FDA Pulmonary-Allergy Drugs Advisory Committee

FDA Charge to the Committee

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

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U.S. Food and Drug Administration
November 8, 2022

BDA MDI

- Combination budesonide and albuterol **– new combination**

- 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)**

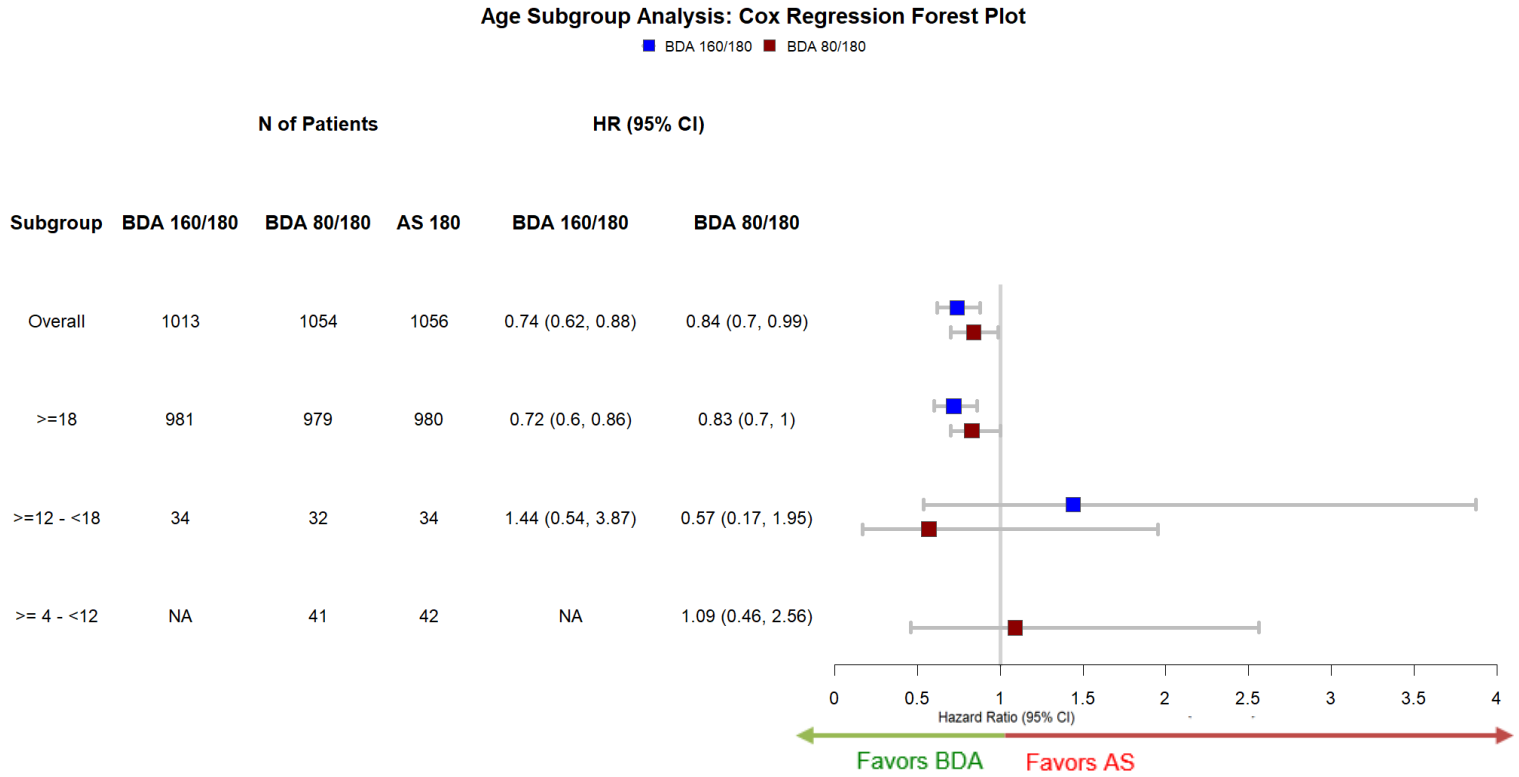
- **Proposed indication – new**

  "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"

