U.S. FOOD & DRUG ADMINISTRATION

FDA Pulmonary-Allergy Drug Advisory Committee

Overview of the Clinical Program and Clinical and Statistical Considerations

NDA 214070: budesonide/albuterol sulfate metered dose inhaler for the as-needed treatment of asthma

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November 8, 2022

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BDA MDI

- **Dosage form and strengths:**
  - Inhalation aerosol: pressurized metered dose inhaler (MDI) that delivers a combination of budesonide (40 µg or 80 µg) and albuterol sulfate (90 µg) per inhalation
- **Proposed dosing regimen:**
  - **≥12 years:** 2 inhalations of 80/90 µg **(160/180)**
  - **≥4 to <12 years:** 2 inhalations of 40/90 µg **(80/180)**
  - Not to exceed 6 doses / 24 hours
- **Proposed indication:**

  "for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older"
- **Novel indication, first ICS/SABA fixed dose combination, new intended use for ICS**

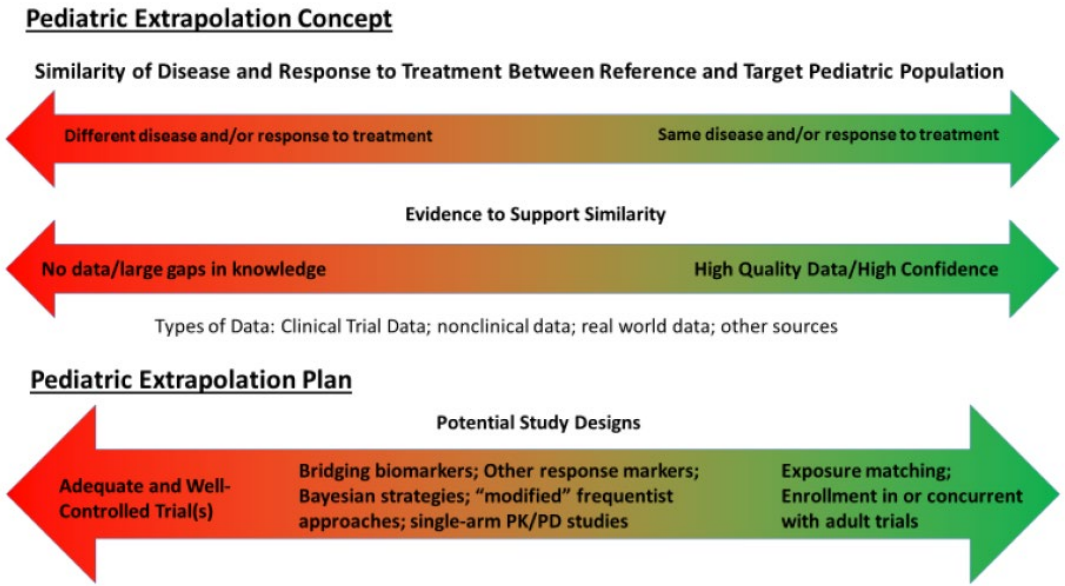
Terminology

- **Drug classes:**
  - ICS: inhaled corticosteroid
  - SABA: short-acting beta$_2$-adrenergic agonist
  - LABA: long-acting beta$_2$-adrenergic agonist
  - LAMA: long-acting muscarinic antagonist
  - SCS: systemic corticosteroids
- **Drug names:**
  - BD: budesonide
  - AS: albuterol sulfate
  - **BDA 160/180 (High Dose)**: budesonide 160 µg / albuterol sulfate 180 µg
  - **BDA 80/180 (Low Dose)**: budesonide 80 µg / albuterol sulfate 180 µg

Meeting Goals

- Discuss the data to support the **efficacy** of BDA for the proposed indication
  - Discuss if **extrapolation** of adult data to pediatric subjects is appropriate and if additional data are needed
- Discuss the **safety** data for BDA for the proposed indication
  - Discuss any specific pediatric safety concerns
- Discuss whether the data support a favorable **benefit risk assessment** for use of BDA:
  - In patients ≥18 years
  - In patients ≥12 to <18 years
  - In patients ≥4 to <12 years

Pediatric Extrapolation



Source: FDA Draft Guidance for Industry: E11A Pediatric Extrapolation, 2022.

High Degree of Extrapolation Appropriate, if:

- Disease the same in adult and pediatric patients.
- Response to treatment the same in adult and pediatric patients.
- High confidence in evidence.
- No significant knowledge gaps.

FDA Clinical & Statistical Presentations

- Present background for understanding BDA development program
- Provide an overview of BDA development program
- Provide efficacy and safety results, with focus on pediatric subgroups
- Summarize key concerns and uncertainties
- Present questions to the committee

BACKGROUND

Asthma Overview

Chronic respiratory disease, characterized by inflammation, bronchoconstriction, and airway hyper-responsiveness

- Epidemiology: common, adult and pediatric prevalence 8% in US
- Natural history: variable range of severity and symptoms
  - Acute exacerbations
    - Rx with PRN SABA and systemic corticosteroids
    - Morbidity & mortality
- Treatment goals: control symptoms and prevent exacerbations
  - **Controller** inhalers (ICS, LABA, LAMA) and **reliever** inhalers (SABA)

CDC 2018.

Current Reliever Treatments for Asthma

- Current FDA-approved treatments
  - SABA only class approved in US & AS in various formulations accounts for majority of clinical use
  - No reliever therapies with indication to prevent severe exacerbations
- Paradigm shift in approach to reliever treatment
  - PRN ICS & LABA (formoterol)
    - 'SMART' (single maintenance and reliever therapy) in GINA & NAEPP guidelines
      - No ICS/LABA fixed dose combination FDA-approved with reliever indication
  - PRN ICS & SABA
    - Alternative recommendation for mild disease in GINA & NAEPP guidelines
      - If approved, BDA would be first ICS/SABA fixed dose combination
- Extensive literature on ICS to prevent or abort exacerbations, inconclusive

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

PIVOTAL TRIAL DESIGN

Pivotal Trials for Registration

- **MANDALA**
  - Contribution of ICS to ICS/SABA as PRN in preventing severe acute asthma exacerbations
  - Agency views as primary source of efficacy data

- **DENALI**
  - Contribution of each component (ICS and SABA) to effect on lung function
  - Agency views as supportive evidence, safety data for higher dose and mild population, satisfying combination rule

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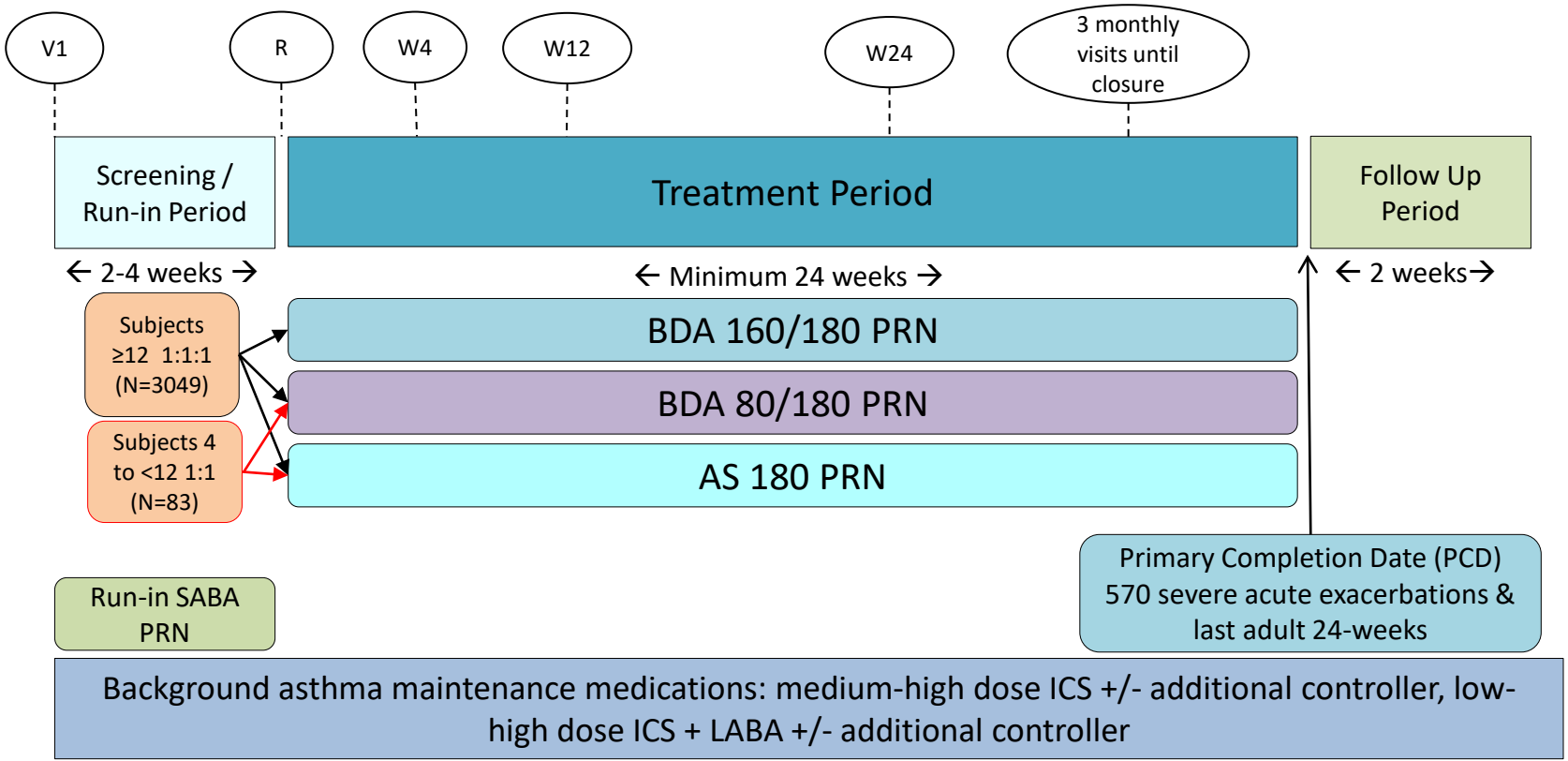
MANDALA Study Design



Source: Clinical reviewer; PRN=as needed

MANDALA Population

Representative of moderate-severe asthma: e.g., GINA guideline steps 2-5

Key Inclusion Criteria

- Subjects ≥4 years of age with asthma defined by GINA criteria for at least 1 year.
- Receiving 1 of the following asthma maintenance therapies for at least 3 months:
  - Medium to high dose ICS
  - Medium to high dose ICS + LTRA, LAMA, or theophylline
  - Low to high dose ICS + LABA, with or without LTRA, LAMA, or theophylline.
- Prebronchodilator FEV1 ≥40 to <90% PN for adults, and ≥60% PN for subjects aged 4 to 17 years.
- Asthma Control Questionnaire 7 (ACQ-7) and ACQ-5 scores ≥1.5.
- At least 1 severe asthma exacerbation within 12 months prior to Visit 1.
- Use of Ventolin PRN for asthma systems on at least 3 days / week during the run-in period.

