AVILLION

Budesonide/Albuterol Sulfate Metered Dose Inhaler (BDA MDI)

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

November 8, 2022

Summary Presentation

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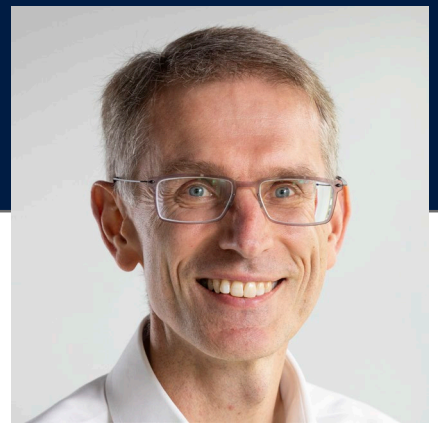
Global Franchise Head, Core Inhaled Products

AstraZeneca



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Budesonide/Albuterol Sulfate Metered Dose Inhaler (BDA MDI) for Asthma Rescue Therapy

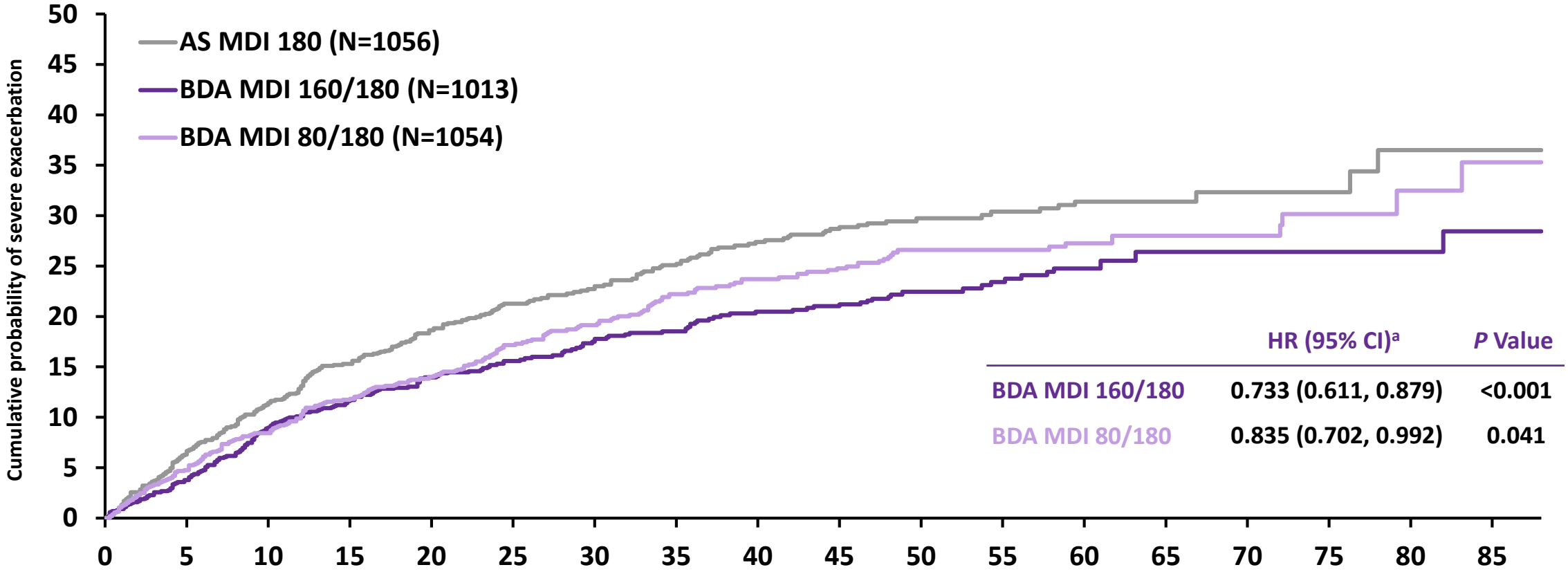
- Severe asthma exacerbations remain a major issue across all ages and a need for safe and effective preventative therapies exists
- Albuterol monotherapy for rescue is associated with increased risk of severe asthma exacerbations[1-6]
- BDA is a novel asthma rescue treatment presented in pMDI
  - Albuterol (short-acting β_2 agonist, SABA) provides rapid relief of symptoms
  - Budesonide (inhaled corticosteroid, ICS) treats variable airway inflammation
- Clinical premise behind development
  - BDA MDI would reduce severe asthma exacerbation risk by treating increasing airway inflammation when worsening symptoms occur

BDA MDI drug/device combination product

[1]Bateman ED, et al. *Eur Respir J*. 2022;59(5):2101402; [2]Bloom CI, et al. *Adv Ther*. 2020;37(10):4190-4208; [3]Bollinger ME, et al. *Ann Allergy Asthma Immunol*. 2019;122(4):381-386; [4]Suissa S, et al. *Eur Respir J*. 1994;7(9):1602-1609; [5]Spitzer WO, et al. *N Engl J Med*. 1992;326(8):501-506; [6]Nwaru BI, et al. *Eur Respir J*. 2020;55(4):1901872.

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.

BDA 160/180 Efficacy Profile

MANDALA

↓ **27% reduction** in **severe exacerbation** risk[a]

↓ **24% reduction** in annualized rate of **severe exacerbations**[b]

↓ **33% reduction** in **systemic corticosteroid** use[c]

↑ **odds** of having a **clinically meaningful improvement** in **asthma control** and **quality of life**[d,e]

Data from MANDALA.

[a]The hazard ratio (HR) for severe exacerbation risk for BDA MDI 160/180 versus AS MDI 180 in patients ≥12 years of age was 0.733 (95% confidence interval [CI], 0.611, 0.879), corresponding to a 27% risk reduction (*P*<0.001).

[b]Rate reduction for BDA MDI 160/180 versus AS MDI 180 (rate ratio [RR] 0.76; 95% CI, 0.62, 0.93; *P*=0.008).

