
Ethnicity, n (%)	Hispanic or Latinx	19 (46.3)	22 (52.4)
Lung function at baseline (L)			
FEV_1 prebronchodilator, mean (SD)		1.6 (0.56)	1.6 (0.53)
FEV_1 prebronchodilator % predicted, mean (SD)		83.5 (19.5)	84.9 (15.2)

Patterns of Use: BDA MDI Use Is Similar to Albuterol; Children Have More Days of No Rescue Use Than the Overall Population

MANDALA, Children ≥4 to <12 Years



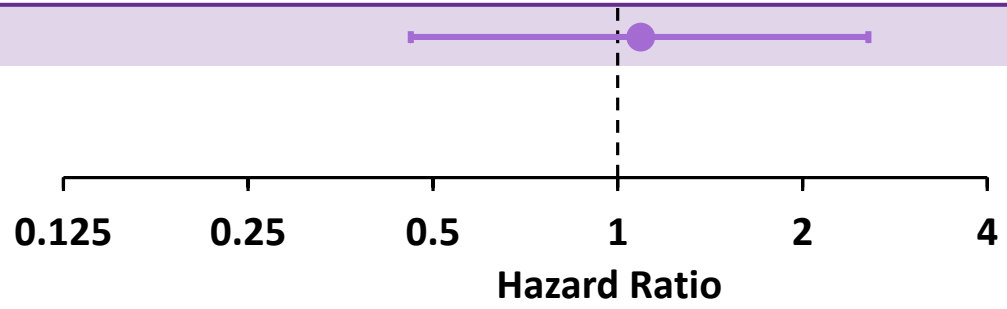
Error bars represent standard error (SE).

Children: Severe Asthma Exacerbation Results

MANDALA, Children ≥4 to <12 Years

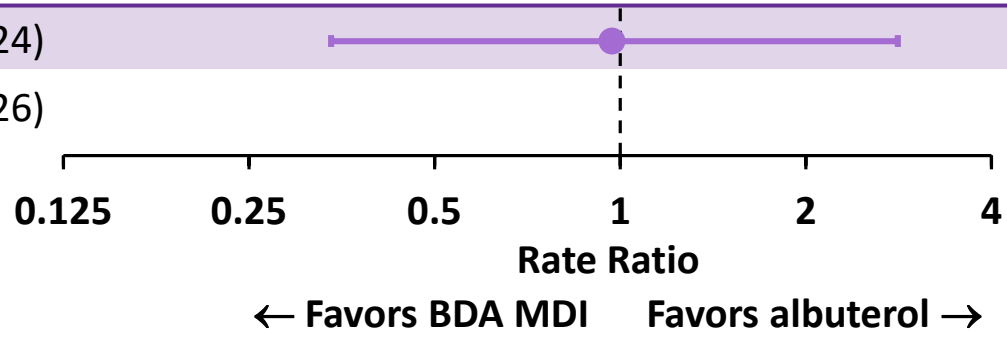
Time to First Severe Exacerbation (Primary Endpoint) Comparison vs AS MDI 180

Treatment Group	Number (%) of Patients With a Severe Exacerbation	Hazard Ratio (95% CI)	*P* Value (2-sided)
BDA MDI 80/180 (N=41)	11 (26.8)	1.09 (0.46, 2.56)	0.847
AS MDI 180 (N=42)	10 (23.8)		



Annualized Rate of Exacerbation (Secondary Endpoint) Comparison vs AS MDI 180

	Annualized Rate Estimate (95% CI)	Rate Ratio (95% CI)	*P* Value (2-sided)
BDA MDI 80/180 (N=41)	0.58 (0.27, 1.24)	0.97 (0.34, 2.82)	0.962
AS MDI 180 (N=42)	0.60 (0.28, 1.26)		



Treatment by age group interaction for primary endpoint, *P*=0.315.

Children: Secondary Endpoints

MANDALA, Children ≥4 to <12 Years

Secondary Endpoint (BDA MDI 80/180 vs AS MDI 180)	BDA MDI 80/180 (N=41) vs AS MDI 180 (N=42)			
	BDA MDI 80/180 Estimate (n)	AS MDI 180 Estimate (n)	Treatment Comparison (95% CI)	*P* Value
Annualized total SCS dose, % difference in means[a]	2.1 mg/kg/subject (41)	1.8 mg/kg/subject (41)	**+19%**	0.559
ACQ-5[b] MCID at Week 24, % responders (odds ratio)	53.8% (39)	48.8% (41)	5.0% difference **1.27 (0.53, 3.08)**	0.595
PAQLQ[c] MCID at Week 24, % responders (odds ratio)	50.0% (36)	43.2% (37)	6.8% difference **1.29 (0.49, 3.41)**	0.610

[a]Percentage difference in arithmetic means.
[b] ≥6-<12 only; endpoint not validated for children 4 and 5 years old.
[c] Only includes ages ≥7 years.

Bayesian Extrapolation From the Overall Population to Adolescent and Children Subgroups

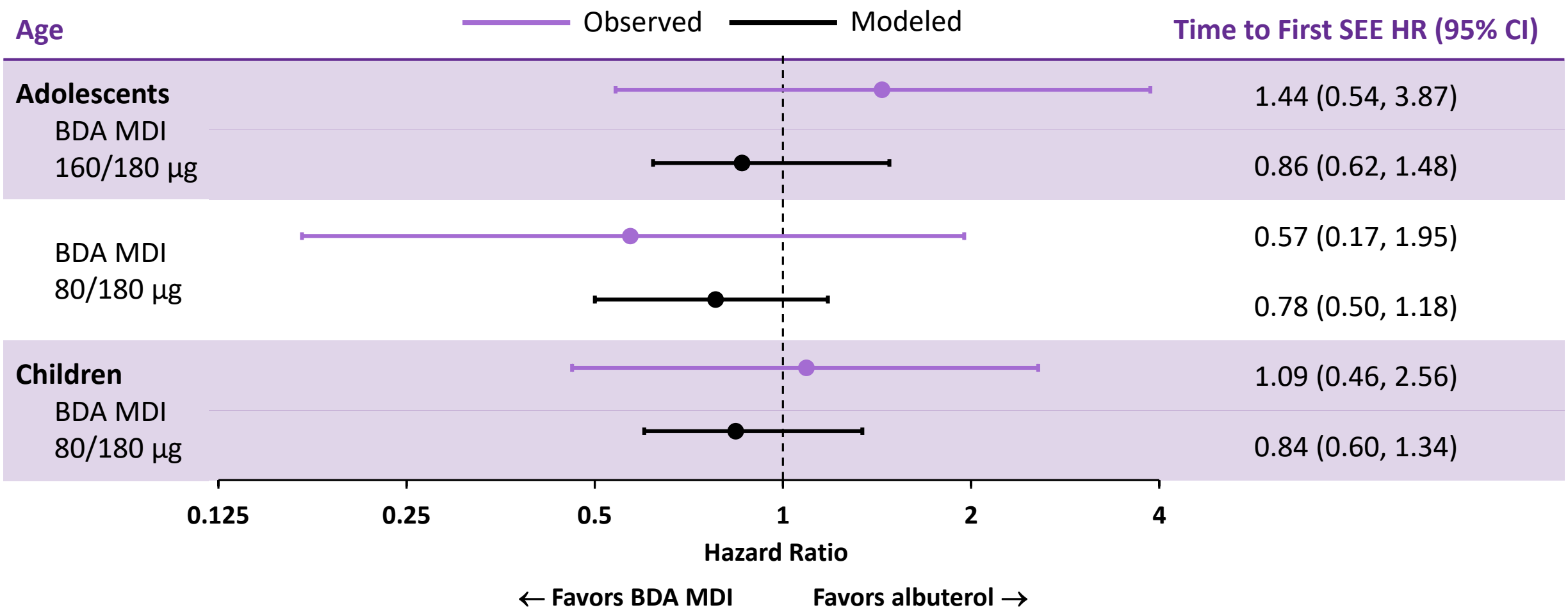
MANDALA

- Extrapolation to the 2 pediatric subgroups was performed using a Bayesian borrowing approach
  - Bayesian modeling is a *formal* synthesis of available data, providing efficacy estimates in subgroups that reflect what was learned across the trial
  - Extrapolation is an accepted model commonly used to estimate effects in subgroups[1]
  - Model-based estimates are improved because they are less prone to effects of outliers than stand-alone observations in small subgroups

[1]Committee for Medicinal Products for Human Use. ICH Harmonised Guideline Pediatric Extrapolation: E11A, Step 2b. April 4, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf.

Bayesian Analysis Supports Efficacy in Both Pediatric Subpopulations

MANDALA, Primary Endpoint



SEE = severe exacerbation event.