Key Exclusion Criteria

- SCS use within 6 weeks of Visit 1 or chronic use of OCS (≥3 weeks/month).
- Receipt of any biologics, marketed or investigational, within 3 months or 5-half lives of Visit 1, whichever is longer.
- Current smokers or former smokers with >10 pack-year history or with cessation <6 months of Visit 1.
- Asthma with previous history of intubation for hypercapnia, respiratory arrest, hypoxic seizures, or syncope.

GINA = Global Initiative for Asthma
PN = predicted normal

MANDALA Endpoints

- **Primary**
  - Time to first severe asthma exacerbation
- **Secondary**
  - Annualized rate of severe asthma exacerbations
  - Total SCS exposure over the treatment period (mg/subject)
  - ACQ-5 change from baseline and responder analysis at Week 24
    - Responders: Week 24 – baseline ≤-0.5 (MCID)
  - AQLQ12+ & PAQLQ change from baseline and responder analysis at Week 24
    - Responders: Week 24 – baseline ≥0.5 (MCID)

ACQ5=Asthma Control Questionnaire 5
MCID=minimal clinically important difference
AQLQ12+=Asthma Quality of Life Questionnaire 12+
PAQLQ=Pediatric Asthma Quality of Life Questionnaire

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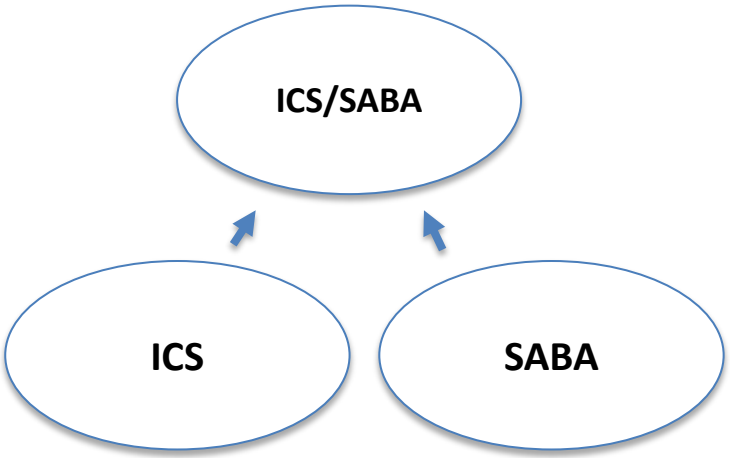
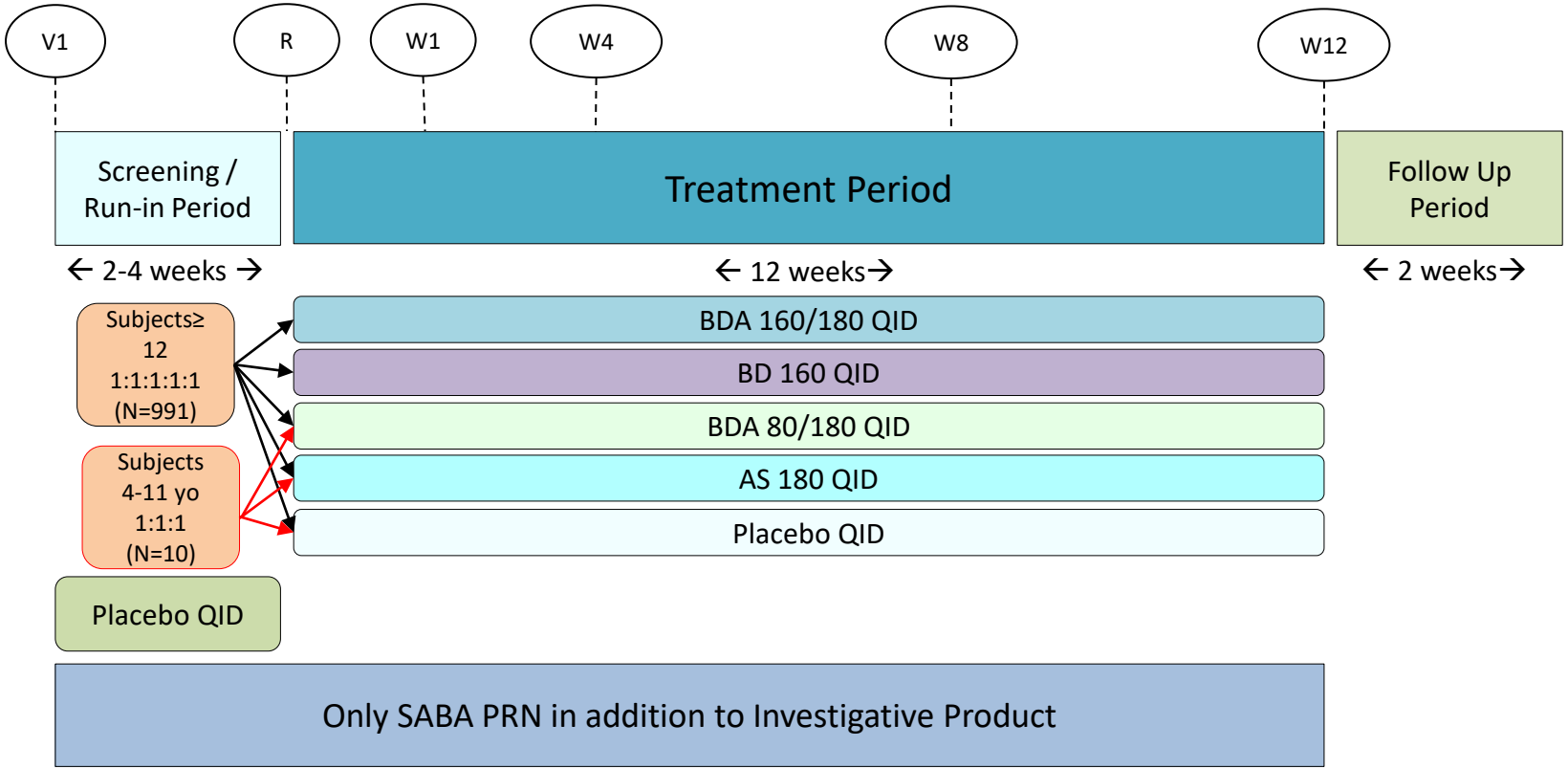
Regulatory Consideration: Combination Rule

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component…is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy." (*21CFR300.50a*)



Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products, 2006

DENALI Study Design



Source: Clinical reviewer; QID=four times daily

DENALI Population

Representative of mild asthma: e.g., GINA guideline steps 1-2

Key Inclusion Criteria

- Subjects ≥4 years of age with asthma as defined by GINA criteria for at least 6 months.
- Receiving 1 of the following inhaled asthma medications with stable dosing for at least 1 month:
  - PRN SABA
  - Stable low-dose ICS with PRN SABA.
- Prebronchodilator FEV1 ≥50 to <85% PN for adults, and ≥50% PN for subjects aged 4 to 17 years.
- Use of Ventolin ≥2 days out of 7 prior to visit 2.

Key Exclusion Criteria

- SCS use within 3 months before visit 1 and ≥3 weeks of SCS within 6 months prior.
- Current smokers or former smokers with >10 pack-year history or cessation <6 months of visit 1.
- Asthma with previous history of intubation for hypercapnia, respiratory arrest, hypoxic seizures, or syncope.
- Use of ≥12 actuations per day of Ventolin during run-in period:
  - ≥2 days out of 14
  - ≥3 days out of 15-21
  - ≥4 days out of 22 or more.

GINA = Global Initiative for Asthma
PN = predicted normal

DENALI Endpoints

- **Primary**
  - Change from baseline in FEV1 AUC 0-6 hours over 12 weeks
  - Change from baseline in trough FEV1 at week 12
- **Secondary**
  - Time to onset of 15% increase in FEV1 on day 1 and duration of effect on day 1
  - ACQ-7 responder analysis
    - Responder: Week 12 – baseline ≤-0.5 (MCID)
  - Trough FEV1 at week 1

AUC=area under the curve
ACQ7=Asthma Control Questionnaire 7
MCID=minimal clinically important difference

SUMMARY OF EFFICACY RESULTS

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Full Analysis Set

MANDALA	Number of Subjects, n (%)			
Randomized	**BDA MDI (160/180 mcg) N = 1016**	**BDA MDI (80/180 mcg) N = 1057**	**AS MDI (180 mcg) N = 1059**	**Total N = 3132**
Full analysis set (FAS)*	**1013 (100)**	**1054 (100)**	**1056 (100)**	**3123 (100)**
Adults (≥18)	979 (96.6)	981 (93.1)	980 (92.8)	2940 (94.1)
Adolescents (≥12 - < 18)	34 (3.4)	32 (3.0)	34 (3.2)	100 (3.2)
Children (≥4 - < 12)	NA	41 (3.9)	42 (4.0)	83 (2.7)