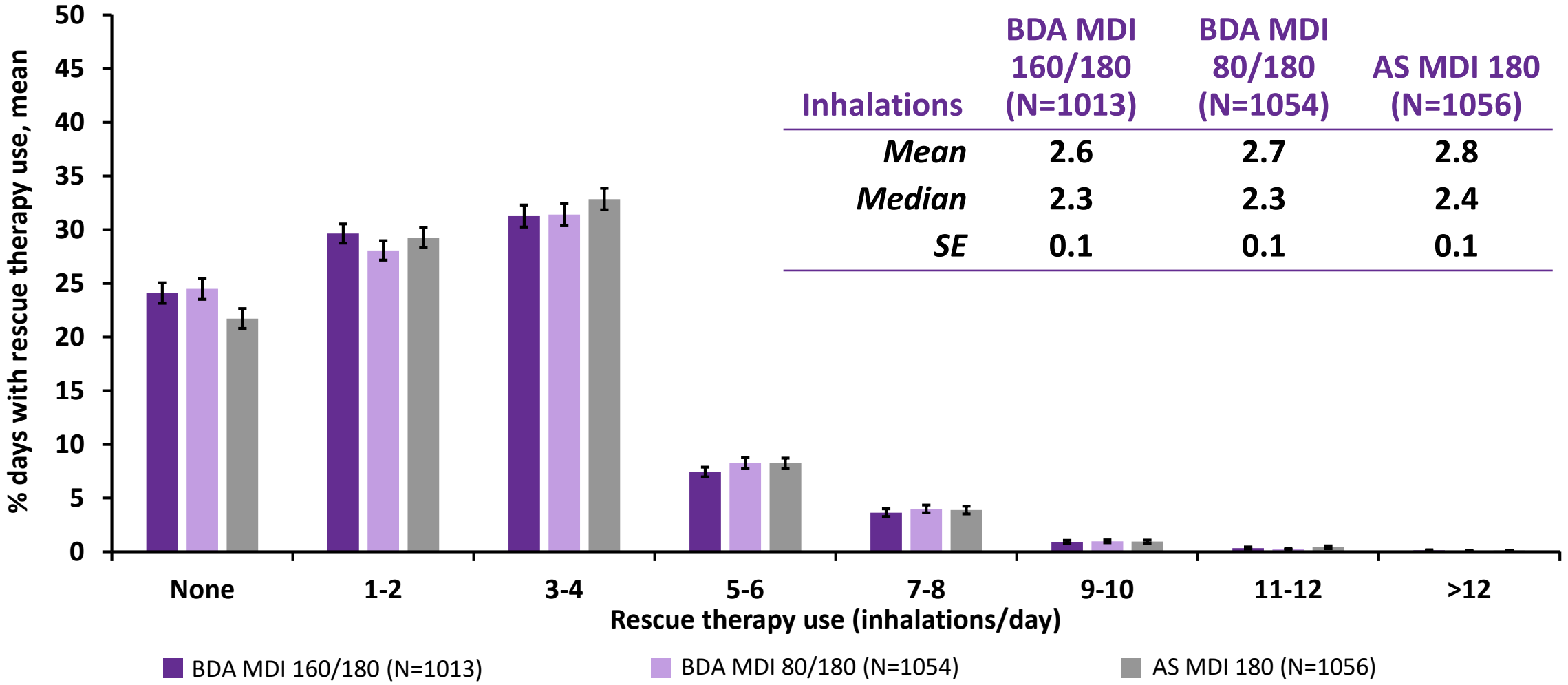
[c]33% reduction in mean annualized total SCS dose (mg/patient) relative to AS MDI (*P*=0.002).

[d]ACQ-5 odds ratio for BDA MDI 160/180 versus AS MDI 180 was nominally significant (1.22 [95% CI, 1.02, 1.47; *P*=0.033]).

[e]AQLQ+12 odds ratio was nominally significant for BDA MDI 160/180 versus AS MDI 180 (1.23 [95% CI, 1.02, 1.48; *P*=0.028]).

BDA MDI Pattern of Use Is Low and Similar to Albuterol

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

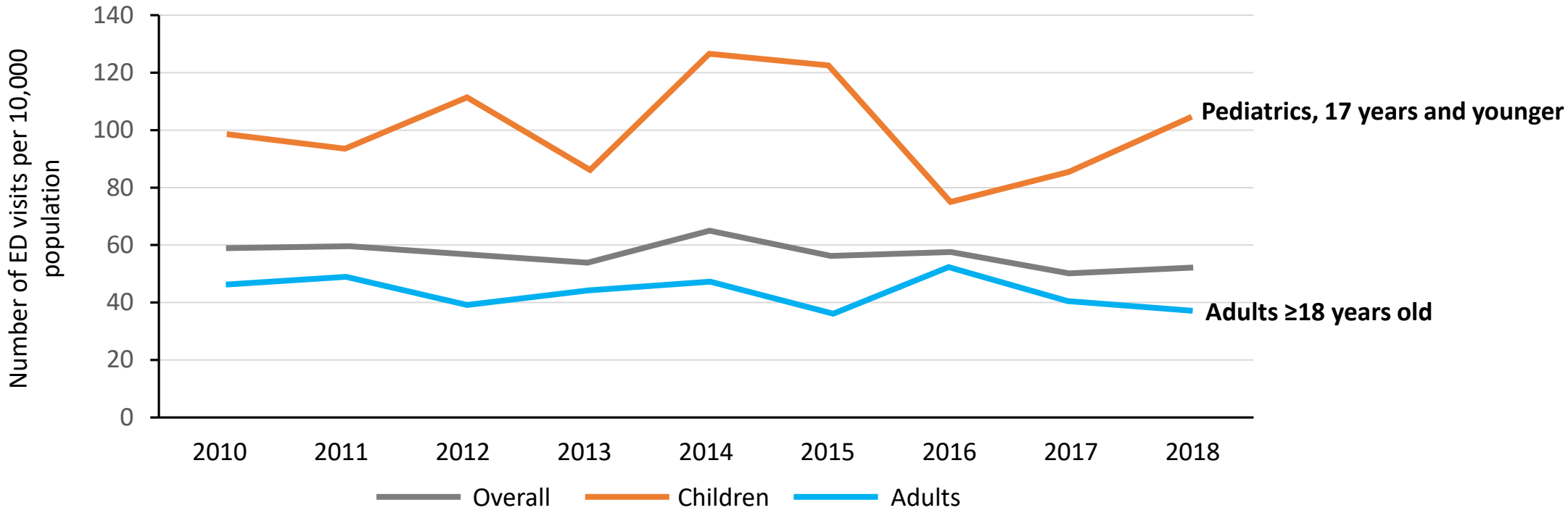
Error bars represent standard error (SE).

Positive Overall Benefit-Risk for BDA MDI

- Three positive Phase 3 studies in >4,000 patients
- BDA 160/180 compared with albuterol resulted in statistically and clinically relevant reductions in severe exacerbation risk
- BDA MDI safety profile consistent with the known risks of both mono-components
- AstraZeneca and Avillion consider
  - BDA MDI benefits outweigh any potential risks
  - BDA MDI would be an important new rescue medicine to prevent severe asthma exacerbations
  - Proposed indication reflects clinical utility of BDA MDI: “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”

Burden of Asthma Exacerbations in Patients ≤ 17 Years of Age

Asthma emergency department (ED) visit rate* (per 10,000 population) by age group† and year: United States 2010-2018[1]



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[2]

*Crude ED visits rate per 10,000 population.
†Child, persons aged 17 years and younger; Adult, persons aged 18 years and older.
[1]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. Accessed October 25, 2022; [2]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.