BDA MDI Was Well Tolerated in Adolescents

MANDALA, Adolescents ≥12 to <18 Years

Category and System Organ Class	Patients, n (%)		
	BDA MDI 160/180 (N=34)	BDA MDI 80/180 (N=32)	AS MDI 180 (N=34)
Any AE (≥12-<18 years)	**13 (38.2)**	**11 (34.4)**	**15 (44.1)**
Infections and infestations	7 (20.6)	9 (28.1)	8 (23.5)
Nervous system disorders	2 (5.9)	0	2 (5.9)
Respiratory, thoracic, and mediastinal disorders	4 (11.8)	1 (3.1)	4 (11.8)
Gastrointestinal disorders	2 (5.9)	2 (6.3)	2 (5.9)
Skin and subcutaneous tissue disorders	0	1 (3.1)	2 (5.9)
General disorders and administration site conditions	0	0	2 (5.9)
Injury, poisoning, and procedural complications	1 (2.9)	2 (6.3)	3 (8.8)
SAE	1 (2.9)	0	2 (5.9)
AEs leading to treatment discontinuation	0	0	0

BDA MDI Was Well Tolerated in Children

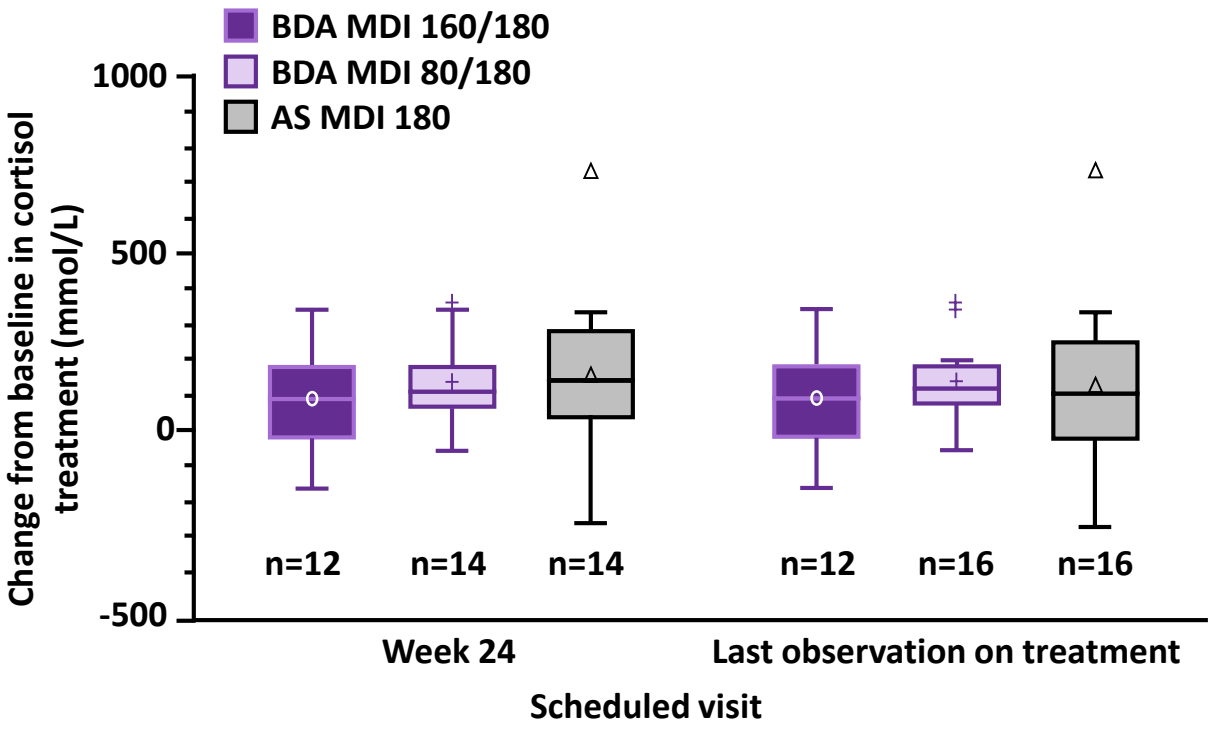
MANDALA, Children ≥4 to <12 Years

Category and System Organ Class	Patients, n (%)	
	BDA MDI 80/180 (N=41)	AS MDI 180 (N=42)
Any AE (≥4-<12 years)	**17 (41.5)**	**17 (40.5)**
Infections and infestations	11 (26.8)	11 (26.2)
Respiratory, thoracic, and mediastinal disorders	4 (9.8)	6 (14.3)
Skin and subcutaneous tissue disorders	2 (4.9)	0
Injury, poisoning, and procedural complications	2 (4.9)	1 (2.4)
SAE	1 (2.4)	1 (2.4)
AEs leading to discontinuation	1 (2.4)	0

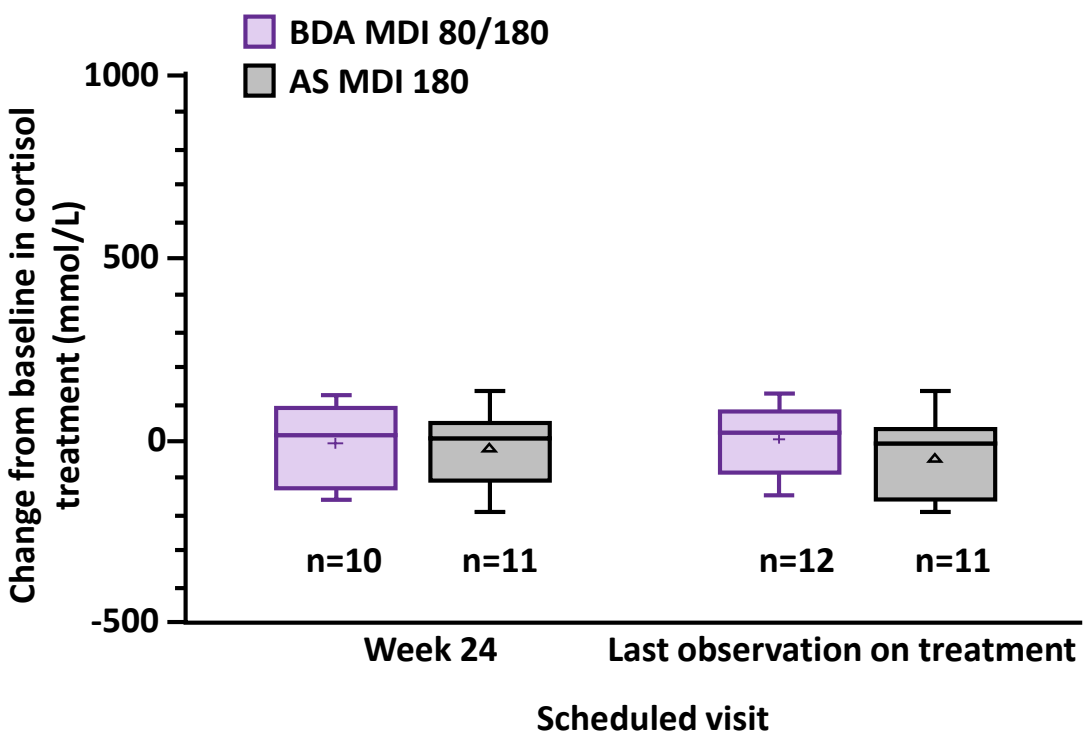
Changes in Morning Serum Cortisol: Similar Between BDA MDI and Albuterol

MANDALA

Adolescents



Children



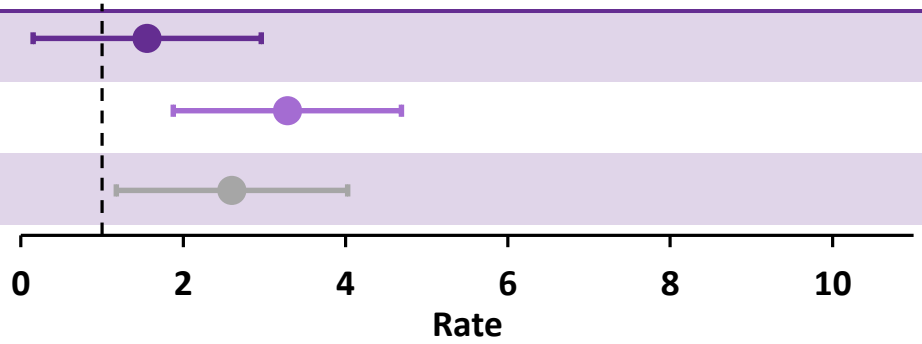
AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; N = number of patients in treatment group.
The box represents the interquartile range (IQR). The whiskers represent 1.5*IQR. Values outside of the 1.5*IQR are plotted as individual points.
The plotted symbol within the box represents the mean; the horizontal line within the box represents the median.

No Substantial Difference in Growth Velocity Between BDA MDI and Albuterol (Not a Controlled Growth Study)

MANDALA

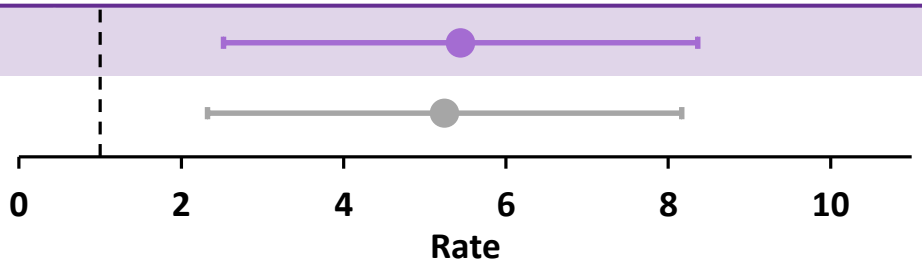
Adolescents

	Treatment Group	n	Least-Squares Mean Growth Rate (cm/year)	95% CI
Excluding implausible measurements[a]	BDA MDI 160/180 (N=34)	25	1.555	(0.150, 2.961)
	BDA MDI 80/180 (N=32)	26	3.284	(1.878, 4.690)
	AS MDI 180 (N=34)	25	2.600	(1.175, 4.025)



Children

	Treatment Group	n	Least-Squares Mean Growth Rate (cm/year)	95% CI
Excluding implausible measurements[a]	BDA MDI 80/180 (N=41)	28	5.441	(2.567, 8.316)
	AS MDI 180 (N=42)	29	5.244	(2.323, 8.164)