Source: Statistical Reviewer

* All subjects who were randomized to treatment and took any amount of IP

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Subjects who discontinued randomized treatment	100 (9.8)	122 (11.5)	141 (13.3)	363 (11.6)
Subject decision	52 (5.2)	62 (5.9)	74 (7.0)	188 (6.0)
Adverse event	11 (1.1)	9 (0.9)	9 (0.8)	29 (0.9)
Lack of therapeutic response	1 (0.1)	2 (0.2)	2 (0.2)	5 (0.2)
Others	36 (3.5)	49 (4.6)	56 (5.3)	141 (4.5)
Subjects withdrew from study	93 (9.2)	122 (11.5)	137 (12.9)	352 (11.2)
Withdrawal by subject	48 (4.7)	56 (5.3)	68 (6.4)	172 (5.5)
Lost to follow-up	19 (1.9)	26 (2.5)	22 (2.1)	67 (2.1)
Adverse event	4 (0.4)	7 (0.7)	7 (0.7)	18 (0.6)
Others	22 (2.2)	33 (3.1)	40 (3.8)	95 (3.0)

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Primary Endpoint Efficacy Results

Primary Analysis of Time to First Severe Exacerbation, Efficacy (While-on-treatment) Estimand† (MANDALA, FAS)

Treatment Group	N	Number (%) of Subjects with a Severe Exacerbation	Comparison Versus AS MDI 180		
			Hazard Ratio	95% CI	P-value
High Dose Efficacy					
BDA MDI 160/180	1013	207 (20)	0.73	0.61, 0.88	<0.001
AS MDI 180	1014	266 (26)			
Low Dose Efficacy					
BDA MDI 80/180	1013 + 41*	241 (23)	0.83	0.70, 0.99	0.041
AS MDI 180	1014 + 42*	276 (26)			

† Included data before discontinuation of randomized treatment or change in maintenance therapy

* Number of children 4 to 11 years

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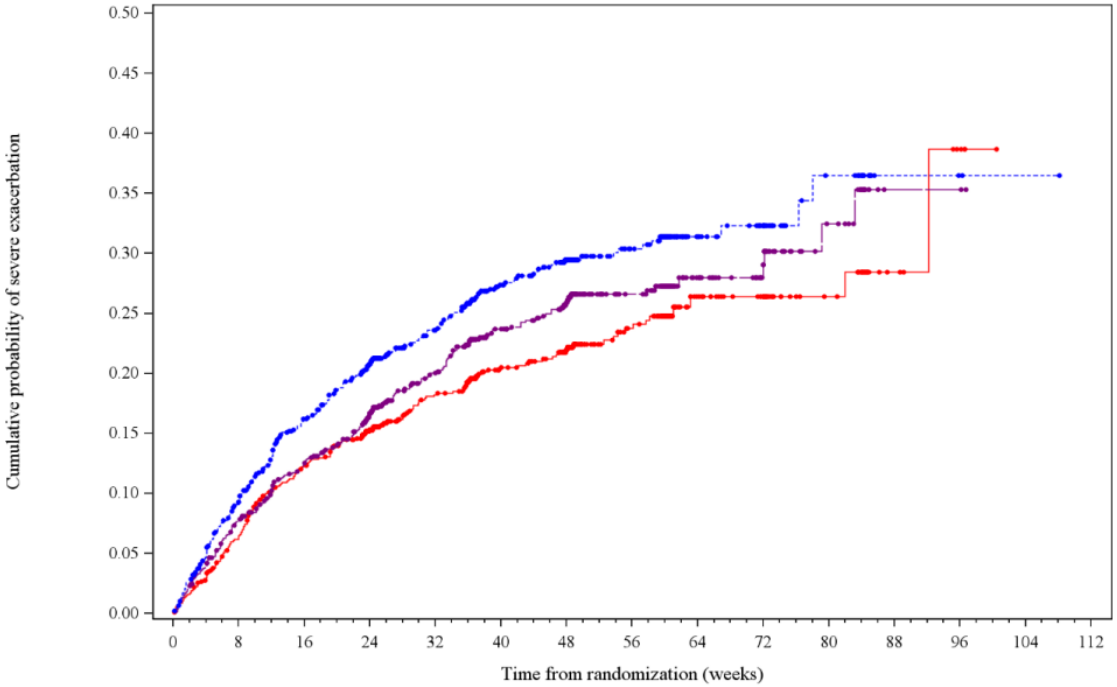

Number of patients at risk

BDA MDI 160/180	1013	936	863	761	551	442	389	229	79	65	37	9	4	0	0
BDA MDI 80/180	1054	958	888	777	550	433	372	228	88	69	28	2	2	0	0
AS MDI 180	1056	937	835	725	519	401	346	211	79	64	29	3	2	1	0

Source: The Applicant's CSR

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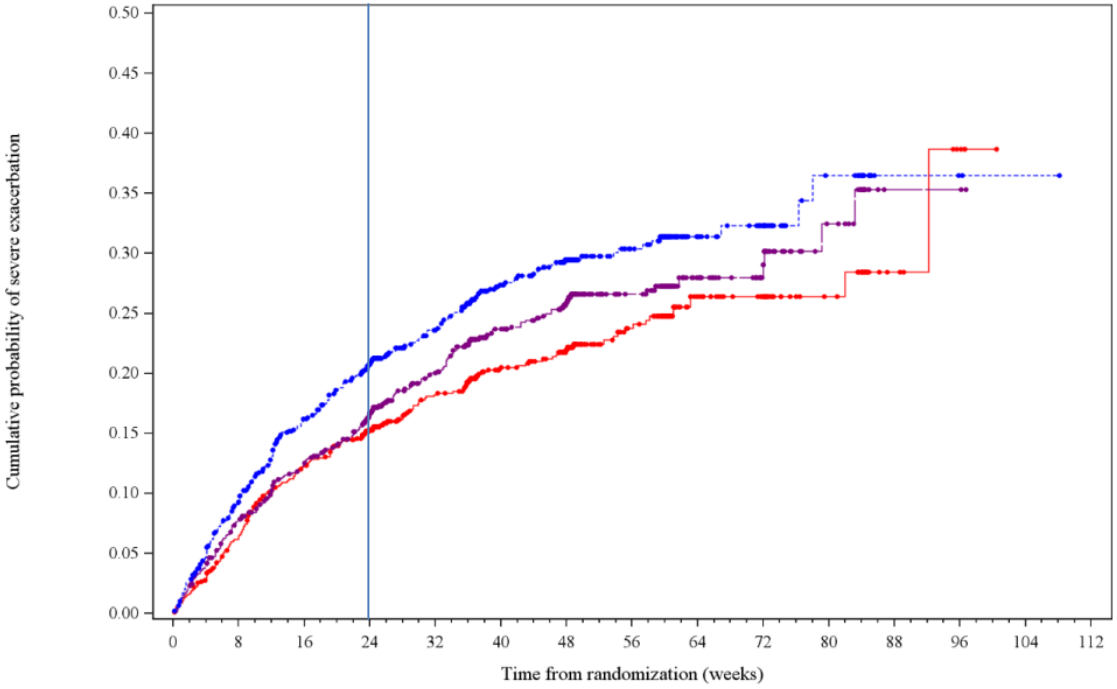

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Secondary Endpoints Efficacy Results

Key Secondary Efficacy Endpoints, Efficacy Estimand (MANDALA, FAS)

Secondary Endpoints	Treatment Group	Comparison Versus AS MDI 180		
		Estimate	95% CI	P-value
Annualized severe exacerbation rate	BDA MDI 160/180	RR= 0.76	0.62, 0.93	0.008*
	BDA MDI 80/180	RR= 0.80	0.66, 0.98	0.028*
Total annualized dose of systemic corticosteroid (mg/subject)	BDA MDI 160/180	% Diff = -33.4	NA	0.002*
	BDA MDI 80/180	% Diff = -24.8	NA	0.060
ACQ-5 minimal important difference at Week 24, responder status	BDA MDI 160/180	OR = 1.22	1.02, 1.47	0.034
	BDA MDI 80/180	OR = 1.13	0.95, 1.35	0.172
AQLQ+12 minimal important difference at Week 24, responder status	BDA MDI 160/180	OR = 1.23	1.02, 1.48	0.028
	BDA MDI 80/180	OR = 1.11	0.92, 1.34	0.260

*Results statistically significant

Source: Statistical Reviewer

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Efficacy Findings for Consideration

- **Pediatric Efficacy**
  - Efficacy for adults supported by significant delay in time to first severe exacerbation
  - Uncertainty regarding efficacy for high dose BDA (160/180 µg) in adolescents (12-17; n = 68)
  - Uncertainty regarding efficacy for low dose BDA (80/180 µg) in children (4-11; n = 83)