BDA MDI Pediatric Regulatory Background

- FDA recommended inclusion of:
  - Children in addition to adolescents (Pre-IND meeting)
  - Children ≥4 years in the Phase 3 Program (End of Phase 2 meeting)
- Initial Pediatric Study Plan (iPSP) for MANDALA:
  - Target: ~100 adolescents (≥12-18 years) and ~100 children (≥4-<12 years)
  - Actual enrollment: 100 adolescents and 83 children
- FDA recommended Bayesian analysis to support efficacy in both pediatric populations

Clinical and Pharmacologic Rationale for Extrapolation of BDA MDI Benefit Across Age Groups

- General FDA guidance is that 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[1,2]
- Rationale to extrapolate from adults to adolescents and children with asthma
  - Guidelines use the same principles for diagnosis, assessment, and treatment strategies[3]
  - Similar airway inflammation and bronchoconstriction during exacerbations[4]
  - Treatment of severe exacerbations is the same
  - Similar treatment effects of rescue ICS/fast-acting bronchodilators to reduce severe exacerbation risk[5,6]
  - The same endpoints in clinical trials are used to measure efficacy

[1]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; [2]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; [3]Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. www.ginasthma.org; [4]Chedevergne F, et al. *Arch Dis Child.* 2000;82(suppl II):ii6-ii9; [5]Jorup C, et al. *Eur Respir J*. 2018;51(1):1701688; [6]Bisgaard H, et al. *Chest*. 2006;130(6):1733-1743.

BDA MDI Efficacy – Adolescents
MANDALA

- Primary endpoint point estimate favored BDA MDI 80/180 and for BDA MDI 160/180 it favored albuterol
  - Bayesian modeling with limited borrowing from overall population results in favorable point estimates for both BDA MDI doses, although with credible intervals crossing unity

- Secondary endpoints favored both BDA MDI doses compared with albuterol
  - Reduced annualized severe asthma exacerbation rate
  - Reduced systemic corticosteroid use
  - Higher odds of having a clinically meaningful response in ACQ-5 and AQLQ+12

Adolescents: ≥12 to <18 years.

BDA MDI Safety – Adolescents

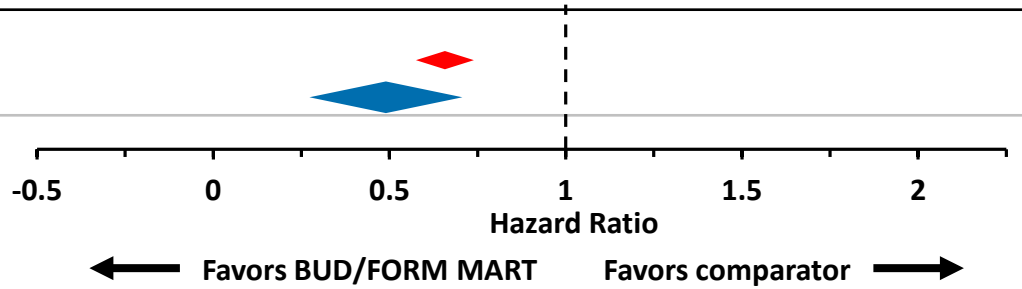
- **MANDALA** (BDA MDI 160/180, N=34; BDA MDI 80/180, N=32)
  - Incidences of adverse events were low
  - Both BDA doses were similarly well tolerated
  - The safety profile in adolescents was similar to that in adults and consistent with the known risks of both mono-components

- **DENALI** (BDA BDI 160/180, N=4; BDA MDI 80/180, N=7)
  - Too few patients in BDA MDI arms to assess safety

Adolescents: ≥12 to <18 years.

Consistent Budesonide/Formoterol Rescue Data in Adults and Adolescents Support Extrapolation of BDA MDI Efficacy

	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)



- Post hoc pooled meta-analysis of data from 6 studies in >1800 adolescents demonstrates treatment benefit for budesonide/formoterol combination used as rescue therapy
- Consistent results observed in adolescents and adults support extrapolation of BDA MDI efficacy from adults to adolescents

[1]Jorup C, et al. *Eur Respir J*. 2018;51(1):1701688. Copyright © ERS 2022.
Adults defined as aged ≥18 years; adolescents defined as aged 12-17 years (including four 11-year-olds).

BDA MDI 160/180 Dose Is Proposed for Adolescents

- Efficacy results appear to favor BDA MDI 80/180 over 160/180 dose; however, this is likely due to chance as a result of the low numbers of adolescent patients and events

- Implausible that the lower BDA MDI dose would outperform in adolescents given the clear dose-response favoring BDA MDI 160/180 in the overall population across all endpoints and noting that the patterns of use for both BDA doses were similar

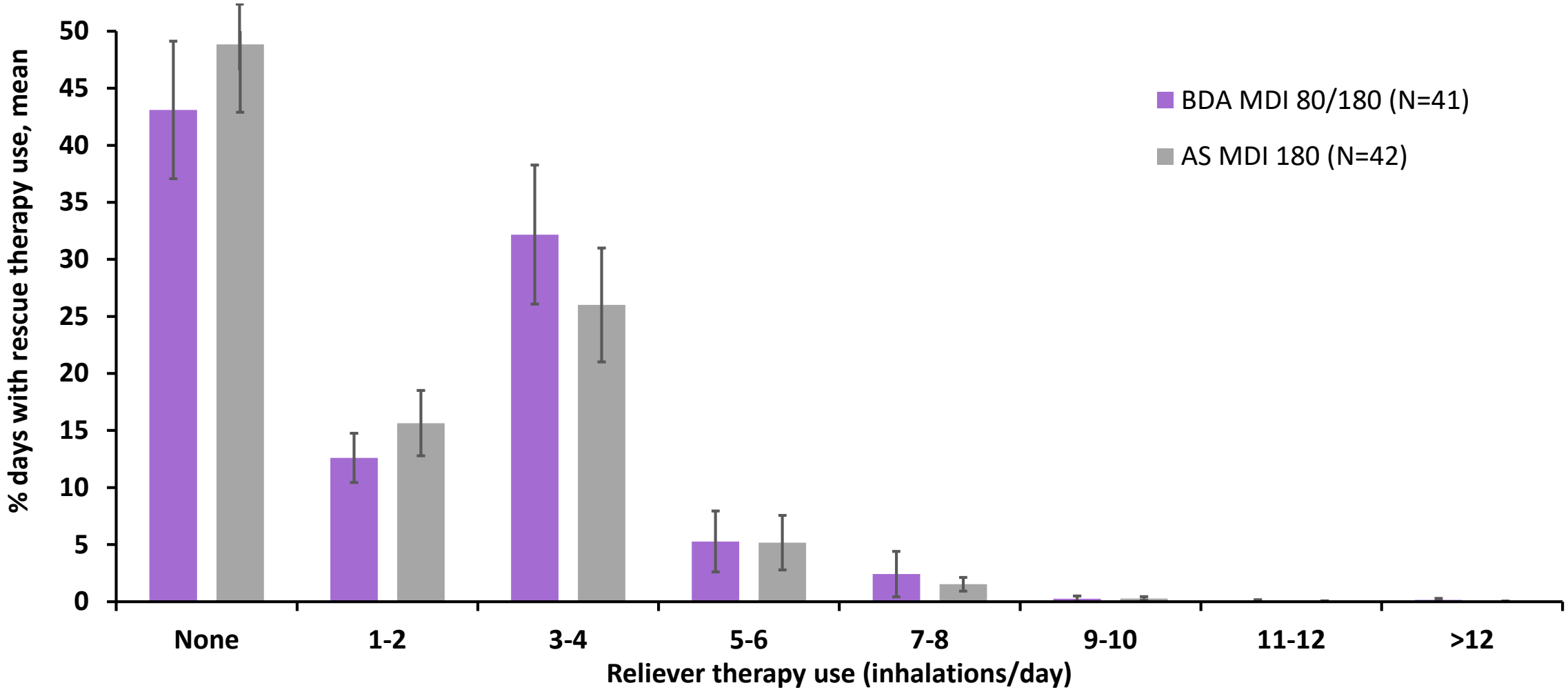
- Both BDA doses were well tolerated with no unexpected safety findings