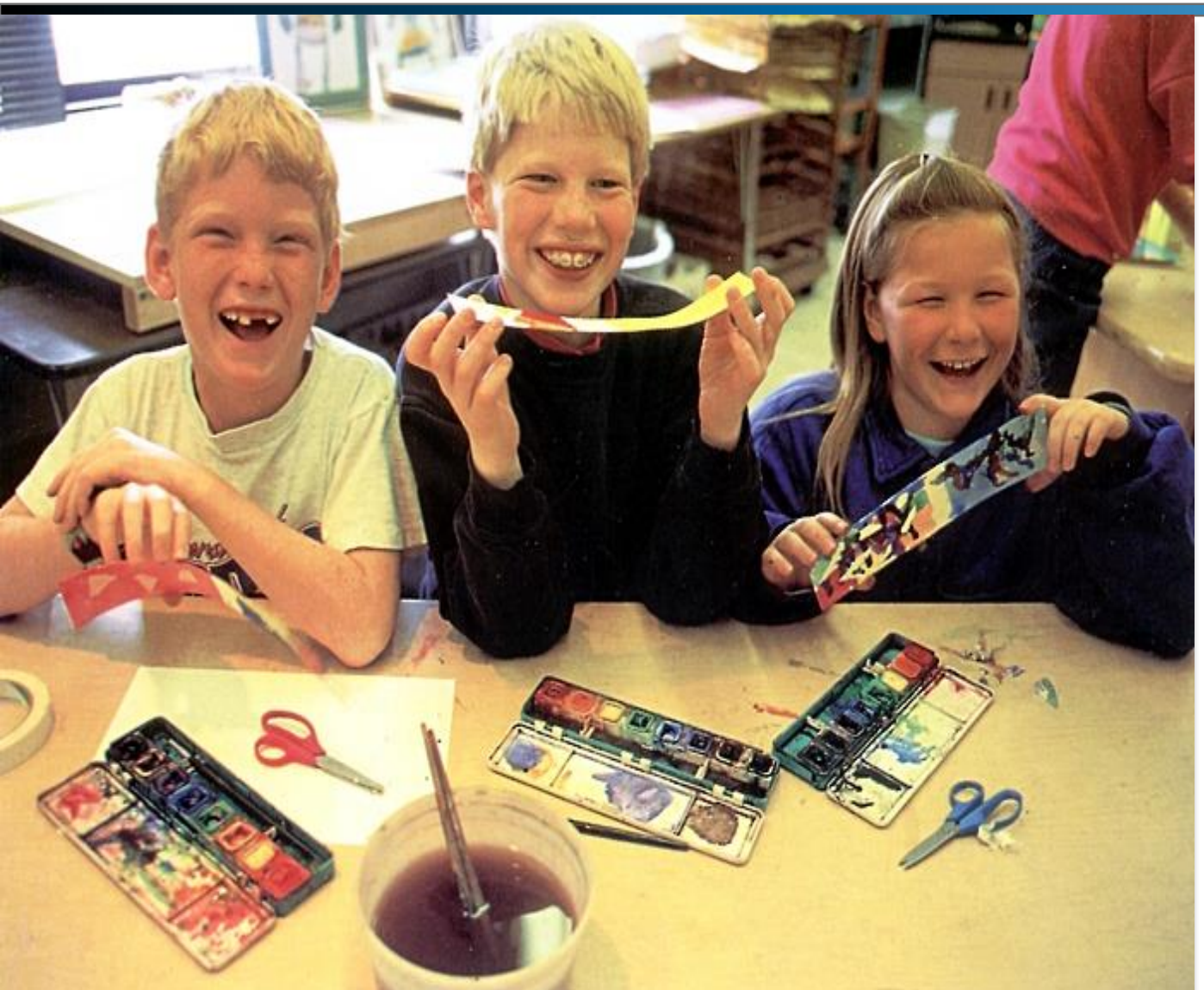
AS = albuterol sulfate; BDA = budesonide/albuterol sulfate; MDI = metered dose inhaler; N = number of patients in treatment group; n = number of patients in analysis.
Growth rate is defined as the change from baseline in height, from randomization up to the last height observation on treatment, divided by the exposure time on study (years). Growth rate is analyzed using ANCOVA, adjusted for age, gender, and randomized treatment group.
[a]Heights from 2 children with measurements greater at baseline than end of study were excluded.

Pediatric Favorable Benefit-Risk Profile

- BDA MDI safety is in line with the well-established safety profile of albuterol and budesonide
  - No new safety findings with BDA MDI were identified in pediatric subgroups
- Clinical and pharmacologic rationale for extrapolation from overall population to adolescents and children is based on similarities across the ages in
  - Airway inflammation and bronchoconstriction during an exacerbation
  - Treatment of severe exacerbations is the same
  - Guidelines using the same principals for asthma diagnosis, assessments, and treatment strategies
  - Similar treatment effects on severe exacerbations are observed with ICS/fast-acting bronchodilators as rescue
- High plausibility of BDA MDI as needed decreasing severe exacerbation risk is based on MANDALA overall population results and published literature
- A significant unmet need exists for BDA MDI in patients with asthma, including adolescents and children

Clinical Context for BDA MDI in Pediatric Asthma

Kevin R. Murphy, MD
Boys Town National Research Hospital
Director of Clinical Research
Clinical Professor
Department of Pediatrics
University of Nebraska Medical Center



Preventing Asthma Exacerbations in Adolescents and Children

Kevin R. Murphy, MD

Boys Town National Research Hospital
Director of Clinical Research

Clinical Professor
Department of Pediatrics
University of Nebraska Medical Center

Image courtesy of Dr. Murphy.

BOYS TOWN National Research Hospital®

Asthma: Most Common Chronic Disease in Adolescents and Children That Has Significant Burden of Disease

Severe Asthma Exacerbations

Healthcare Resource Utilization

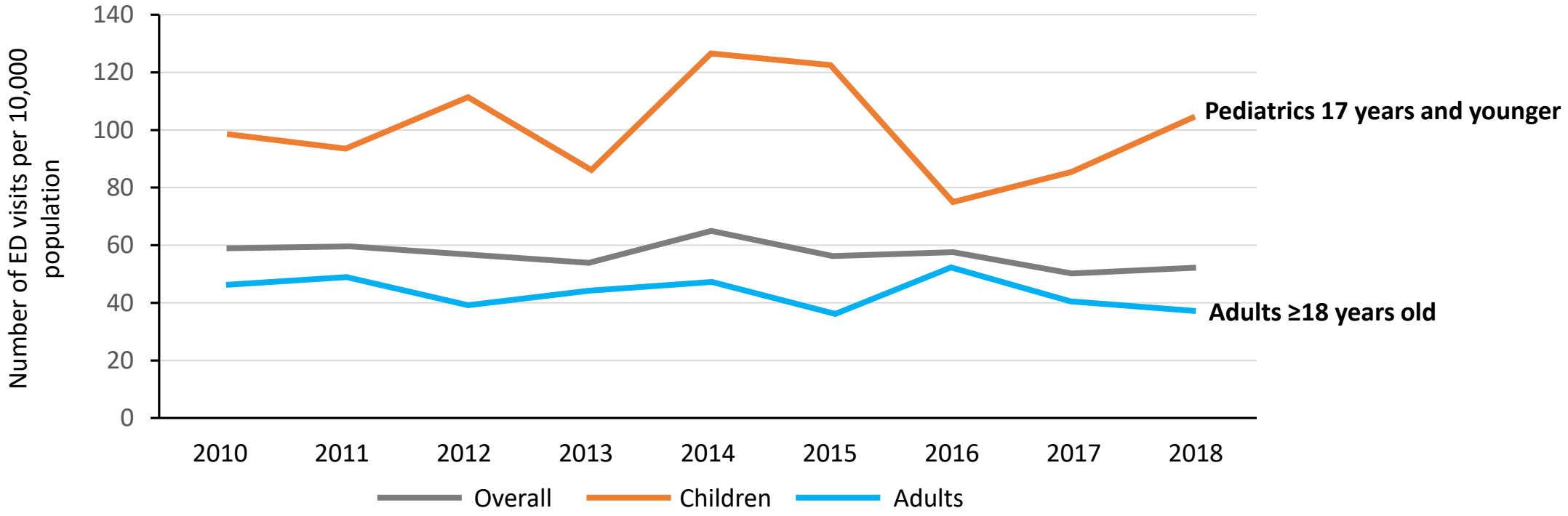
- Emergency room visits
- Hospitalizations
- Repeated systemic corticosteroid use leading to significant adverse reactions

Effects on Patient and Family Quality of Life

- Missed school
- Struggle with sleep and ability to concentrate in school
- Missed play and exercise
- Parents miss work
- Financial impact can be significant

Burden of Asthma Exacerbations in Patients ≤17 Years of Age

Asthma emergency department (ED) visit rate[a] (per 10,000 population) by age group[b] and year: United States 2010-2018



[a]Crude ED visits rate per 10,000 population.
[b]Child, persons aged 17 years and younger; Adult, persons aged 18 years and older.
Reprinted from Asthma stats: asthma emergency department (ED) visits, 2010-2018; Data source: Emergency department visits: CDC/NCHS. National Hospital Ambulatory Medical Care Survey (NHAMCS): 2010-2018. https://www.cdc.gov/nchs/ahcd/about_ahcd.htm; https://www.cdc.gov/asthma/asthma_stats/asthma-ed-visits_2010-2018.html. Accessed October 25, 2022.