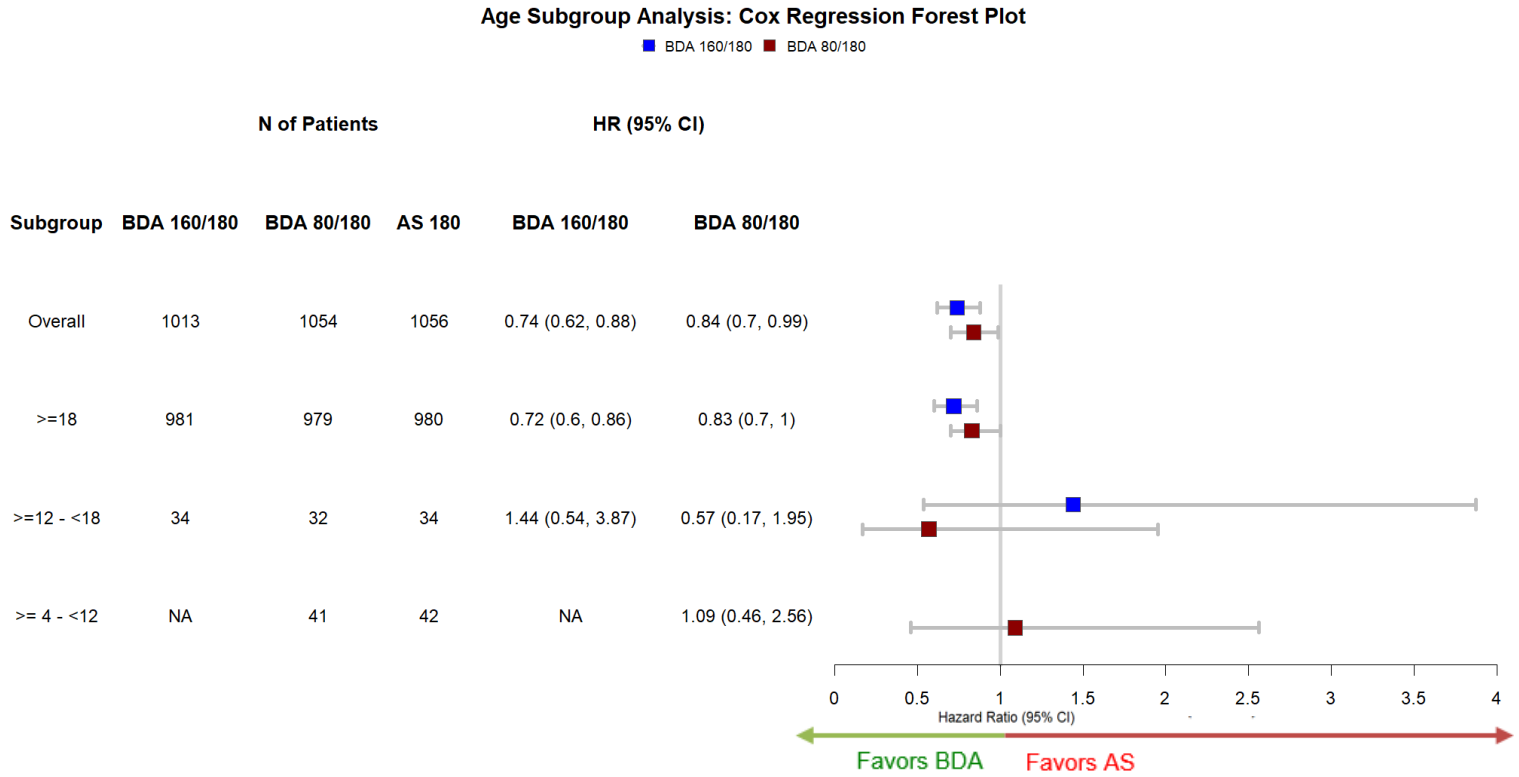
- **Low dose BDA (80/180 µg) Efficacy**
  - Marginal benefit (p-value = 0.041) observed in subjects ≥4 years
    - Sensitivity analysis to the missing data assumption did not appear to support robustness of the efficacy
    - No statistically significant benefit (p-value = 0.052) was demonstrated under supplementary estimand

Pediatric Efficacy: Statistical Analysis Plan

- Sample Size Calculation (MANDALA)
  - 1000 **adult and adolescent subjects** per treatment group and observation of the 570 first severe exacerbation events
    - 87% power to observe a 25% reduction in the risk of severe exacerbation
  - In addition, up to 100 subjects in the 4-to-11 year age group were equally randomized to the AS MDI or to the low dose BDA MDI only

Pediatric Efficacy: Age-Based Subgroup Analysis

Forest Plot for Time to First Severe Exacerbation, Efficacy Estimand, Age-Based Subgroups (FAS)



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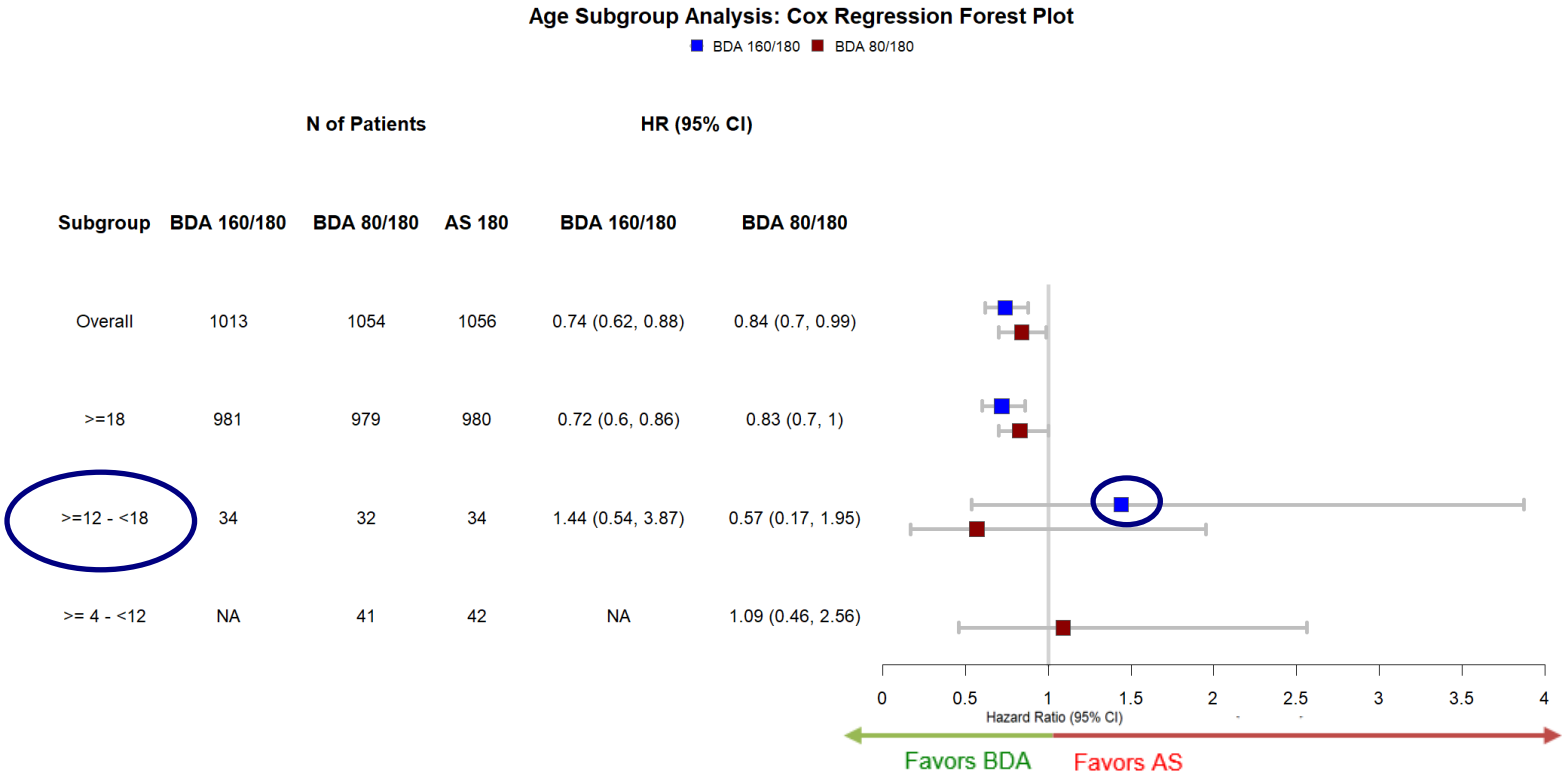

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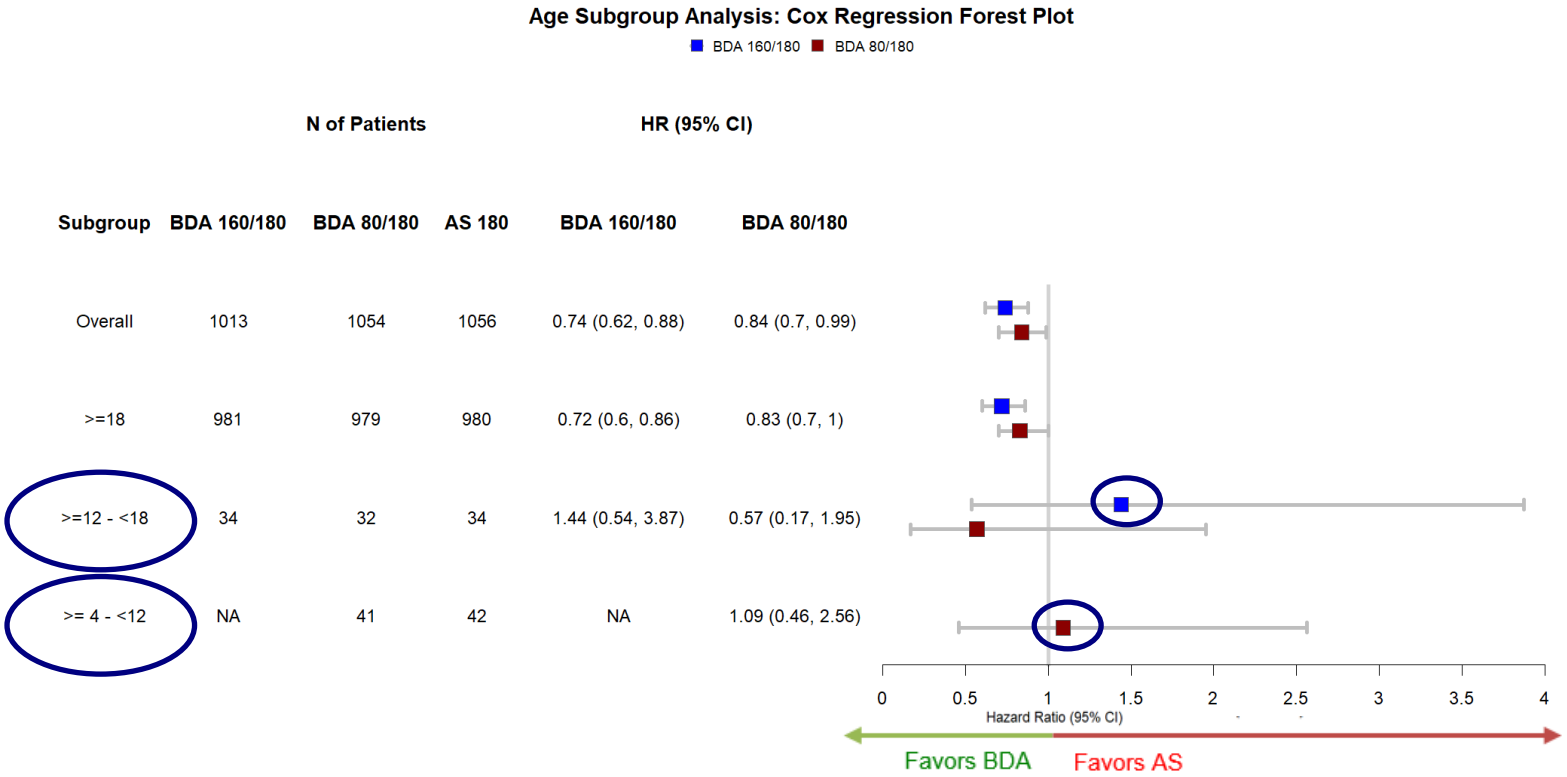