BDA MDI 80/180 Efficacy – Children

- Uncertainty in BDA MDI benefit with point estimates for both severe exacerbation endpoints, approximately at unity
  - Bayesian modeling with limited borrowing from overall population results in a favorable point estimate, although with credible interval crossing unity
- Secondary endpoints
  - Systemic corticosteroid use numerically lower in the albuterol group
  - For ACQ-5 (in 6- to 11-year-olds) and PAQLQ (in 7- to 11-year-olds), the odds of having a clinically meaningful response were numerically higher in the BDA MDI group

BDA MDI Use in Children Is Low and Similar to Albuterol

MANDALA



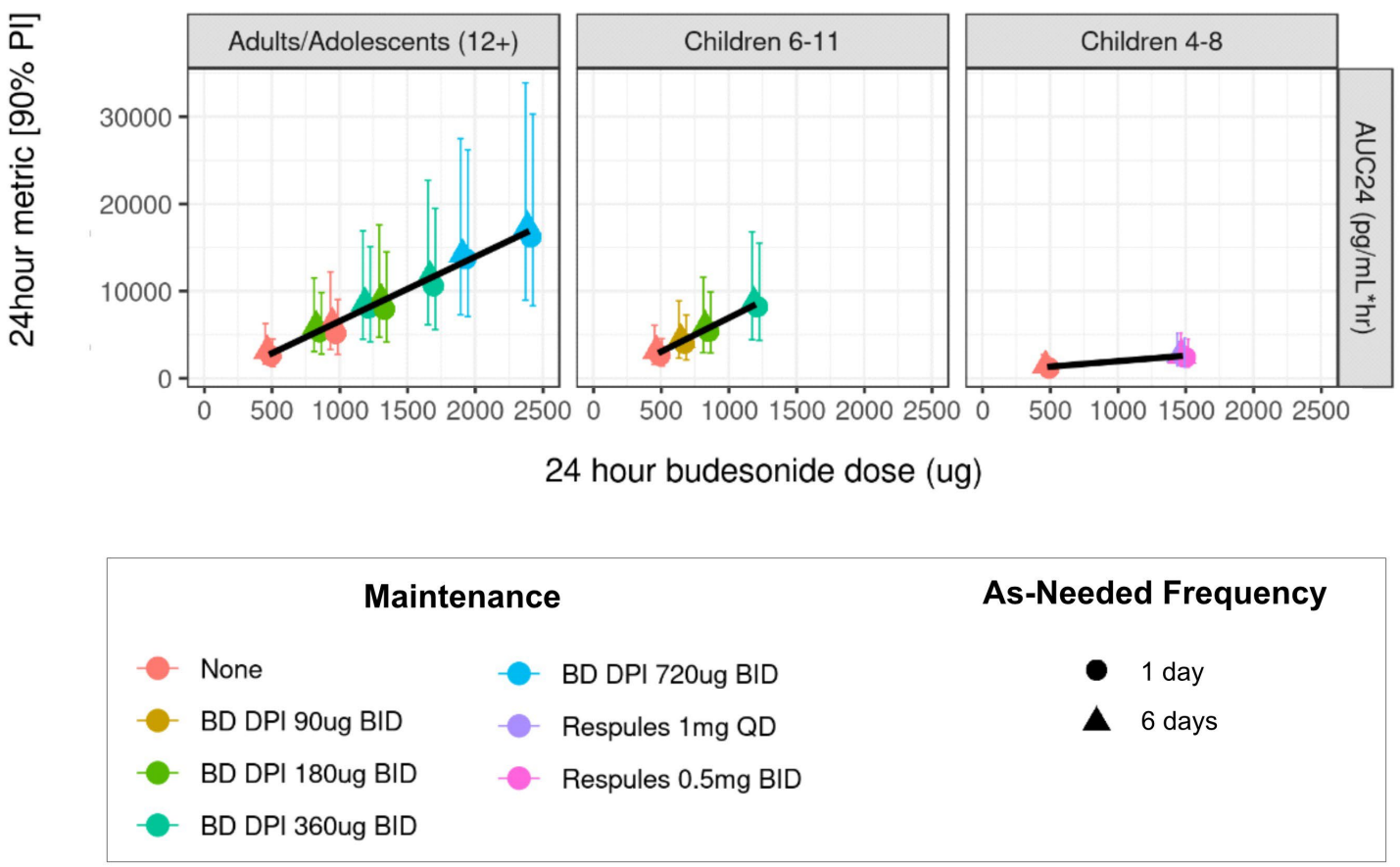
Error bars represent standard error (SE).

BDA MDI Safety - Children

- **MANDALA** (BDA MDI 80/180, N=41)
  - Incidences of adverse events were low
  - The safety profile in children was similar to that in adults and consistent with the known risks of both mono-components
- **DENALI** (BDA 80/180, N=3)
  - Too few children in BDA MDI arms to assess safety