Two Approaches to Address the Unmet Need in Pediatric Asthma

Preventing Severe Asthma Exacerbations

Increasing ICS maintenance dose ×7 days after worsening symptoms first appear

- STICS (5-11 years of age)[1]

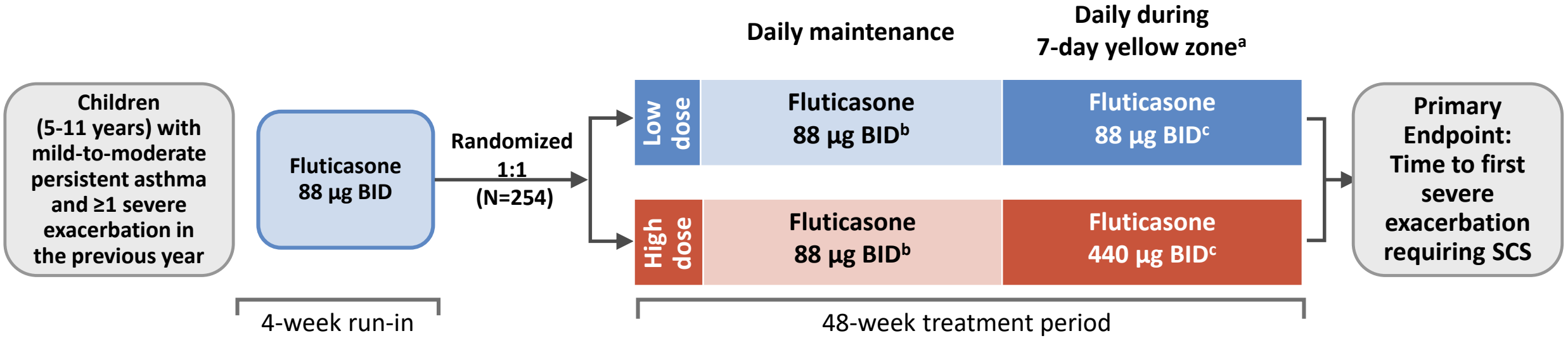
Combination of ICS/ fast-acting bronchodilator used as rescue to treat worsening symptoms when they begin

- Meta-analysis of 6 studies (adolescents)[2]
- TREXA (6-18 years of age)[3]
- STAY (4-11 years of age)[4]

[1]Jackson DJ, et al. *N Engl J Med*. 2018;378(10): 891-901; [2]Jorup C, et al. *Eur Respir J*. 2018;51(1):1701688; [3]Martinez FD, et al. *Lancet.* 2011;377(9766):650-657; [4]Bisgaard H, et al. *Chest*. 2006;130(6):1733-1743.

Study Design

STICS[1]



- Randomized, double-blind, parallel-group trial (17 centers in the US)
- Patients treated for 48 weeks with maintenance low-dose ICS (FP 88 µg BID) and randomized to either continue the same dose (low-dose group) or use a quintupled dose (high-dose group) for 7 days at the early signs of loss of asthma control ("yellow zone")

Clinical Question

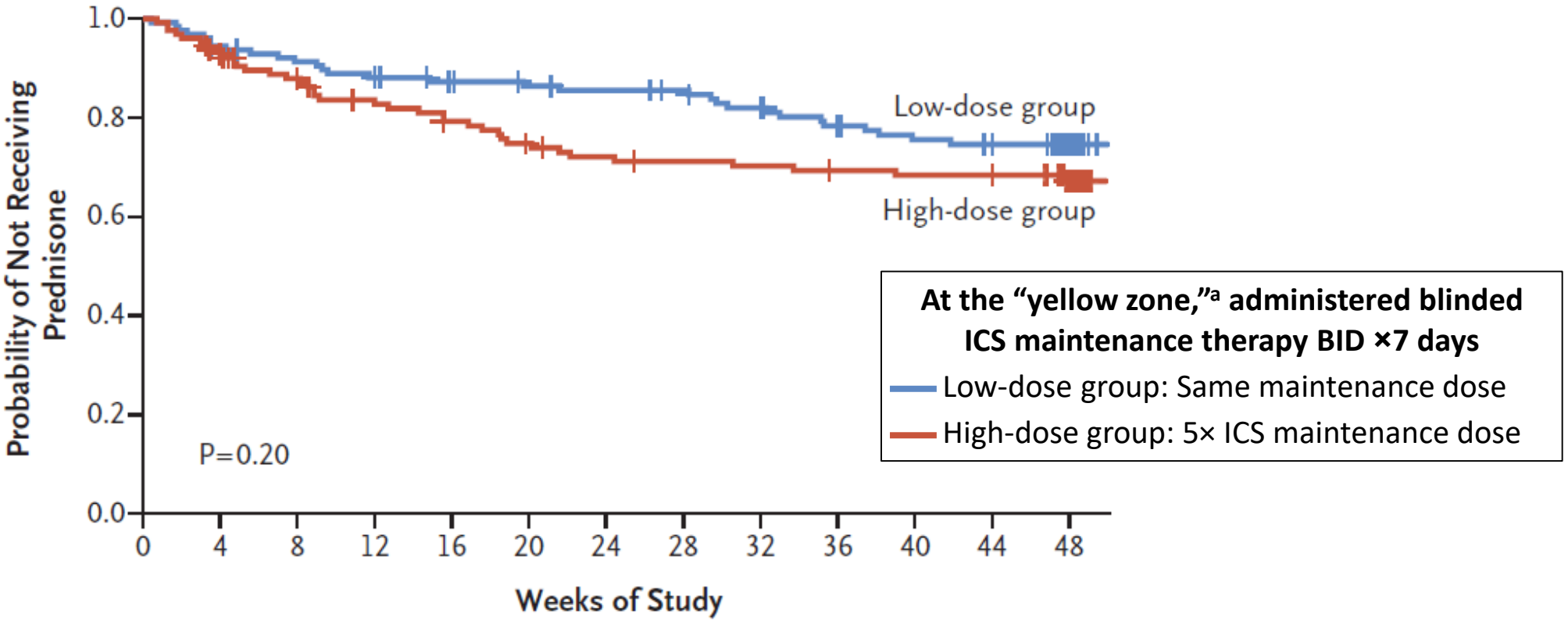
- Does quintupling the dose of ICS for 7 days at the early signs of loss of asthma control prevent asthma exacerbations in school-age children with mild-to-moderate persistent asthma?

[a]Yellow zone defined as occurrence of any of the following: the use of 2 doses (4 inhalations) of albuterol in 6 hours or 3 doses (6 inhalations) in 24 hours, or one night awakening due to asthma treated with albuterol.
[b]Open label. [c]Double-blind.
BID = twice daily; FP = fluticasone propionate; ICS = inhaled corticosteroid; OCS = oral corticosteroids.
[1]Jackson DJ, et al. *N Engl J Med*. 2018;378(10): 891-901.

Time to First Severe Exacerbation

STICS[1]

Children 5-11 years old with a history of ≥1 severe exacerbation in the previous year; both groups administered open-label, low-dose fluticasone pMDI (88 µg BID) as maintenance therapy ("green zone")



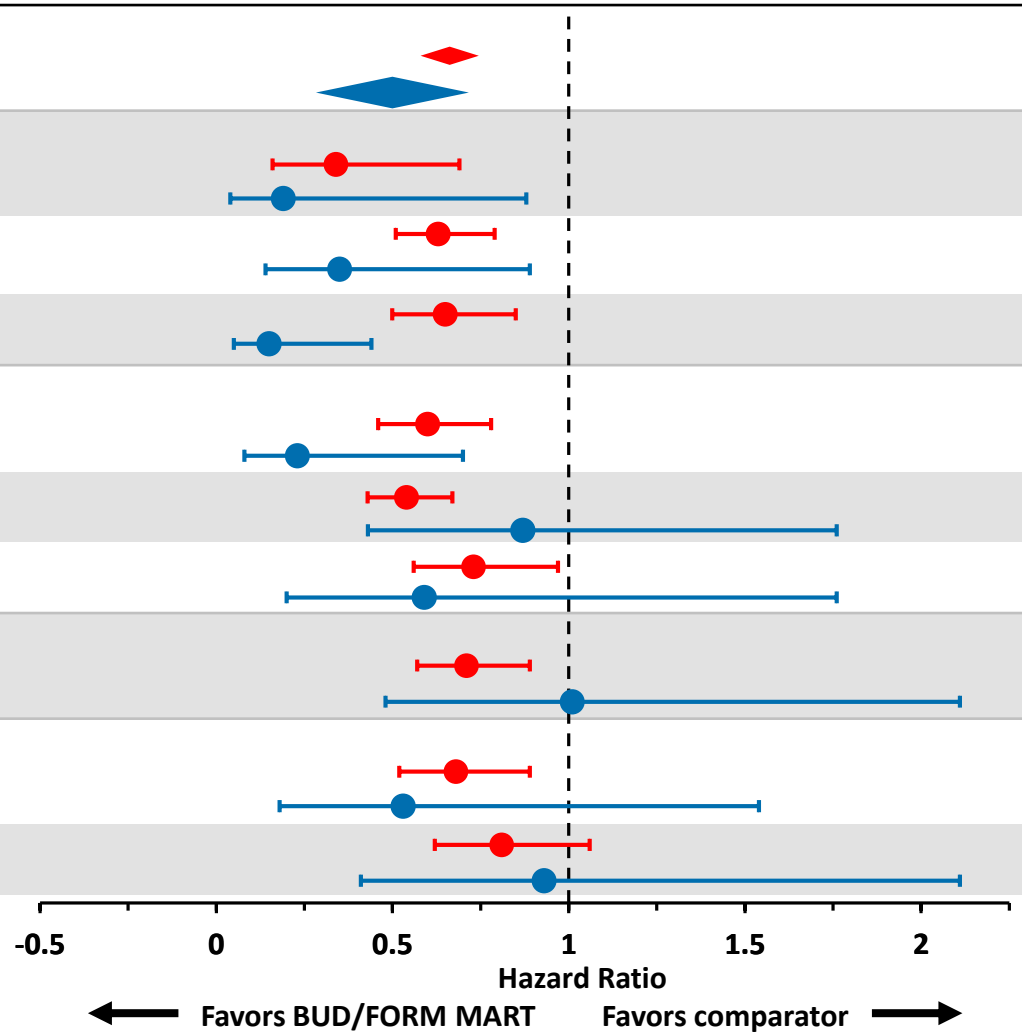
[a]Yellow zone = occurrence of any of the following: the use of 2 doses (4 inhalations of albuterol in 6 hours or 3 doses (6 inhalations) in 24 hours, or one night awakening due to asthma treated with albuterol.