Source: Statistical Reviewer

Pediatric Efficacy: Bayesian Analysis

- Possible decision rule supporting pediatric efficacy
  - 95% Credible Interval (Bayesian confidence interval) excludes null value

- Two Bayesian borrowing approaches conducted
  - Robust Mixture Prior
  - Bayesian Hierarchical Model

Pediatric Efficacy: Bayesian Analysis for Adolescents — Robust Mixture Prior Approach by FDA

Borrowing Required to Establish Efficacy of *High Dose* BDA in *Adolescents (12 to <18)*

Bayesian Weight on Adults in Prior	Median HR	95% Credible Interval for HR	Number of Borrowed Adult Events	Percentage of Total Events from Adults
0	1.41	(0.54, 3.68)	0	0.0%
0.25	0.98	(0.58, 3.35)	95	84.8%
0.5	0.78	(0.60, 2.95)	218	92.8%
0.75	0.75	(0.61, 2.36)	334	95.2%
0.9	0.74	(0.61, 1.62)	403	96.0%
0.95	0.74	(0.61, 0.98)	427	96.2%
1	0.73	(0.61, 0.88)	455	96.4%

Source: Statistical Reviewer

High degree of Bayesian borrowing (>95%) required to achieve meaningful results.

Pediatric Efficacy: Bayesian Analysis for Children — Robust Mixture Prior Approach by FDA

Borrowing Required to Establish Efficacy of *Low Dose* BDA in *Children (4 to <12)*

Bayesian Weight on Adults in Prior	Median HR	95% Credible Interval for HR	Number of Borrowed Adult Events	Percentage of Total Events from Adults
0	1.08	(0.47, 2.50)	0	0%
0.25	0.86	(0.55, 2.13)	175	88.8%
0.5	0.84	(0.64, 1.79)	313	93.4%
0.75	0.84	(0.69, 1.34)	409	94.9%
0.9	0.83	(0.70, 1.02)	458	95.4%
0.95	0.83	(0.70, 1.00)	478	95.6%
1	0.83	(0.70, 0.99)	494	95.7%

Source: Statistical Reviewer

High degree of Bayesian borrowing (> 95%) required to achieve meaningful results.

Pediatric Efficacy: Bayesian Analysis — Bayesian Hierarchical Model Approach by Applicant

Observed and Modeled Estimates in Each Age Subgroup by Dose

Group	HR (95% Interval) [Events]		
	Observed	Modeled	Percentage of Total Events Borrowed
BDA MDI 80/180			
4-<12	1.09 (0.46, 2.56) [21]	0.84 (0.60, 1.34) [96]	78.1%
12-<18	0.57 (0.17, 1.95) [11]	0.84 (0.50, 1.18) [83]	86.8%
18-<65	0.83 (0.68, 1.01) [398]	0.82 (0.69, 0.97) [526]	24.3%
65+	0.81 (0.53, 1.24) [87]	0.80 (0.62, 1.08) [196]	55.6%
BDA MDI 160/180			
12-<18	1.44 (0.54, 3.87) [16]	0.86 (0.62, 1.48) [80]	80.0%
18-<65	0.68 (0.55, 0.83) [362]	0.73 (0.59, 0.87) [417]	13.2%
65+	0.89 (0.59, 1.33) [95]	0.83 (0.65, 1.12) [201]	52.7%

Note: Bayesian hierarchical model with age and dose group based on weak borrowing (Tau=2.0)

Source: The Applicant's Additional Exploratory Analysis Version 1.0

Estimand Strategy for Intercurrent Events

- Efficacy estimand (primary)
  - Treatment discontinuation or change in maintenance therapy (**While-on-treatment strategy**)
    - follow-up for events was censored among subjects with these intercurrent events in the primary analysis

- De facto estimand (supplementary)
  - Treatment discontinuation or change in maintenance therapy **(Treatment policy strategy**)
    - included all severe exacerbations, including those post randomized treatment discontinuation, or following changes in maintenance therapy in the primary analysis

Frequency Distribution of Intercurrent Events

MANDALA	Number of Subjects, n (%)			
	High Dose Efficacy (N = 3040)		Low Dose Efficacy (N = 3123)	
	BDA MDI (160/180) N = 1013	AS MDI (180) N = 1014	BDA MDI (80/180) N = 1054	AS MDI (180) N = 1056
Intercurrent events	**79 (7.2)**	**97 (9.6)**	**100 (9.5)**	**101 (9.6)**
Chg in maintenance therapy	4 (0.4)	3 (0.3)	11 (1.0)	3 (0.3)
Treatment discontinuation	75 (7.4)	94 (9.3)	89 (8.4)	98 (9.3)

Source: Statistical Reviewer

Supplementary Estimand

Primary Analysis of Time to First Severe Exacerbation, De Facto (Treatment policy) Estimand†
(MANDALA, FAS)

Treatment Group	N	Number (%) of Subjects with a Severe Exacerbation	Comparison Versus AS MDI 180		
			Hazard Ratio	95% CI	P-value
High Dose Efficacy					
BDA MDI 160/180	1013	212 (21)	0.74	0.62, 0.89	<0.001
AS MDI 180	1014	270 (27)			
Low Dose Efficacy					
BDA MDI 80/180	1013 + 41*	248 (24)	0.84	0.71, 1.002	0.052
AS MDI 180	1014 + 42*	280 (27)			

† Included all severe exacerbations, including those post randomized treatment discontinuation, or following changes in maintenance therapy

* Number of children 4 to 11 years

Source: Statistical Reviewer

Sensitivity of Primary Analysis to Missing Data

- Missing rate <10% and balanced among treatment groups
- The result for high dose BDA was robust to the missing data assumption (censoring-at-random)
- The result for low dose BDA was not likely robust to the missing data assumption (censoring-at-random)

Pivotal Trials for Registration

- **MANDALA**
  - Contribution of ICS to ICS/SABA as PRN in preventing severe acute asthma exacerbations
  - Agency views as primary source of efficacy data

- **DENALI**
  - Contribution of each component (ICS and SABA) to effect on lung function
  - Agency views as supportive evidence, safety data for higher dose and mild population, satisfying combination rule

Primary Endpoint Efficacy Results

Primary Analysis of FEV1 $AUC_{0\text{-}6hours}$ and Trough FEV1, Efficacy Estimand (FAS ≥12 Years)

Variable	Visit	Comparison	Least Squares Mean	Comparison Between Groups		
				Difference in Least Squares Means	95% CI	P-value
Change from baseline FEV1 $AUC_{0\text{-}6hours}$ (mL)	Treatment average over 12 weeks	AS MDI 180 (N=196) vs. Placebo MDI (N=196)	157.2 vs. 96.7	60.5	7.7, 113.4	0.03
		BDA MDI 160/180 (N=197) vs. Placebo MDI (N=196)	258.6 vs. 96.7	161.9	109.4, 214.5	<0.01
		BDA MDI 160/180 (N=197) vs. BD MDI 160 (N=199)	258.6 vs.178.0	80.7	28.4, 132.9	<0.01
Change from baseline in trough FEV1 (mL)	Week 12	BD MDI 160 (N=199) vs. Placebo MDI (N=196)	108.9 vs. 35.6	73.3	4.5, 142.1	0.04
		BDA MDI 160/180 (N=197) vs. Placebo MDI (N=196)	135.5 vs. 35.6	99.9	31.0, 168.7	0.01
		BDA MDI 160/180 (N=197) vs. AS MDI 180 (N=196)	135.5 vs. 2.7	132.8	63.8, 201.9	<0.01
		BDA MDI 80/180 (N=200) vs. Placebo MDI (N=196)	123.5 vs. 35.6	87.9	18.9, 156.8	0.01
		BDA MDI 80/180 (N=200) vs. AS MDI 180 (N=196)	123.5 vs. 2.7	120.8	51.6, 190.0	<0.01

Source: Statistical Reviewer

Primary Endpoint Efficacy Results

Primary Analysis of FEV1 $AUC_{0\text{-}6hours}$ and Trough FEV1, Efficacy Estimand (FAS ≥12 Years)

Variable	Visit	Comparison	Least Squares Mean	Comparison Between Groups		
				Difference in Least Squares Means	95% CI	P-value
Change from baseline FEV1 $AUC_{0\text{-}6hours}$ (mL)	Treatment average over 12 weeks	AS MDI 180 (N=196) vs. Placebo MDI (N=196)	157.2 vs. 96.7	60.5	7.7, 113.4	0.03
		BDA MDI 160/180 (N=197) vs. Placebo MDI (N=196)	258.6 vs. 96.7	161.9	109.4, 214.5	<0.01
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Change from baseline in trough FEV1 (mL)	Week 12	BD MDI 160 (N=199) vs. Placebo MDI (N=196)	108.9 vs. 35.6	73.3	4.5, 142.1	0.04
		BDA MDI 160/180 (N=197) vs. Placebo MDI (N=196)	135.5 vs. 35.6	99.9	31.0, 168.7	0.01
		BDA MDI 160/180 (N=197) vs. AS MDI 180 (N=196)	135.5 vs. 2.7	132.8	63.8, 201.9	<0.01
		BDA MDI 80/180 (N=200) vs. Placebo MDI (N=196)	123.5 vs. 35.6	87.9	18.9, 156.8	0.01
		BDA MDI 80/180 (N=200) vs. AS MDI 180 (N=196)	123.5 vs. 2.7	120.8	51.6, 190.0	<0.01

Source: Statistical Reviewer

Summary of Efficacy Results

- MANDALA
  - Primary efficacy endpoint met and supported by secondary endpoints
    - Results in adults (≥18) are statistically significant
    - Results in the two pediatric subgroups (4 to <12 and 12 to <18) are uncertain
      - Wide CI (small sample size) with upper bound exceeding 1
      - High degree of Bayesian borrowing required to achieve meaningful results
    - Low dose BDA provided marginal benefit (p-value = 0.041)
      - Statistical significance lost under supplementary (treatment policy) estimand
      - Results not likely robust to departures from the missing data assumption
- DENALI
  - Dual-primary efficacy endpoints met
    - Combination rule satisfied