Children: ≥4 to 11 years old

Pharmacokinetic Modeling and Simulation of a Worst-Case BDA MDI Dosing Scenario



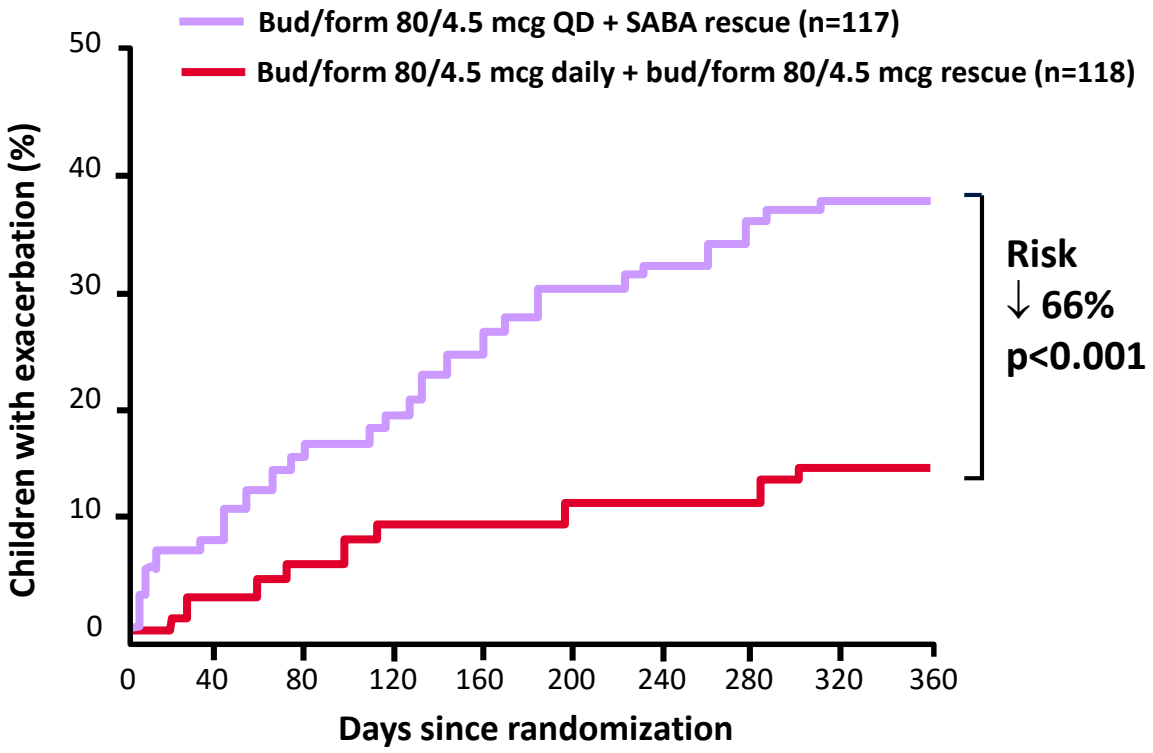
- Maximum BDA MDI dosing[a] was modeled using one dose of BDA MDI every 20 minutes for 6 doses (ie, worst-case), in addition to inhaled maintenance budesonide doses
- Systemic budesonide exposure is lower in children than in adults and adolescents
- MANDALA: BDA MDI use indicates this scenario to be infrequent

[a]For adults and adolescents, BDA MDI 160/180; for children 6-11 and 4-8, BDA MDI 80/180.

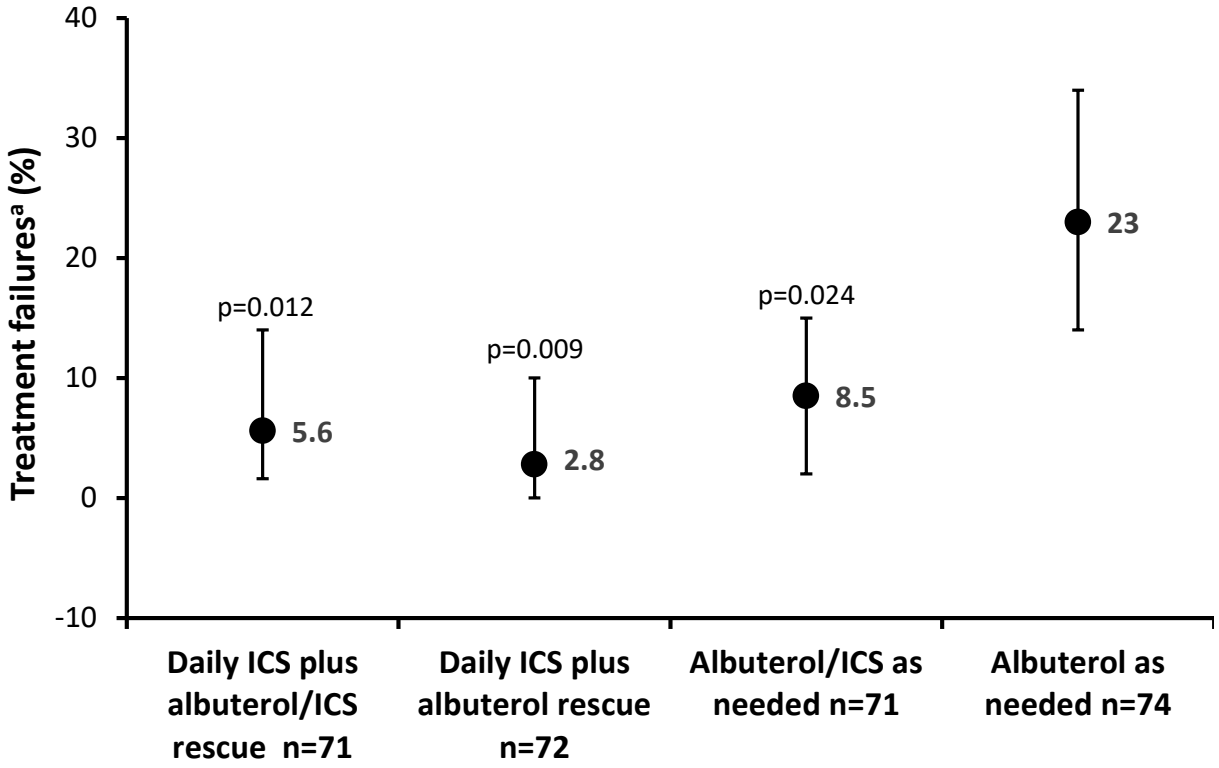
ICS/Fast-Acting Bronchodilator Rescue Concept Supported in Literature

STAY Pediatric Subgroup Analysis[1] and TREXA[2]

STAY study



TREXA study



BUD = budesonide; form = formoterol; SCS = systemic corticosteroids. Hazard ratios are for the comparisons vs albuterol as needed with unadjusted *P* values.

[1]Bisgaard H, et al. *Chest*. 2006;130(6):1733-1743. Study population is 4-11 years old.

[2]Reprinted from The Lancet, Vol. 377, Martinez FD, Chinchilli VM, Morgan WJ, 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. [a] The only criterion met by participants for treatment failure was the requirement for a second dose of prednisone within any 6-month period.

Study population is 6-18 years old. 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.

BDA MDI Positive Benefit-Risk Extends to Adolescents and Children

- BDA MDI safety data are consistent with the well-established safety profile of albuterol and budesonide with no new safety findings identified in pediatric subgroups
- Clinical and pharmacologic rationale to extrapolate BDA MDI efficacy data from adults to adolescents and children
  - Strong plausibility that BDA MDI would reduce severe exacerbation risk based on the overall population results in MANDALA together with published data of ICS/fast-acting bronchodilator rescue combinations
- Given the important unmet need and considering the totality of data, AstraZeneca and Avillion believe the potential benefits of BDA MDI outweigh the potential risks and propose
  - 160/180 µg dose in 12 years of age and older
  - 80/180 µg dose in 4-11 years of age

Clinical Perspective

Neil Skolnik, MD
Professor of Family and Community Medicine
Sidney Kimmel Medical College, Thomas Jefferson University
Jefferson Health
Jenkintown, PA