- **ICS for reliever treatment,** rather than solely as maintenance treatment

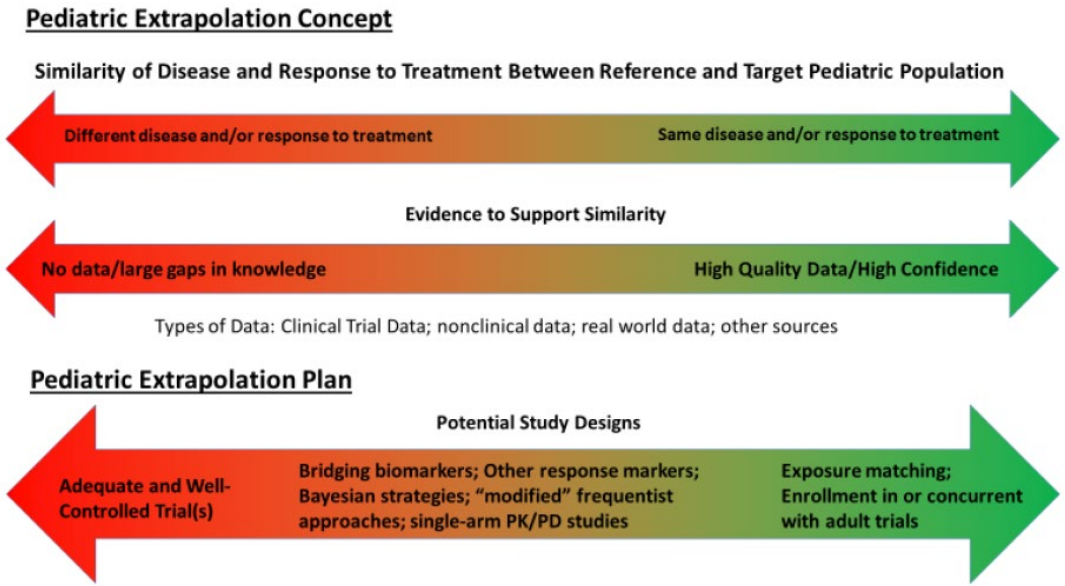
Pediatric Efficacy: Age-Based Subgroup Analysis

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



Source: Statistical Reviewer

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Source: FDA Draft Guidance for Industry: E11A Pediatric Extrapolation, 2022.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

Question 1

DISCUSSION: Discuss the data to support the efficacy of fixed dose combination of budesonide and albuterol sulfate metered dose inhaler (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 if extrapolation of adult data to pediatric subjects is appropriate and, if so, discuss the appropriate degree of extrapolation in these age groups.

Question 2

DISCUSSION: Discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.

Question 3

VOTE: 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?

Question 4

VOTE: 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?

Question 5

VOTE: 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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ADMINISTRATION

FDA Pulmonary-Allergy Drugs Advisory Committee

FDA Overview of the Clinical Program

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

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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"

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

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 for severe exacerbations
    - Morbidity & mortality, for patients with all ranges of severity & age groups
- 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
      - BDA would be first FDA-approved ICS/SABA fixed dose combination

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

Unique Features of BDA

- New indication to prevent progression to (severe) exacerbations
- ICS for reliever treatment, rather than solely as maintenance treatment
- Fixed dose combination of ICS/SABA