SUMMARY OF SAFETY RESULTS

SUMMARY OF SAFETY RESULTS

Safety Review

- Safety reviewed from individual trials, data not pooled
- Adverse Events (AEs) analyzed in Safety Analysis Set (SAS)
- Applicant & Agency prespecified ICS-related AEs
- Analyses by randomized treatment & background ICS (low/medium/high)

Safety Database

Trial	Safety N	Safety N by Age Group
MANDALA	• Randomized: 3,132 • SAS total: 3,127	• ≥4 to <12: 83 • ≥12 to <18: 100 • ≥18: 2944
DENALI	• Randomized: 1,001 • SAS total: 1,000	• ≥4 to <12: 10 • ≥12 to <18: 25 • ≥18: 965
Total	4,127	• ≥4 to <12: 93 • ≥12 to <18: 125 • ≥18: 3,909

Source: Clinical reviewer; SAS=safety analysis set

BDA Exposure

Comparison of Budesonide Systemic Exposure Between Adults (Study ELBRUS) and Children (Study BLANC) Following a Single Dose of BDA MDI

Geometric Mean (gCV%) of PK Parameters	Study ELBRUS in Adult Healthy Subjects		Study BLANC in Asthma Patients 4 to 8 Years of Age	
	BDA 160/180 µg (n=66)	Pulmicort Flexhaler 180 µg (n=66)	BDA 160/180 µg (n=11)	Pulmicort Respules 1000 µg (n=10)
C_{max} (pg/mL)	263 (49.7)	417 (40.9)	116 (46.6)	447 (156)
AUC_{0-t} (pg*h/mL)	916 (36.9)	1235 (37.3)	398 (46.3)	985 (78.7)
AUC_{0-inf} (pg*h/mL)	968 (34.8)	1279 (36.7)	NA	NA

Source: Clinical Pharmacology Reviewer.

Comparison of Total Budesonide Systemic Exposure ($AUC_{0-24hours}$) Between Adults and Pediatrics Under the 'Worst-Case Scenario Use' (12 Inhalations BDA MDI/Daily Plus the Maximum BD DPI Maintenance Dose)

Age Group	BDA MDI Maximum Dose[1]	Maximum BD DPI Maintenance Dose	Total BD Exposure in Pediatrics Relative to Adults Under Worst-Case Scenario Use
Adults	12 inhalations (960 µg)/day	720 µg BID[2]	1.0
Adolescents(≥12 yrs)[2]	12 inhalations (960 µg)/day	360 µg BID[2]	0.68
Children 9-11 yrs[2]	12 inhalations (480 µg)/day	360 µg BID[2]	0.48
Children 4-8 yrs	12 inhalations (480 µg)/day	1000 µg QD or 500 µg BID[3]	0.21

Source: Clinical Pharmacology Reviewer.

[2] Approved maximum BD dose from Pulmicort Flexhaler (6 to 17 years of age)
[3] Approved maximum BD dose from Pulmicort Respule (1 to 8 years of age)
[4] No observed PK data in children 9 to 18 years of age from the BDA program, the simulated results are based on adult bioavailability value

Pivotal Trials for Registration

- **MANDALA**
  - Contribution of ICS to ICS/SABA as PRN in preventing severe acute asthma exacerbations
  - Agency views as primary source of efficacy data

- **DENALI**
  - Contribution of each component (ICS and SABA) to effect on lung function
  - Agency views as supportive evidence, safety data for higher dose and mild population, satisfying combination rule

MANDALA BDA Use Pattern

Population	Mean duration treatment period (days)	Proportion subjects with ≥24 weeks treatment period (N, %)	Mean / median daily inhalations per IP
Safety Analysis Set, All Ages (N=3,127)	305	2,744 (88%)	• BDA 160/180: 2.6 / 2.3 • BDA 80/180: 2.6 / 2.3 • AS: 2.8 / 2.4
≥12 years to <18 years (N=100)	227	70 (70%)	• BDA 160/180: 2.9 / 3.1 • BDA 80/180: 2.6 / 1.7 • AS: 2.3 / 2.4
≥4 years to <12 years (N=83)	235	55 (66%)	• BDA 80/180: 2.1 / 1.0 • AS: 1.8 / 1.2

Source: Clinical Reviewer. IP=investigative product.

- <1% of all subjects used ≥12 inhalations on ≥2 days: 1 adolescent, 2 children

MANDALA Safety Overview

Number of Subjects with any Category of Adverse Event in the Randomized Treatment Period (Safety Analysis Set)

	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)
Any AE causally related to randomized treatment	21 (2.1)	20 (1.9)	16 (1.5)
Any AE leading to discontinuation of IP	10 (1.0)	9 (0.9)	9 (0.9)
Any SAE (including events with outcome of death)	53 (5.2)	40 (3.8)	48 (4.5)
Any AE with outcome of death	4 (0.4)	2 (0.2)	1 (0.1)

Source: Clinical Reviewer.

MANDALA Serious Adverse Events

- Most SAEs isolated events
- 8 deaths: 7 in randomized treatment period
- Higher incidence of COVID-19 in BDA 160/180 arm:
  - 1.1% vs 0.5% in 80/180 and 0.8% in AS
- Higher incidence of asthma in AS arm:
  - 1.9% vs 0.7% in BDA 160/180 and 0.8% in 80/180
  - Driven by subjects on medium & high dose background ICS
- Analyses stratified by background ICS and IP usage did not identify clear pattern of risk with additive effects of ICS

Results not unexpected for population and drug classes. No new signals identified.

MANDALA Adverse Events

Number of Subjects with Most Common (>2%) Adverse Events during the Randomized Treatment Period, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=1015)	BDA MDI 80/180 (N=1055)	AS MDI 180 (N=1057)
Preferred Term			
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)
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)
Asthma	18 (1.8)	20 (1.9)	35 (3.3)
Back pain	27 (2.7)	23 (2.2)	20 (1.9)
Influenza	21 (2.1)	23 (2.2)	14 (1.3)
Sinusitis	15 (1.5)	17 (1.6)	24 (2.3)

Source: Clinical Reviewer.

Most adverse events were mild to moderate and consistent with known risks of drugs classes. No new signals identified.

MANDALA Pediatric Adverse Events

Number of Subjects ≥4 to < 18with any Category of Adverse Event in the Randomized Treatment Period, Stratified by Age (Safety Analysis Set)

	BDA MDI 160/180	BDA MDI 80/180		AS MDI 180	
	≥12 - <18 (N=34)	≥4 - <12 (N=41)	≥12 - <18 (N=32)	≥4 - <12 (N=42)	≥12 - <18 (N=34)
Any AE	13 (38.2)	17 (41.5)	11 (34.4)	17 (40.5)	15 (44.1)
Any AE causally related to randomized treatment	0	2 (4.9)	0	0	0
Any AE leading to discontinuation of IP	0	1 (2.4)	0	0	0
Any SAE	1 (2.9)	1 (2.4)	0	1 (2.4)	2 (5.9)

Source: Clinical Reviewer.

Most adverse events were not serious or severe. Subjects <18 contributed a small number of adverse events to total.

MANDALA Pediatric Serious Adverse Events

Number of Subjects 4 to <18 with a Serious Adverse Event during the Randomized Treatment Period, by Preferred Term, Stratified by Age (Safety Analysis Set)

	BDA MDI 160/180	BDA MDI 80/180		AS MDI 180	
	≥12 - <18 (N=34)	≥4 - <12 (N=41)	≥12 - <18 (N=32)	≥4 - <12 (N=42)	≥12 - <18 (N=34)
Preferred Term					
Asthma	0	0	0	1 (2.4)	2 (5.9)
COVID-19	0	1 (2.4)	0	0	0
Mixed anxiety and depressive disorder	1 (2.9)	0	0	0	0

Source: Clinical Reviewer.

Very few events. Asthma-related only in AS arm (medium or high dose background ICS).

MANDALA Pediatric Adverse Events

Number of Subjects 4 to <18 with Most Common Adverse Events (>1 Subject per Arm) With Greater Frequency in BDA vs AS during the Randomized Treatment Period, by Preferred Term (Safety Analysis Set)

	BDA MDI 160/180 (N=34)	BDA MDI 80/180 (N=73)	AS MDI 180 (N=76)
Preferred Term			
Influenza	2 (5.9)	3 (4.1)	4 (5.3)
Rhinitis allergic	2 (5.9)	2 (2.7)	2 (2.6)
Bronchitis	1 (2.9)	3 (4.1)	1 (1.3)
Cough	1 (2.9)	2 (2.7)	2 (2.6)
Suspected COVID-19	1 (2.9)	3 (4.1)	1 (1.3)
Headache	2 (5.9)	0	2 (2.6)
Nasopharyngitis	2 (5.9)	1 (1.4)	1 (1.3)
Sinusitis	0	3 (4.1)	1 (1.3)
Upper respiratory tract infection	0	2 (2.7)	2 (2.6)
Ligament sprain	1 (2.9)	1 (1.4)	1 (1.3)
Toothache	0	2 (2.7)	1 (1.3)
Acute sinusitis	0	1 (1.4)	1 (1.3)
COVID-19	0	1 (1.4)	1 (1.3)
Pharyngitis streptococcal	2 (5.9)	0	0
Pneumonia	1 (2.9)	0	1 (1.3)
Respiratory tract infection viral	0	2 (2.7)	0
Rhinorrhoea	1 (2.9)	0	1 (1.3)
Urticaria	0	1 (1.4)	1 (1.3)
Viral pharyngitis	1 (2.9)	0	1 (1.3)

Source: Clinical Reviewer.