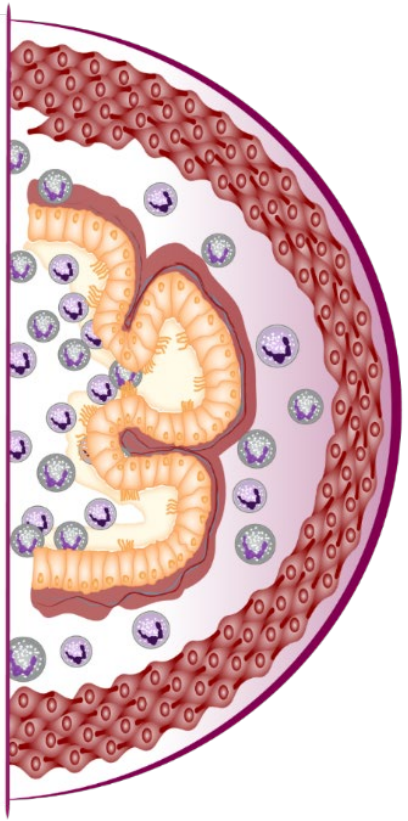
SABAs Treat Bronchoconstriction and ICS Treat Increasing Underlying Inflammation

SABA

Direct Agonism[1]

Binds to β_2-adrenergic receptors, producing airway smooth muscle relaxation

Coupling SABA with ICS prevents β_2-adrenergic receptor downregulation[6,7]



Cross-section Bronchial Airway[8]

ICS

Nongenomic effects occur (within minutes)

- Amplifies β_2-agonist–induced bronchodilation[2]
- Decreases bronchial vascular blood flow[3]
- Suppresses immune mediators[4]

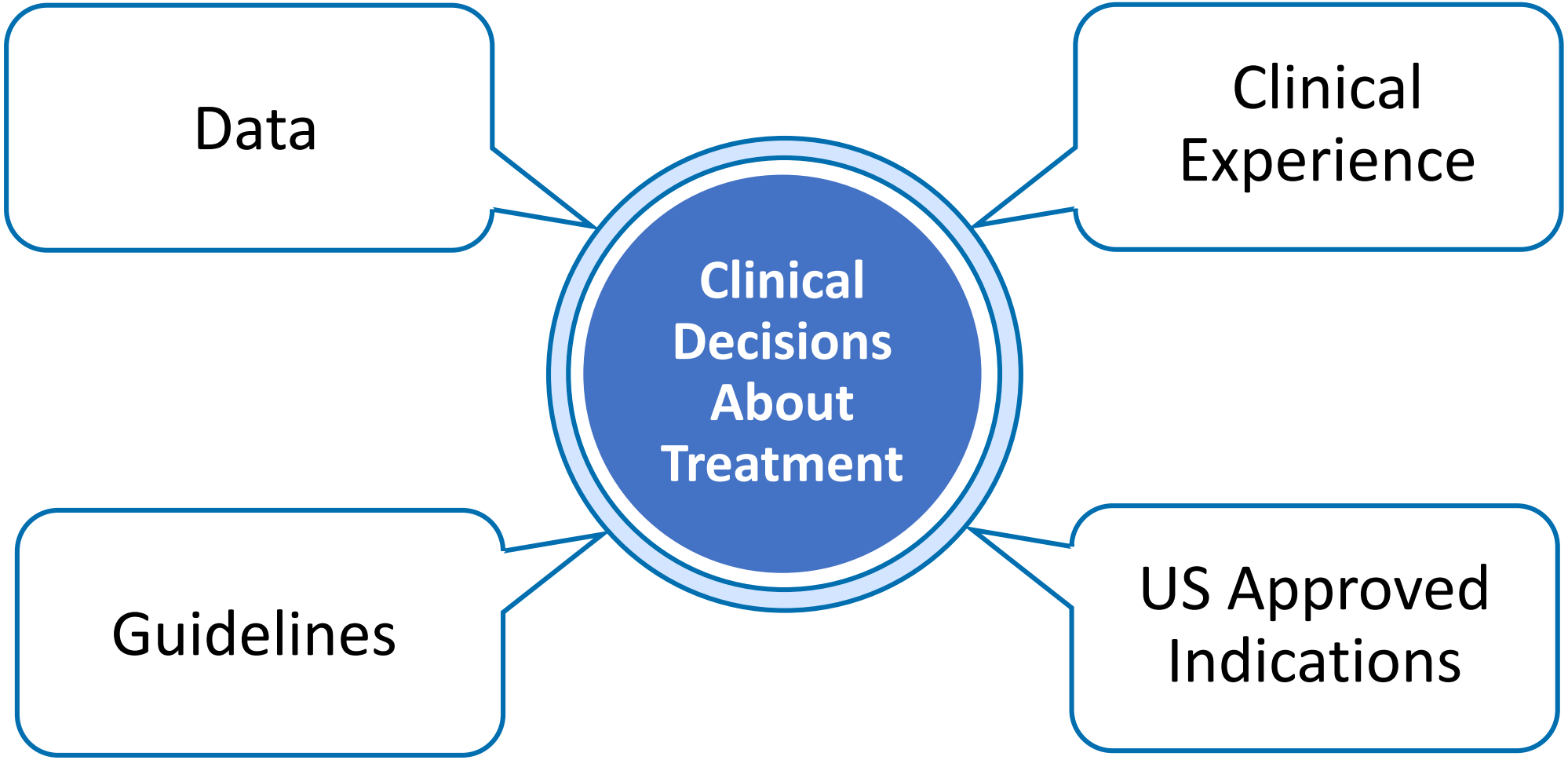
Genomic effects occur (4-24 hours)[3,5]

- Increases anti-inflammatory gene transcription
- Decreases proinflammatory gene transcription
- Increases β_2-receptor gene transcription

ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist.

[1]Amrani Y, et al. *Adv Immunol*. 2017;136:1-28; [2]Koziol-White C, et al. *Am J Physiol Lung Cell Mol Physiol*. 2020;318(2):L345-L355; [3]Alangari AA. *Ann Thorac Med*. 2010;5(3):133-139; [4]Zhou J, et al. *Allergy*. 2008;63(9):1177-1185; [5]Black JL, et al. *Chest.* 2009;136(4):1095-1100. doi:10.1378/chest.09-0354; [6]Johnson M, et al. *Proc Am Thorac Soc*. 2004;1(3):200-206; [7]Williams DM. *Respir Care*. 2018;63(6):655-670; [8]Adapted from the Centre of Excellence in Severe Asthma as part of the Centre of Research Excellence in Severe Asthma. https://toolkit.severeasthma.org.au.