[1]Reprinted from Jackson DJ, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med*. 2018;378(10):891-901. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Adolescents: As-Needed ICS Plus Fast-Acting Bronchodilators Has Proven Efficacy and Safety

Meta-analysis: Jorup et al[1]

First author	Population	Patients with event/total patients in treatment group n/n			Hazard ratio (95% CI)
		BUD/FORM MART	***versus***	**Comparator**	
Pooled analysis	Adults	546/4774		1268/7386	0.65 (0.59-0.72)
	Adolescents	42/692		129/1153	0.49 (0.34-0.70)
		BUD/FORM MART	***versus***	**BUD + TERB**	
Rabe	Adults	10/298		28/289	0.34 (0.16-0.69)
	Adolescents	2/56		9/53	0.19 (0.04-0.88)
Scichittano	Adults	131/891		193/878	0.63 (0.51-0.79)
	Adolescents	6/56		19/65	0.35 (0.14-0.89)
O'Byrne	Adults	90/698		134/712	0.65 (0.50-0.85)
	Adolescents	4/106		24/107	0.15 (0.05-0.44)
		BUD/FORM MART	***versus***	**BUD/FORM + TERB**	
O'Byrne	Adults	90/698		141/686	0.60 (0.46-0.78)
	Adolescents	4/106		15/103	0.23 (0.08-0.70)
Rabe	Adults	129/993		228/1013	0.54 (0.43-0.67)
	Adolescents	14/114		17/125	0.87 (0.43-1.76)
Kuna	Adults	89/906		117/886	0.73 (0.56-0.97)
	Adolescents	5/197		9/213	0.59 (0.20-1.76)
		BUD/FORM MART	***versus***	**BUD/FORM + FORM**	
Rabe	Adults	129/993		181/1022	0.71 (0.57-0.89)
	Adolescents	14/114		14/115	1.01 (0.48-2.11)
		BUD/FORM MART	***versus***	**SAL/FLU + TERB**	
Kuna	Adults	89/906		128/908	0.68 (0.52-0.89)
	Adolescents	5/197		10/211	0.53 (0.18-1.54)
Bousquet	Adults	97/988		118/992	0.81 (0.62-1.06)
	Adolescents	11/163		12/161	0.93 (0.41-2.11)

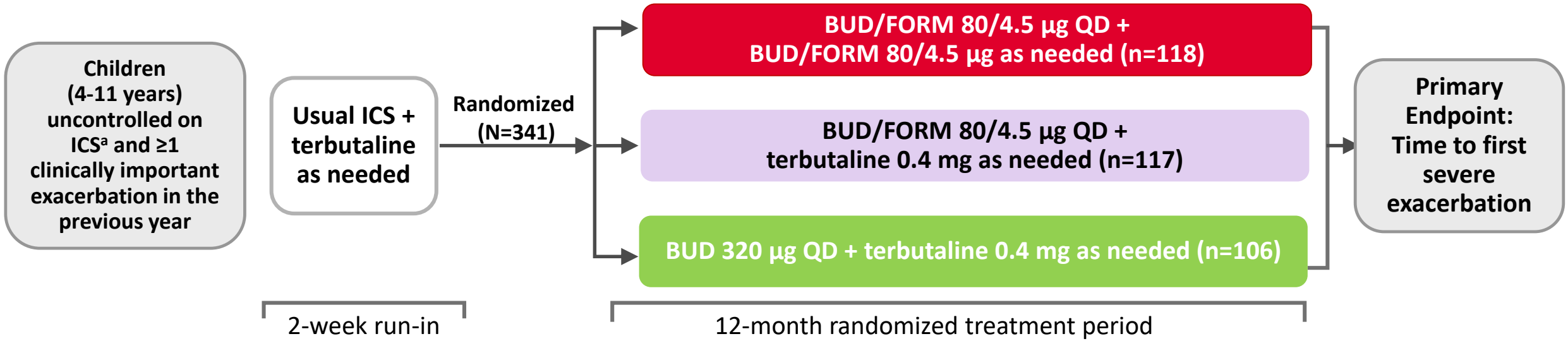


[1]Jorup C, et al. *Eur Respir J*. 2018;51(1):1701688. Copyright © ERS 2022.

Pooled hazard ratio for time to first severe exacerbation: 0.49 (CI, 0.34-0.70).

Study Design

STAY Pediatric Subgroup Analysis[1]



Study Design

- Prospectively planned pediatric analysis of the STAY study
- 12-month, randomized, double-blind trial (41 centers in 12 countries)

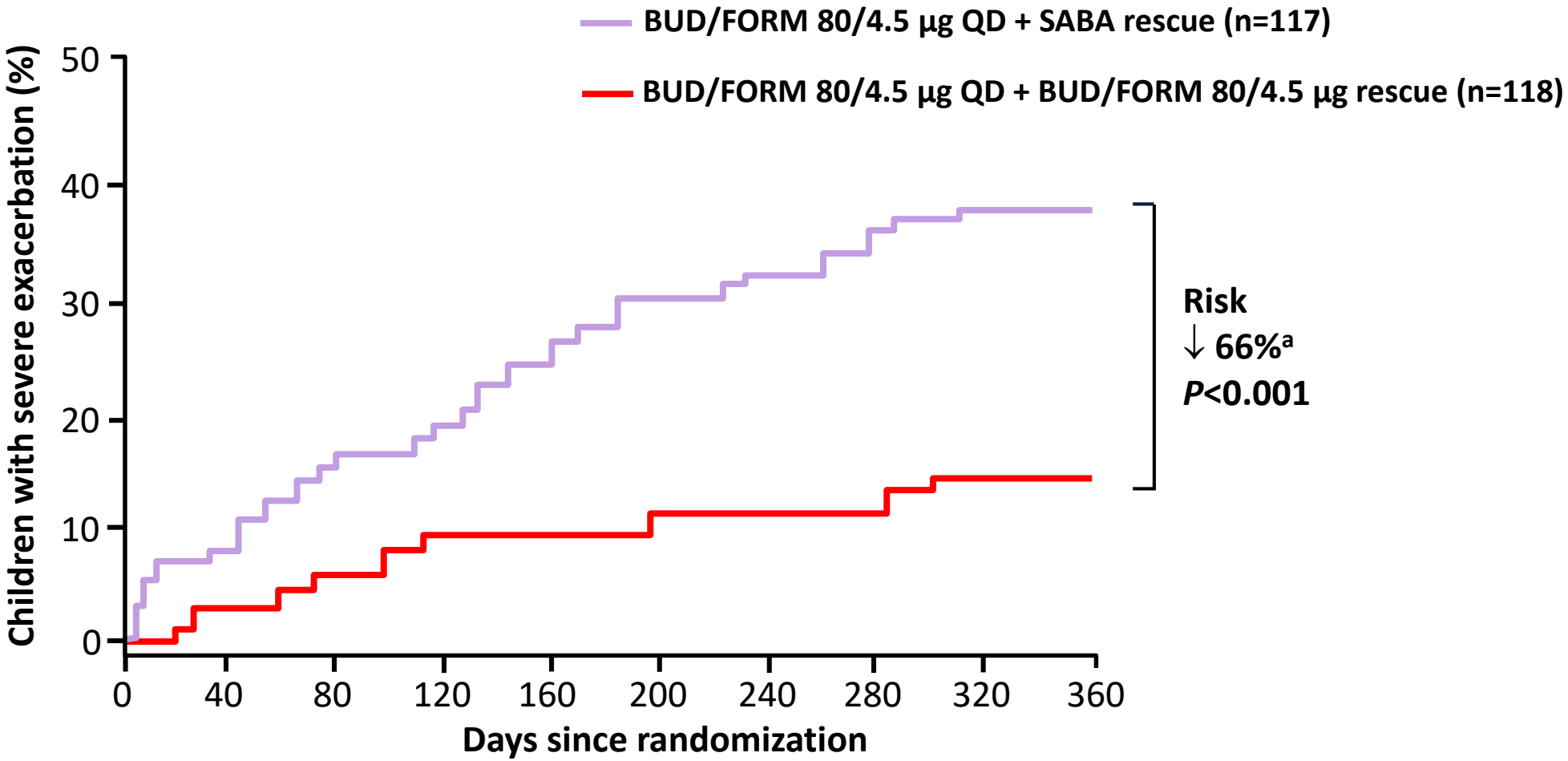
Clinical Question

- What is the efficacy and safety of BUD/FORM maintenance and rescue vs BUD/FORM maintenance or a 4-fold higher maintenance dose of budesonide plus SABA?

[a]200-500 µg/day.
BUD = budesonide; FORM = formoterol; ICS = inhaled corticosteroid; QD = once daily.
[1]Bisgaard H, et al. *Chest*. 2006;130(6):1733-1743.