MANDALA ICS-Related Adverse Events

- Analyzed both local and systemic ICS-related AEs
- Local:
  - Incidence low and balanced across treatment arms
  - Oral candidiasis occurred more in BDA arms vs AS
- Systemic:
  - Incidence low and balanced across treatment arms
  - Most frequent terms: contusion (≈0.5%), insomnia (≈0.5%), depression (≈0.4%), and diabetes mellitus type 2 (≈0.4%)
- Pediatrics:
  - Small sample size and duration of exposure
  - Overall incidence of both local & systemic low
  - No significant pattern by age group

Pivotal Trials for Registration

- **MANDALA**
  - Contribution of ICS to ICS/SABA as PRN in preventing severe acute asthma exacerbations
  - Agency views as primary source of efficacy data

- **DENALI**
  - Contribution of each component (ICS and SABA) to effect on lung function
  - Agency views as supportive evidence, safety data for higher dose and mild population, satisfying combination rule

DENALI Safety Overview

Number of Subjects with any Category of Adverse Event in the Randomized Treatment Period (Safety Analysis Set)

	BDA MDI 160/180 (N=197)	BDA MDI 80/180 (N=204)	BD MDI 160 (N=199)	AS MDI 180 (N=201)	Placebo MDI (N=199)
Any AE	66 (33.5)	72 (35.3)	67 (33.7)	62 (30.8)	69 (34.7)
Any AE causally related to randomized treatment	10 (5.1)	6 (2.9)	7 (3.5)	2 (1.0)	3 (1.5)
Any AE leading to discontinuation of IP	2 (1.0)	1 (0.5)	3 (1.5)	2 (1.0)	4 (2.0)
Any SAE	2 (1.0)	4 (2.0)	3 (1.5)	1 (0.5)	3 (1.5)

Source: Clinical Reviewer.

DENALI Pediatric Adverse Events

DENALI, Number of Subjects ≥4 to <18 With Any Category of Adverse Event in the Randomized Treatment Period, Safety Analysis Set

	BDA MDI 160/180	BDA MDI 80/180		BD MDI 160	AS MDI 180		Placebo MDI	
	>=12 - <18 (N=4)	>= 4 - <12 (N=3)	>=12 - <18 (N=7)	>=12 - <18 (N=5)	>= 4 - <12 (N=4)	>=12 - <18 (N=5)	>= 4 - <12 (N=3)	>=12 - <18 (N=4)
Any AE	0	0	2 (28.6)	2 (40.0)	2 (50.0)	1 (20.0)	1 (33.3)	0
Any AE causally related to randomized treatment	0	0	1 (14.3)	0	0	0	0	0
Any SAE	0	0	1 (14.3)	0	0	0	0	0

Source: Clinical Reviewer.

Very few events in subjects <18. Only SAE (asthma) was associated with treatment discontinuation. No new signals identified.

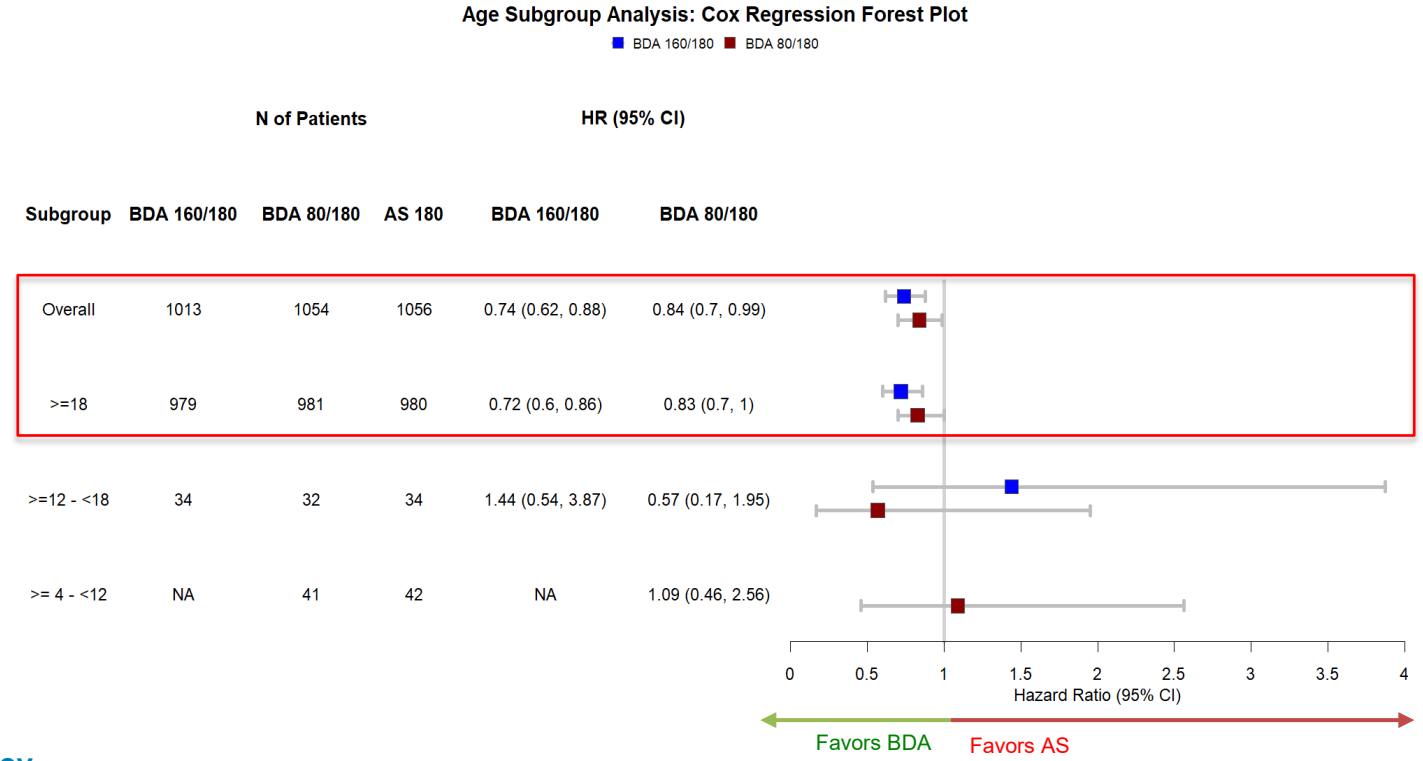
Safety Summary

- **Strengths of safety data:**
  - Adult safety database adequate for review
  - Use of ≥12 inhalations BDA was not a significant issue during study period
  - No new signals identified:
    - Consistent with well-characterized risks of ICS & SABA
    - Background ICS also associated with risk of ICS-related AEs
- **Safety uncertainties:**
  - Scope of pediatric data limited: size and duration of exposure
  - Data does not account for potential overuse in real world
  - Long term effects unknown, e.g., growth, bone density, etc.

SUMMARY & KEY CONSIDERATIONS

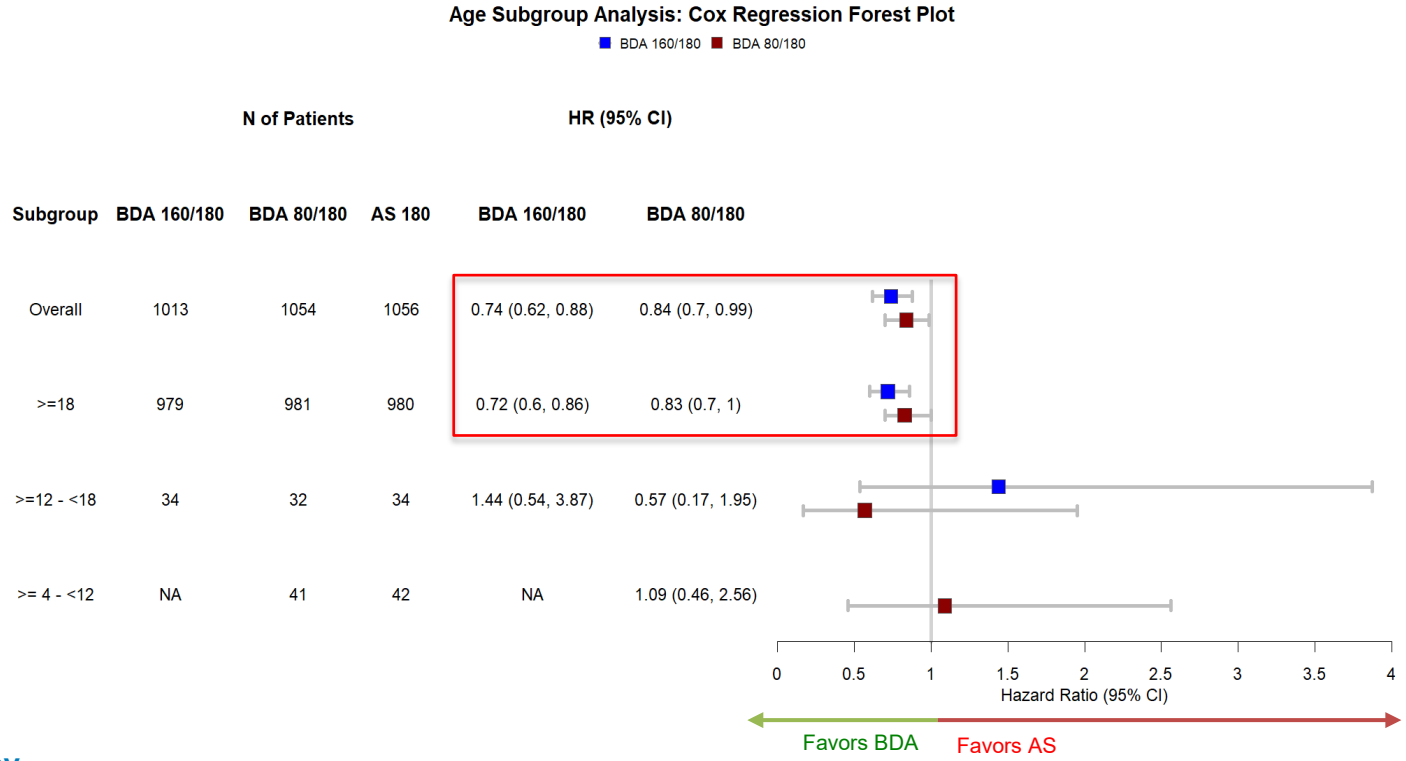
Efficacy Summary: FAS and Adults

Forest Plot for Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand, Age-Based Subgroups (MANDALA, Full Analysis Set; All Ages)