Primary Care Decisions About Treatment



Supportive Slides

ICS as Background Therapy

Adolescents

Adolescents: n (%) of patients on low/medium/high dose background ICS	BDA MDI 160/180 N = 34	BDA MDI 80/180 N = 32	AS MDI N = 34	Total N = 100
Patients on low dose ICS, n (%)	8 (23.5)	12 (37.5)	12 (35.3)	32 (32)
Patients on medium dose ICS, n (%)	20 (58.8)	18 (56.3)	16 (47.1)	54 (54)
Patients on high dose ICS, n (%)	6 (17.6)	2 (6.3)	6 (17.6)	14 (14)

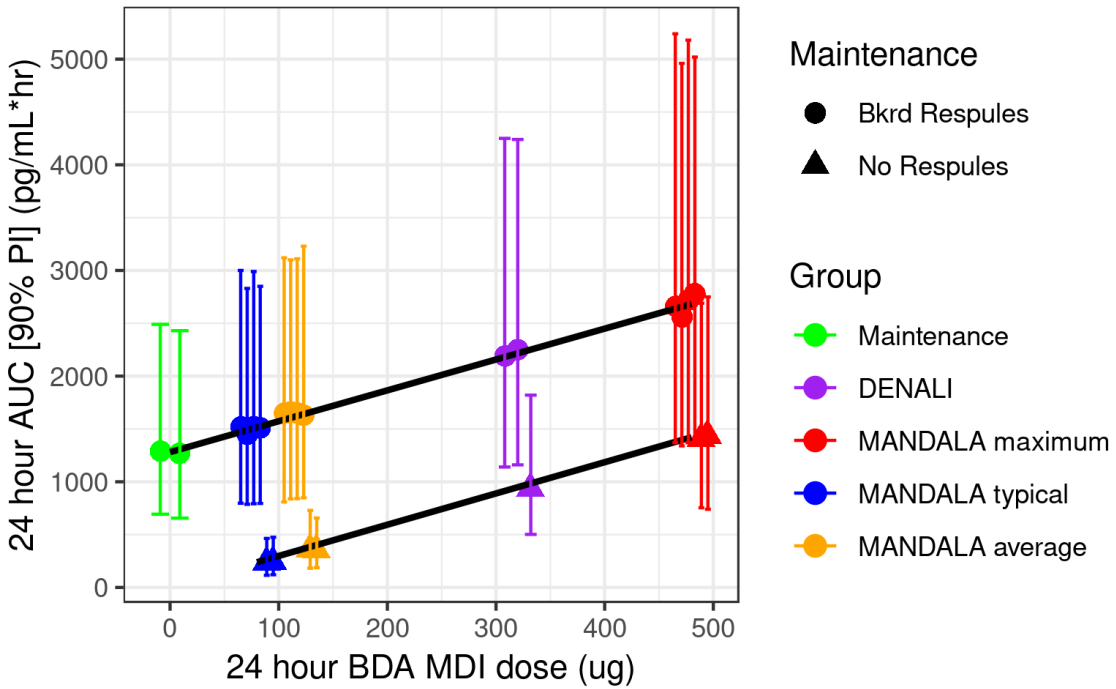
ICS as Background Therapy

Children

Children: n (%) of patients on low/medium/high dose background ICS	BDA MDI 80/180 N = 41	AS MDI N = 42	Total N = 83
Patients on low dose ICS, n (%)	2 (4.9)	2 (4.8)	4 (4.8)
Patients on medium dose ICS, n (%)	26 (63.4)	26 (61.9)	52 (62.7)
Patients on high dose ICS, n (%)	13 (31.7)	14 (33.3)	27 (32.5)

Budesonide Systemic Steady-state Exposure Scale Linearly with Budesonide Dose in Children 4–8 Years Old

Budesonide median AUC values under different dosing scenarios in Children 4 - 8 years



24 hour budesonide dose calculated using labeled dose. AUC24 = area under the concentration-time curve in 24-hours (presented as median and 90% prediction interval (PI)); Cmax = maximum concentration

Severe Asthma Exacerbations

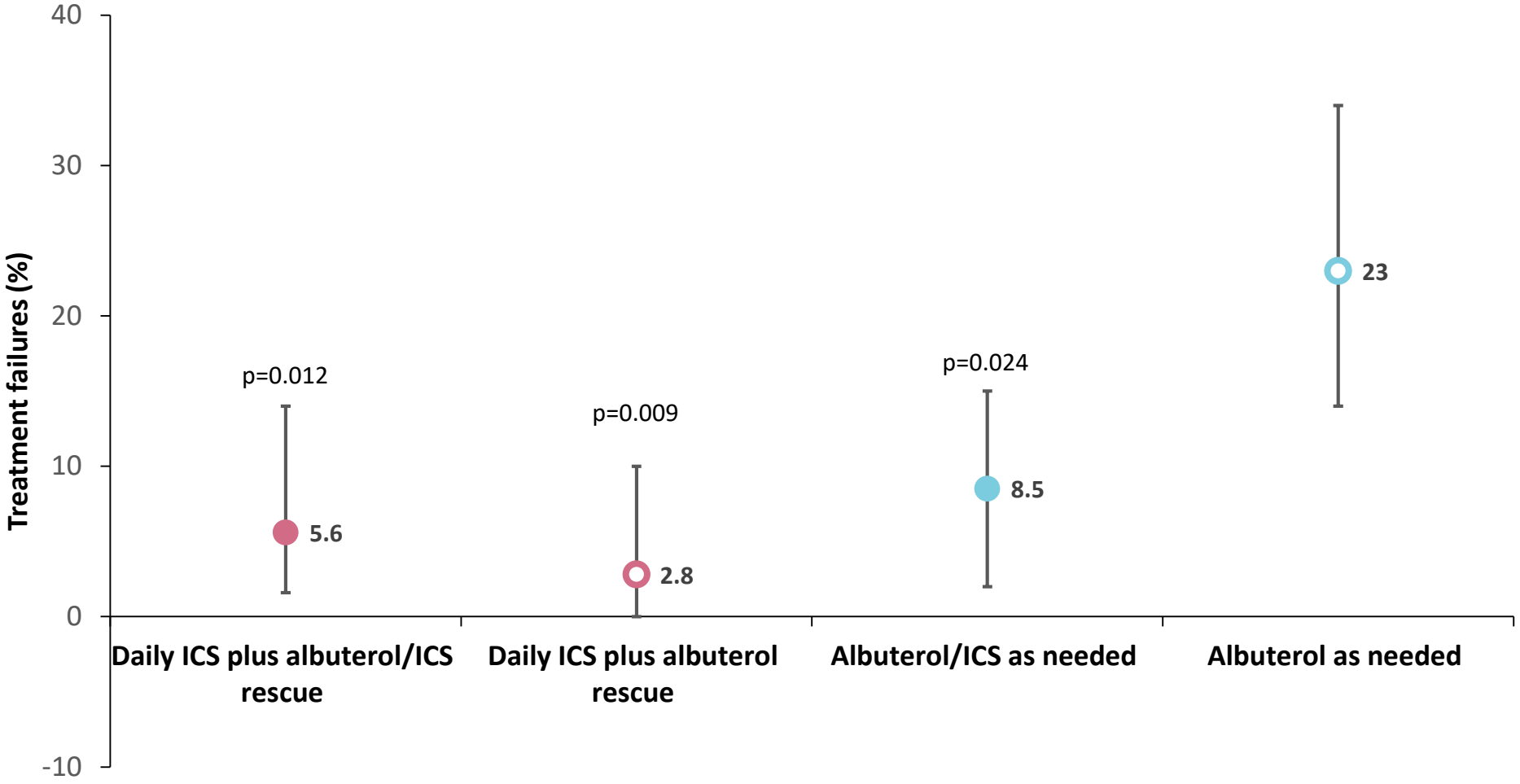
DENALI

Event		BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=201)	BD MDI 160 (N=199)	AS MDI 180 (N=196)	Placebo MDI (N=196)	Total (N=989)
All severe exacerbations							
Patients with at least one n (%)	Yes	4 (2.0)	5 (2.5)	4 (2.0)	20 (10.2)	14 (7.1)	47 (4.8)
	No	193 (98.0)	196 (97.5)	195 (98.0)	176 (89.8)	182 (92.9)	942 (95.2)

N=number of patients in treatment group; n=number of patients in the analysis set.