Formoterol/Budesonide Maintenance and Rescue Therapy in Children Demonstrated Efficacy

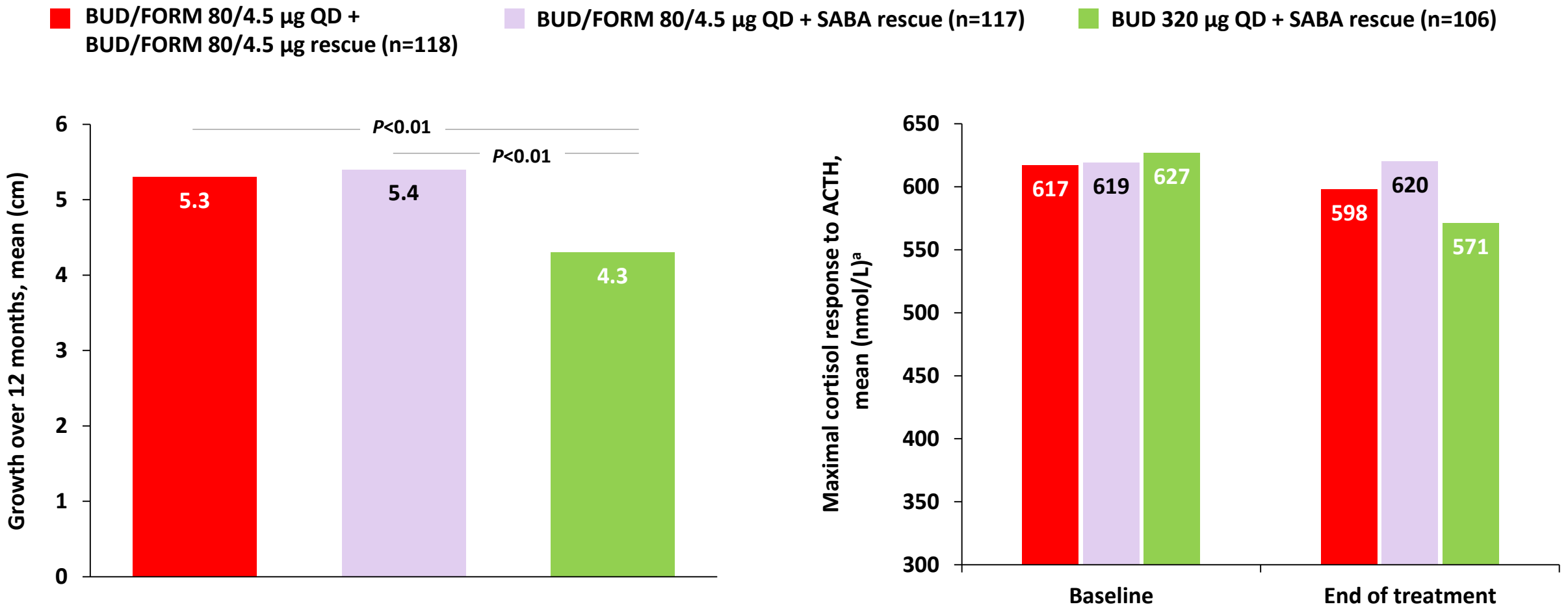
STAY Pediatric Subgroup Analysis[1]



[a]Hazard ratio (HR) = 0.34 (CI, 0.19-0.60).
BUD/FORM MART vs 4× BUD HR = 0.49 (CI, 0.27-0.90), *P*=0.02.
BUD = budesonide; FORM = formoterol; SCS = systemic corticosteroid.
[1]Reprinted from *Chest*, Vol. 130, Bisgaard H, et al, Budesonide/formoterol maintenance plus reliever therapy: A new strategy in pediatric asthma, Pages 1733-1743, Copyright 2006, with permission from Elsevier.

Budesonide/Formoterol/ Maintenance and Rescue Therapy in Children Demonstrated No Effects on Growth Rates or Serum Cortisol Levels

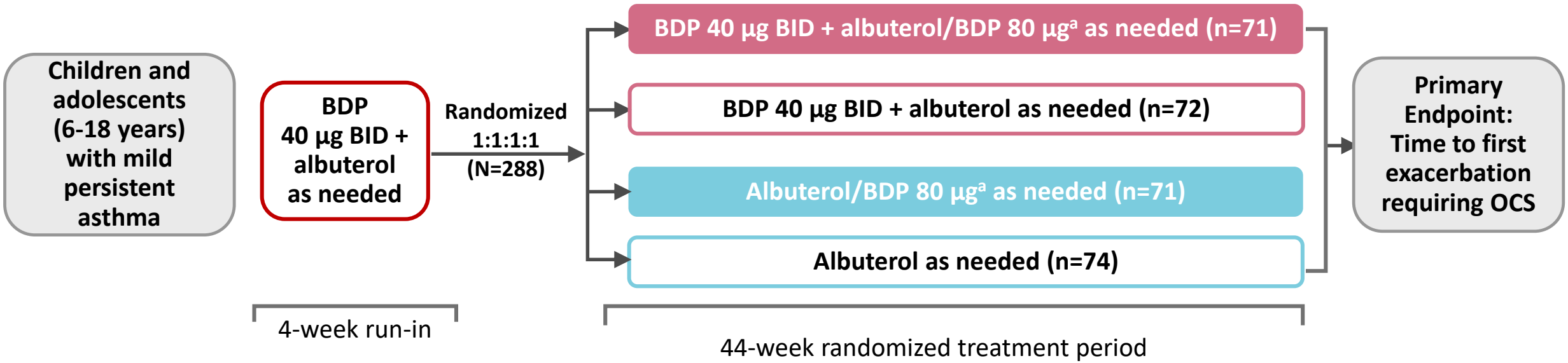
STAY Pediatric Subgroup Analysis[1]



[a]ACTH stimulated, performed in a subgroup of patients (n=55 to 59 in each group).
ACTH = adrenocorticotrophic hormone; BUD = budesonide; FORM = formoterol; QD = once daily.
[1]Bisgaard H, et al. *Chest*. 2006;130(6):1733-1743.

Study Design

TREXA[1]



Study Design

- 44-week, randomized, double-blind, placebo-controlled trial (5 centers in the US)
- Patients entered the randomized period if asthma remained well controlled with no exacerbations during the 4-week run-in

Clinical Questions

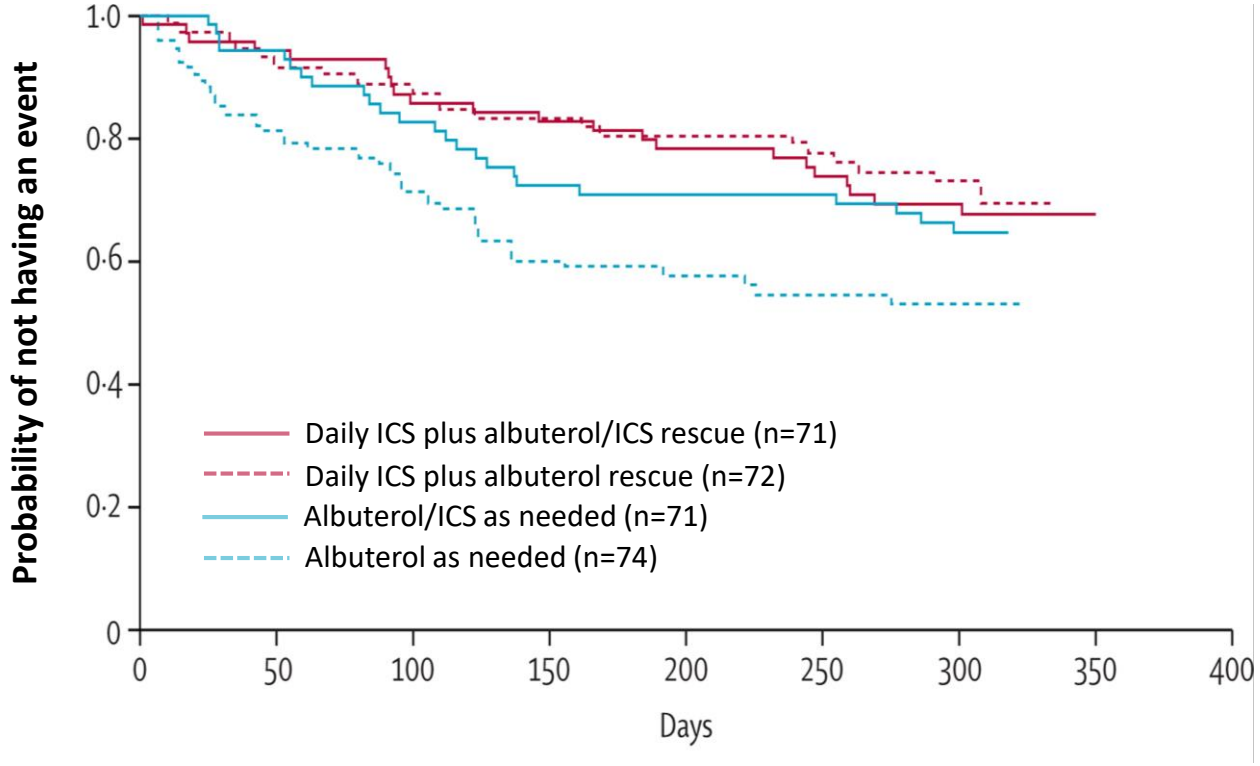
- Does discontinuation of daily ICS in children with well-controlled, mild persistent asthma increase risk of exacerbation?
- Does beclomethasone plus albuterol rescue (± daily beclomethasone) reduce exacerbation risk vs albuterol rescue alone?

[a]Administered as 2 puffs BDP 40 µg for each 2 puffs of albuterol as needed.
BID = twice daily; BDP = beclomethasone dipropionate; ICS = inhaled corticosteroid.
[1]Martinez FD, et al. *Lancet.* 2011;377(9766):650-657.