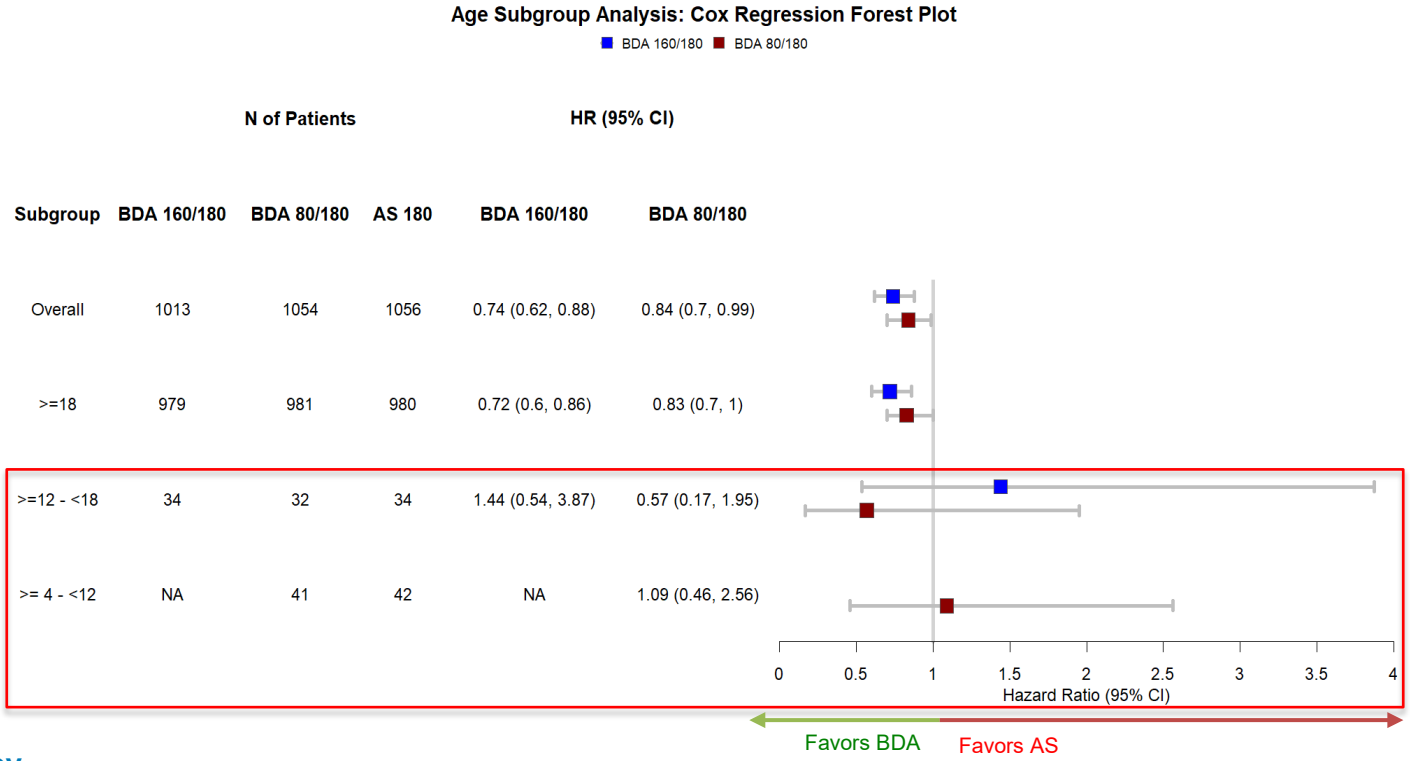
Efficacy Summary: BDA 160/180 vs 80/180

Forest Plot for Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand, Age-Based Subgroups (MANDALA, Full Analysis Set; All Ages)



Pediatric Efficacy Data Inconclusive

Forest Plot for Time to First Severe Exacerbation During the Randomized Treatment Period, Efficacy Estimand, Age-Based Subgroups (MANDALA, Full Analysis Set; All Ages)



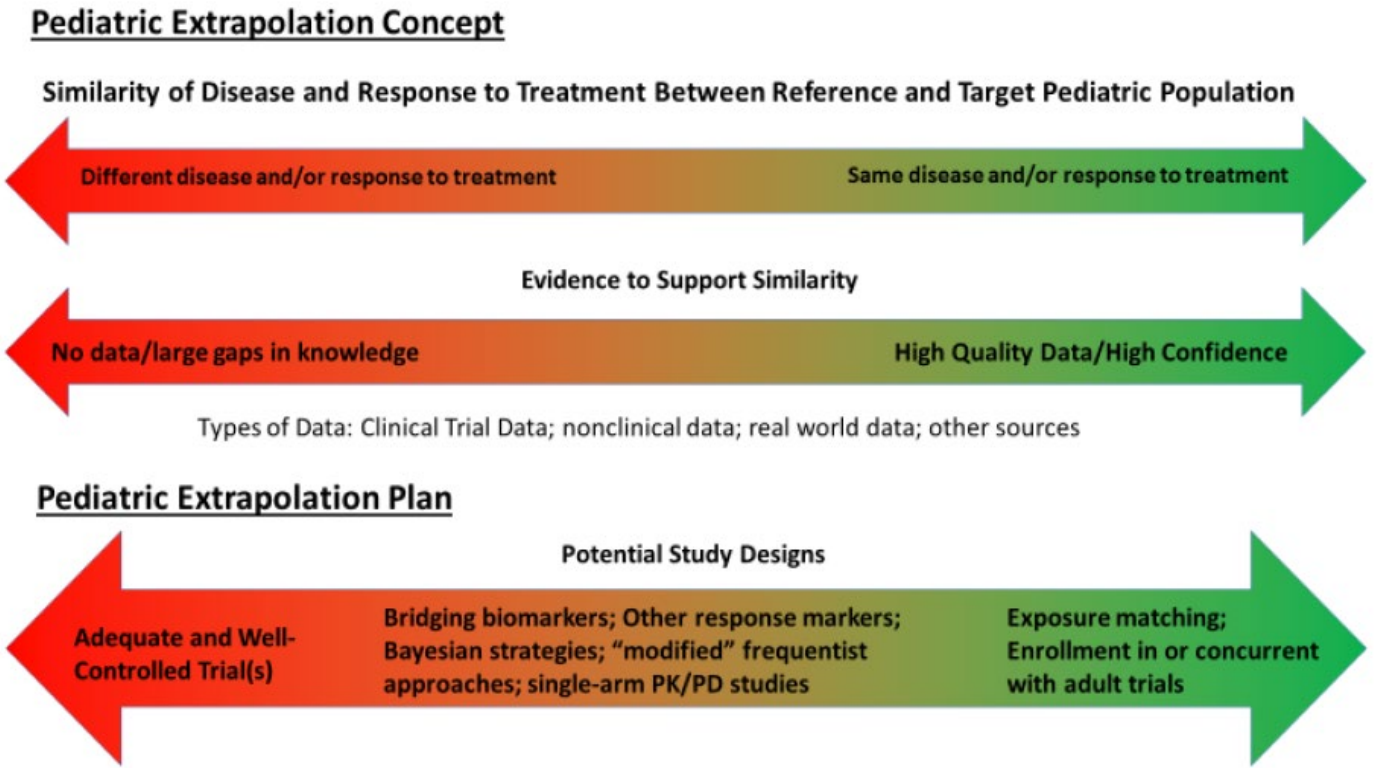
Regulatory Considerations: Pediatric Development

- **BDA:**
  - Applicant proposed enrollment of subjects ≥6 years, and Agency recommended expansion down to ≥4 in both exacerbation and FEV1 trials.
  - Agency recommended Bayesian approach, but no agreement on degree of borrowing or statistical plan.
- **PRECEDENT:**
  - Inhaled products are locally acting. Extrapolation of efficacy based on pharmacokinetic (PK) data not appropriate.
  - Typically, adolescents (≥12 to <18) enrolled in adult efficacy trial. Subsequent dedicated trial in ≥4 to <12.
  - Division has leveraged some degree of extrapolation.

Regulatory Considerations: Pediatric Development

- **BDA: NOVEL COMBINATION, INDICATION, INTENDED USE**
  - Applicant proposed enrollment of subjects ≥6 years, and Agency recommended expansion down to ≥4 in both exacerbation and FEV1 trials.
  - Agency recommended Bayesian approach, but no agreement on degree of borrowing or statistical plan.
- **PRECEDENT: ESTABLISHED INDICATION FOR DRUG OR DRUG CLASS**
  - Inhaled products are locally acting. Extrapolation of efficacy based on pharmacokinetic (PK) data not appropriate.
  - Typically, adolescents (≥12 to <18) enrolled in adult efficacy trial. Subsequent dedicated trial in ≥4 to <12.
  - Division has leveraged some degree of extrapolation.

Pediatric Extrapolation



Source: FDA Draft Guidance for Industry: E11A Pediatric Extrapolation

Preliminary Benefit-Risk Summary

Population	Efficacy	Risk & Risk Mitigation	Uncertainties
≥18 years	• Both pivotal trials met the FDA-agreed upon primary endpoints • BDA 160/180 demonstrated benefit in reducing severe asthma exacerbations and reducing systemic corticosteroid use	• No new signals identified • Labeling and routine pharmacovigilance	• Novel indication and intended use • Effects on asthma control and quality of life • ICS-related adverse events with real world use
≥12 to <18 years	• Efficacy of BDA 160/180 in subjects ≥12 to <18 is inconclusive	• No new signals identified • Labeling and routine pharmacovigilance	• Appropriate degree of extrapolation from adults • Scope of safety database small • Long-term risks not captured
≥4 to <12 years	• Efficacy of BDA 80/180 in subjects ≥4 to <12 is inconclusive	• No new signals identified • Labeling and routine pharmacovigilance	• Appropriate degree of extrapolation from adults • Scope of safety database small • Long-term risks not captured

Questions for the Advisory Committee

- Discuss the data to support the efficacy of BDA for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older.
    - For adolescents (12 to < 18) and young children (4 to < 12), discuss the appropriate degree of extrapolation in these age groups.
- Discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥18 years of age with asthma? If not, what additional data are needed?
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥12 to <18 years of age with asthma? If not, what additional data are needed?
- Do the data support a favorable benefit risk assessment for use of BDA in patients ≥4 to <12 years of age with asthma? If not, what additional data are needed?

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