Treatment Failures Over 12 Months

TREXA[1]

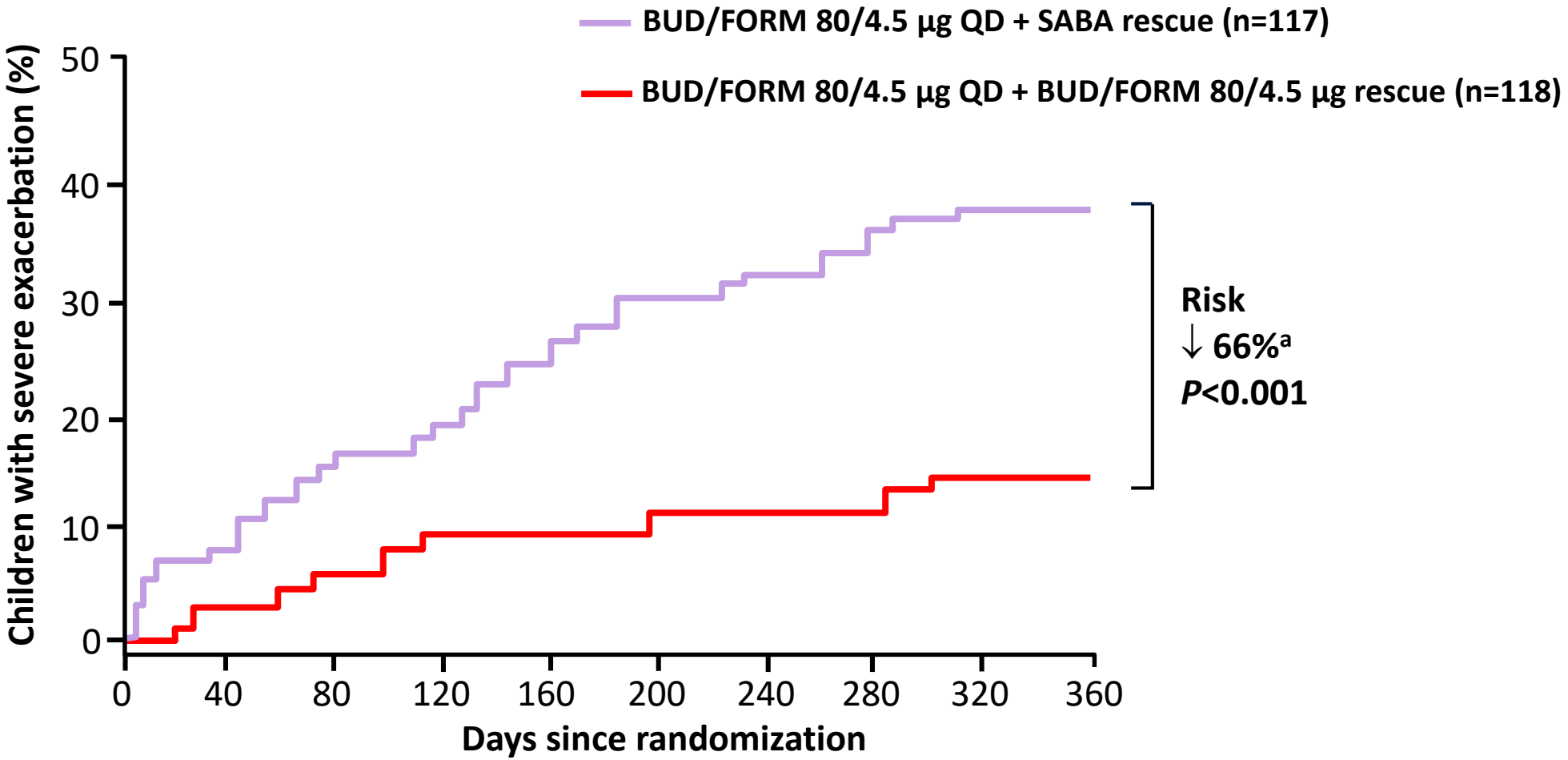


Vertical bars are 95% CIs. *P* values are based on the estimated relative risks from the proportional hazards regression analysis that compared each treatment group with the albuterol group.

[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.

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.

Lung Function at Weeks 12 and 24

Adolescents, ≥12 to <18 years

- FEV1 was an exploratory endpoint in the overall populations, examining the specific subgroups of adolescent and children was a post-hoc analysis.

				Comparison Between Groups		
Timepoint	Comparison	n	Least-Squares Mean (mL)	Differences in Least-Squares Means (mL)	95% CI	p value (2-sided)
Wk 12	BDA 80/180 vs AS MDI	28 26	275.3 72.5	202.8	(34.4, 371.2)	0.02
	BDA 160/180 vs AS MDI	29 26	142.3 72.5	69.8	(-97.2, 236.8)	0.41
Wk 24	BDA 80/180 vs AS MDI	24 19	267.8 71.8	196.0	(1.5, 390.5)	0.048
	BDA 160/180 vs AS MDI	21 19	220.3 71.8	148.5	(-49.2, 346.2)	0.14

- **Week 12 represents a mean improvement over baseline of ~7.8% and 2.7% for low and high dose, respectively**
- **Week 24 represents a mean improvement over baseline of ~7.5% and 5.7% for low and high dose, respectively**

Generally speaking, the MCID for predose lung function improvement is ~100ml for adults.

Lung Function at Weeks 12 and 24

Children, ≥4 to <12 years

- FEV1 change from baseline was an exploratory endpoint in the overall populations; examining the specific subgroups of adolescent and children was a post-hoc analysis

				Comparison Between Groups		
Timepoint	Comparison	n	Least-Squares Mean (mL)	Differences in Least-Squares Means (mL)	95% CI	p value (2-sided)
Week 12	BDA 80/180 vs AS MDI	30 30	146.1 14.6	131.5	(-26.8, 289.8)	0.104
Week 24	BDA 80/180 vs AS MDI	21 23	220.1 36.9	183.2	(-4.3, 370.7)	0.056

- **Week 12 represents a mean improvement over baseline of ~8.2%**
- **Week 24 represents a mean improvement over baseline of ~11.5%**

The NIH funded CLIC studied stated that a 6% improvement is clinically relevant