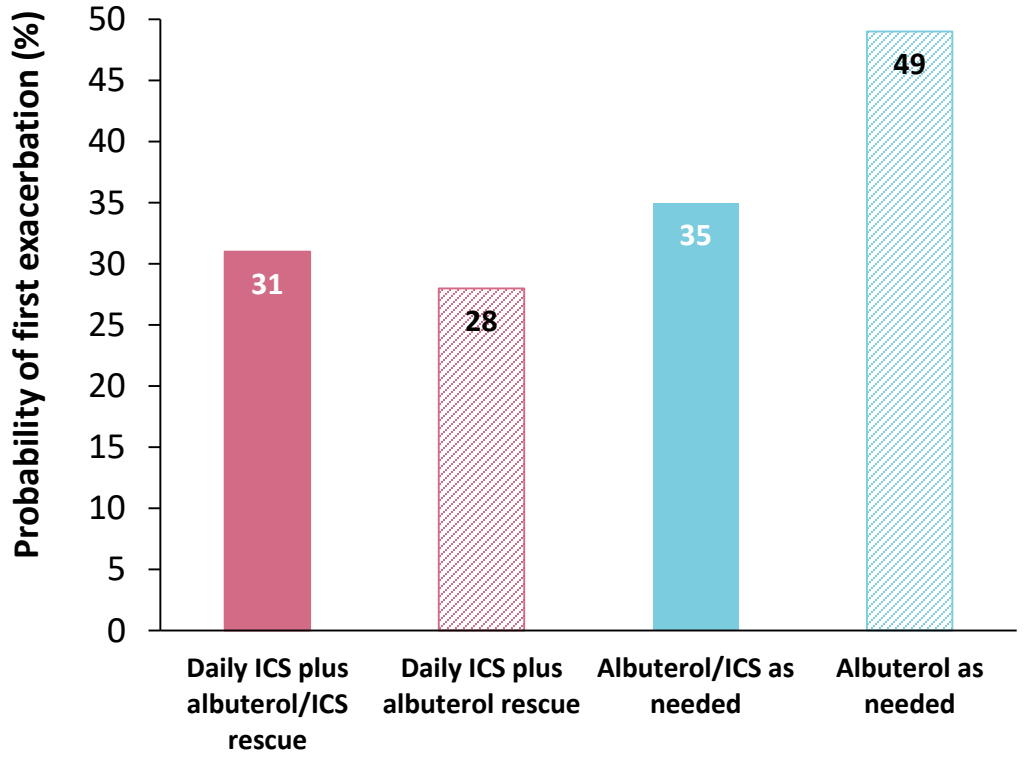
Exacerbation Endpoints

TREXA[1]

Time to first exacerbation requiring prednisone



Frequency of severe exacerbations



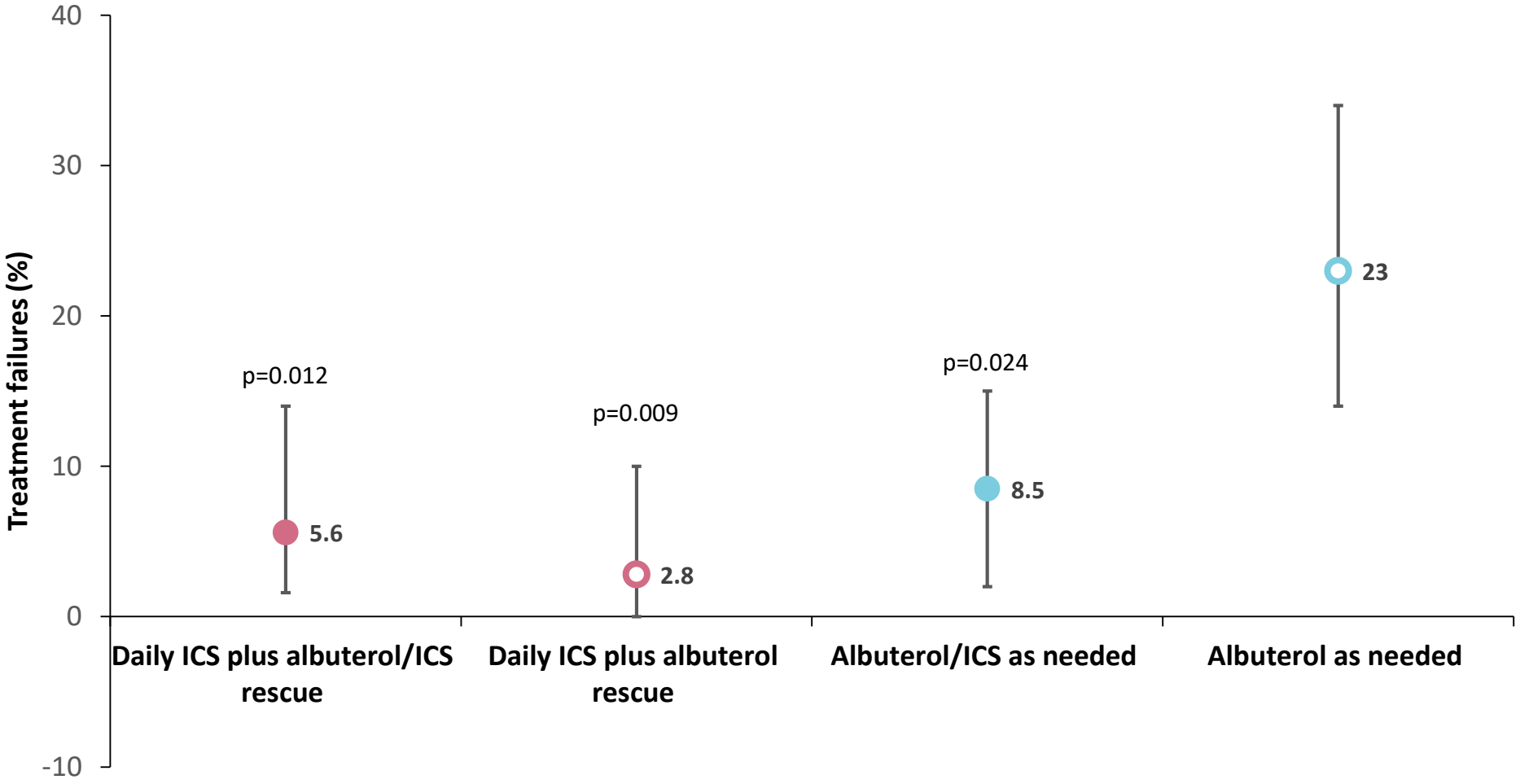
Hazard ratios are for the comparisons vs albuterol as needed with unadjusted *P* values.

Daily ICS plus ICS/albuterol rescue hazard ratio (HR) = 0.56 (CI, 0.32-0.96); *P*=0.033; daily ICS plus albuterol as rescue HR = 0.49 (CI, 0.28-0.85); *P*=0.011; ICS/albuterol as rescue HR = 0.62 (CI, 0.37-1.05); *P*=0.073.

[1]Left figure reprinted from *The Lancet*, Vol. 377, Martinez FD, et al, Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomised, double-blind, placebo-controlled trial, Pages 650-657, Copyright 2011, with permission from Elsevier.

Treatment Failures Over 12 Months

TREXA[1]

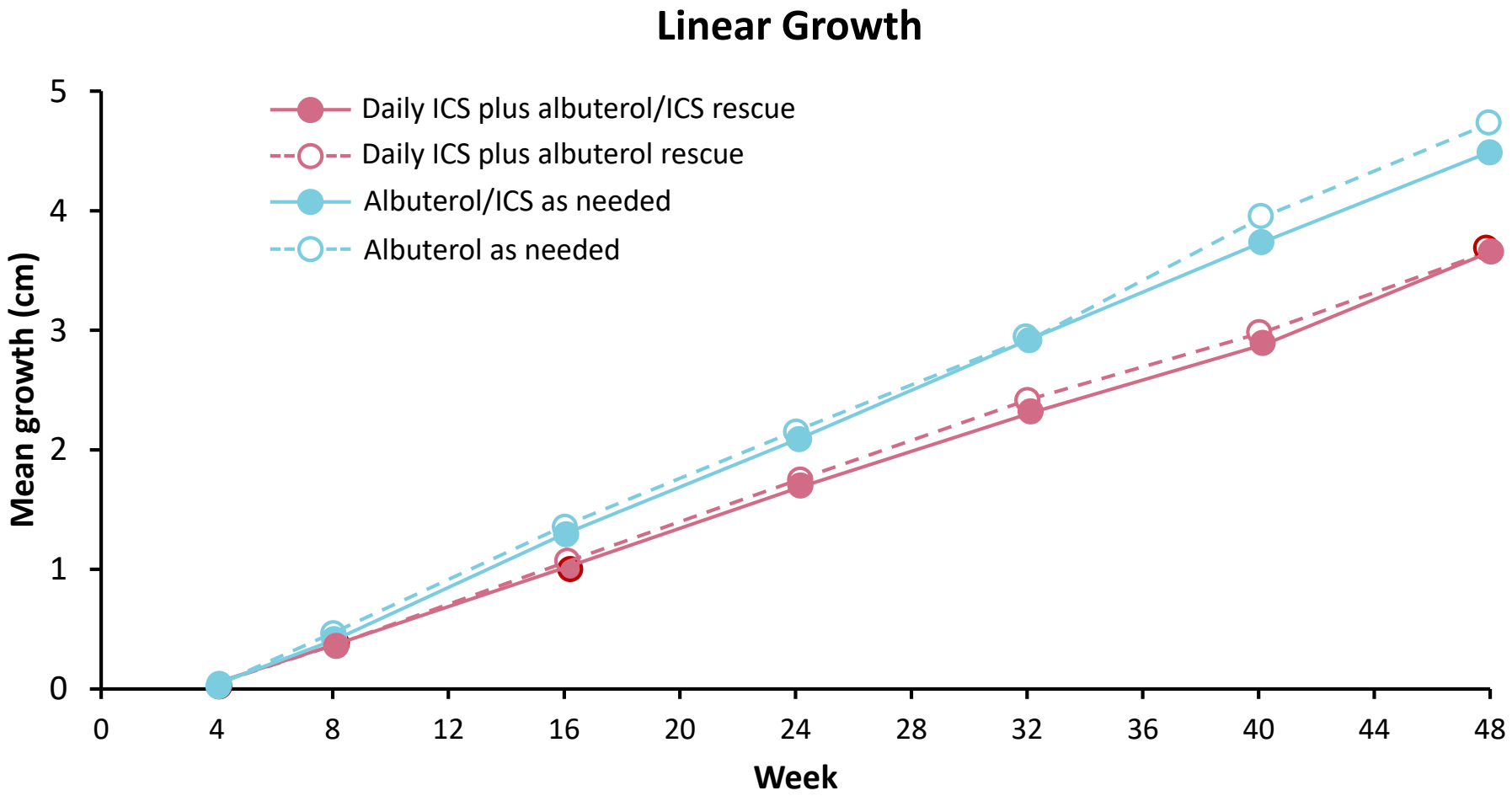


Vertical bars are 95% CIs. *P* values are based on the estimated relative risks from the proportional hazards regression analysis that compared each treatment group with the albuterol group.

[1]Reprinted from *The Lancet*, Vol. 377, Martinez FD, et al, Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomised, double-blind, placebo-controlled trial, Pages 650-657, Copyright 2011, with permission from Elsevier.

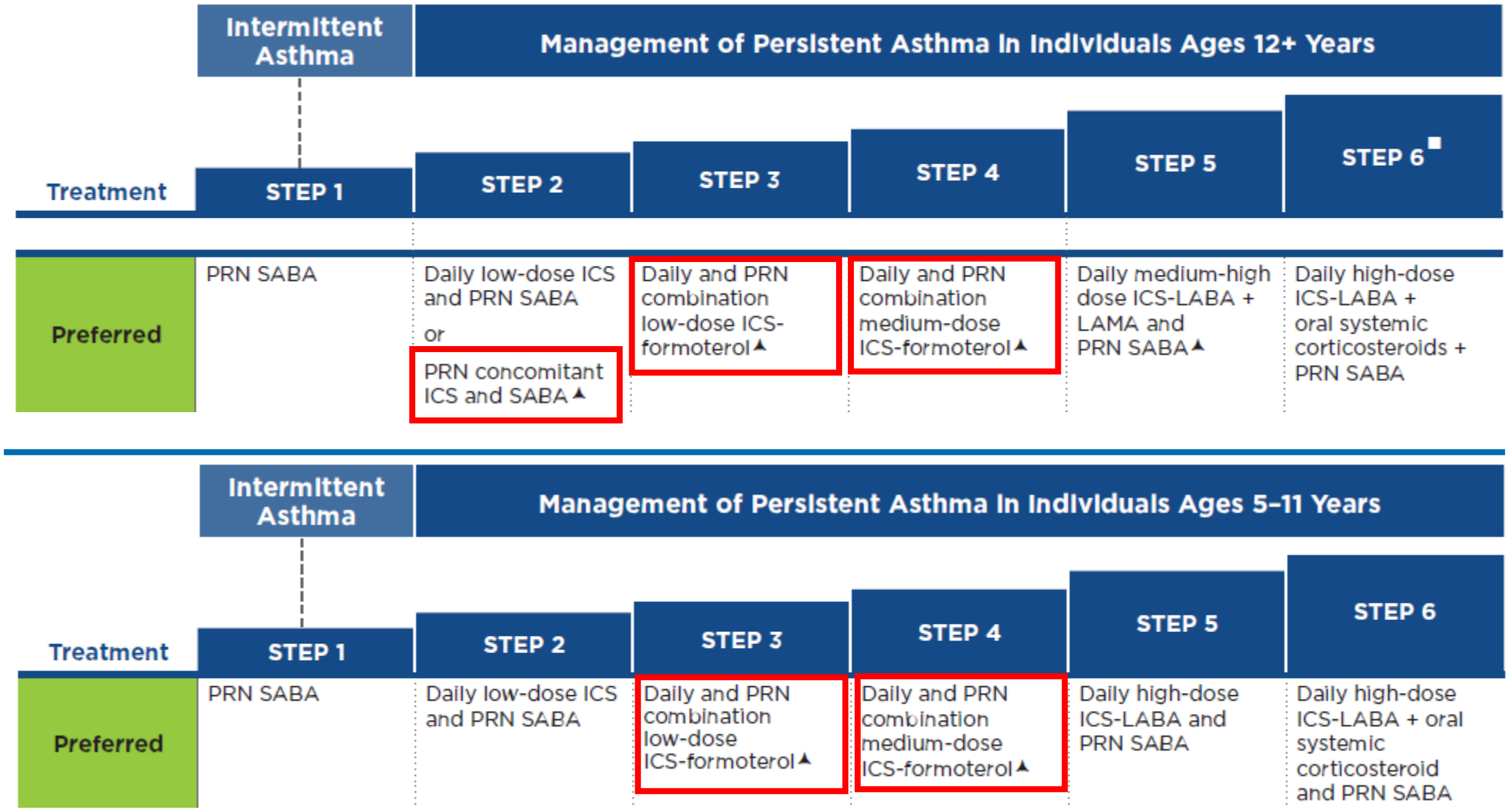
Efficacy Without Growth Effects

TREXA[1]



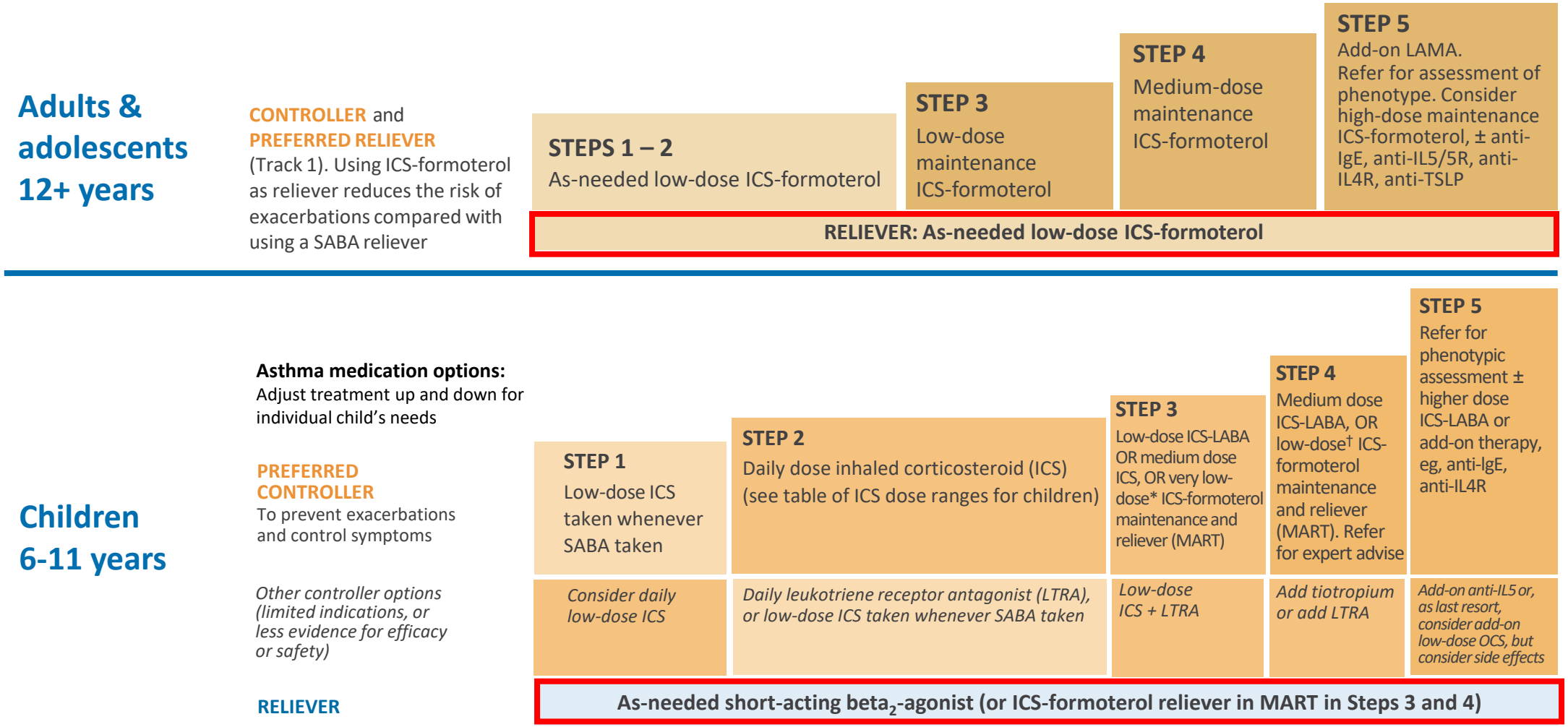
[1]Reprinted from *The Lancet*, Vol. 377, Martinez FD, et al, Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomised, double-blind, placebo-controlled trial, Pages 650-657, Copyright 2011, with permission from Elsevier.

NAEPP Stepwise Approach for Management of Asthma



https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines.

GINA Stepwise Approach for Management of Asthma



*Very low dose: BUD-FORM 100/6 mcg.
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Summary: BDA MDI in Pediatric Populations

- The burden in pediatric asthma is severe asthma exacerbations
- The unmet need is preventing severe asthma exacerbations and the corresponding burden of systemic corticosteroids
- Published data support the combination of ICS/fast-acting bronchodilators used as rescue in adolescents and children
- National and international guidelines increasingly recommend ICS/SABA as rescue in adolescents and children
- BDA MDI has the potential to fulfill the significant unmet need (preventing severe asthma exacerbations) in both adolescents and children

Available Data Justifies the Favorable Benefit-Risk Assessment of BDA MDI in Adolescents and Children

Image courtesy of Dr. Murphy.

Conclusions

Ed Piper, MBBS

Global Franchise Head, Core Inhaled Products

AstraZeneca

BDA MDI Key Clinical Conclusions

- The need for a safe and effective rescue therapy to prevent severe asthma exacerbations applies to adults, adolescents, and children
- BDA MDI rescue resulted in statistically significant and clinically meaningful reductions in severe exacerbation risk vs albuterol
- In addition, BDA MDI 160/180 resulted in
  - Reduction in annualized severe exacerbation rate and mean total SCS exposure
  - Nominally higher odds of clinically relevant improvements in asthma control and quality-of-life measures
- No new safety signals were identified

Favorable Benefit-Risk Profile for BDA MDI in Adult and Pediatric Asthma

- The benefit-risk assessment is favorable in adults
  - BDA MDI 160/180 proposed dose
- We also consider the benefit-risk assessment in both pediatric populations to be favorable
  - BDA MDI safety is consistent with the well-established safety profile of albuterol and budesonide
  - Clinical and pharmacologic rationale to extrapolate efficacy from overall population to adolescents and children
  - Supportive efficacy and safety data from ICS/fast-acting bronchodilator combinations in pediatric asthma