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

Pivotal Trials for Registration

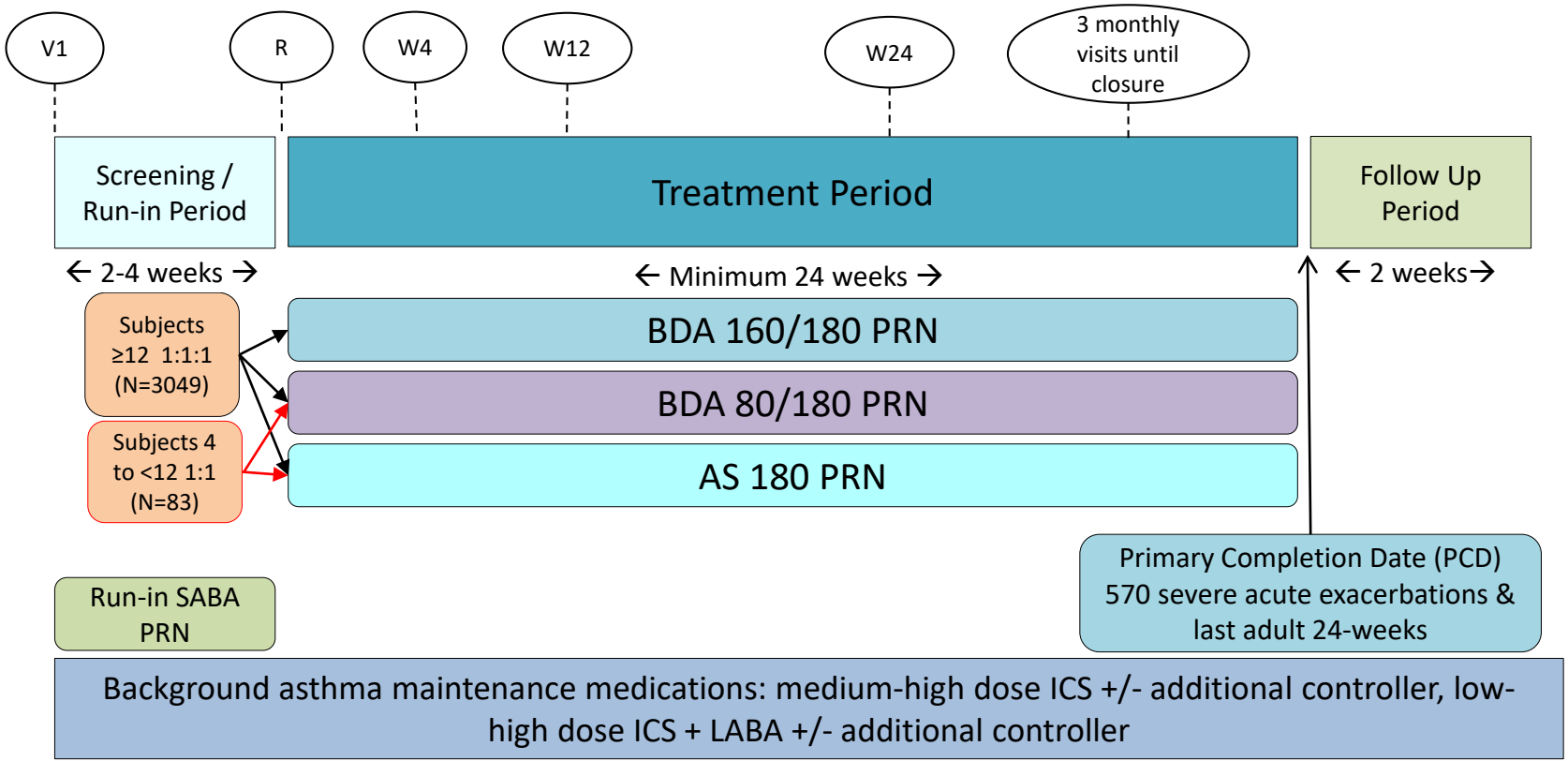
- **MANDALA**
  - Contribution of ICS to ICS/SABA as PRN in preventing severe acute asthma exacerbations
  - Agency views as primary source of efficacy data

- **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

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
  - **Primary focus of discussion for advisory committee**

MANDALA Study Design



Source: Clinical reviewer; PRN=as needed

Pediatric Efficacy: Statistical Analysis Plan

- Sample Size Calculation
  - 1000 **adult and adolescent subjects (≥12 yo)** 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

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

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)			

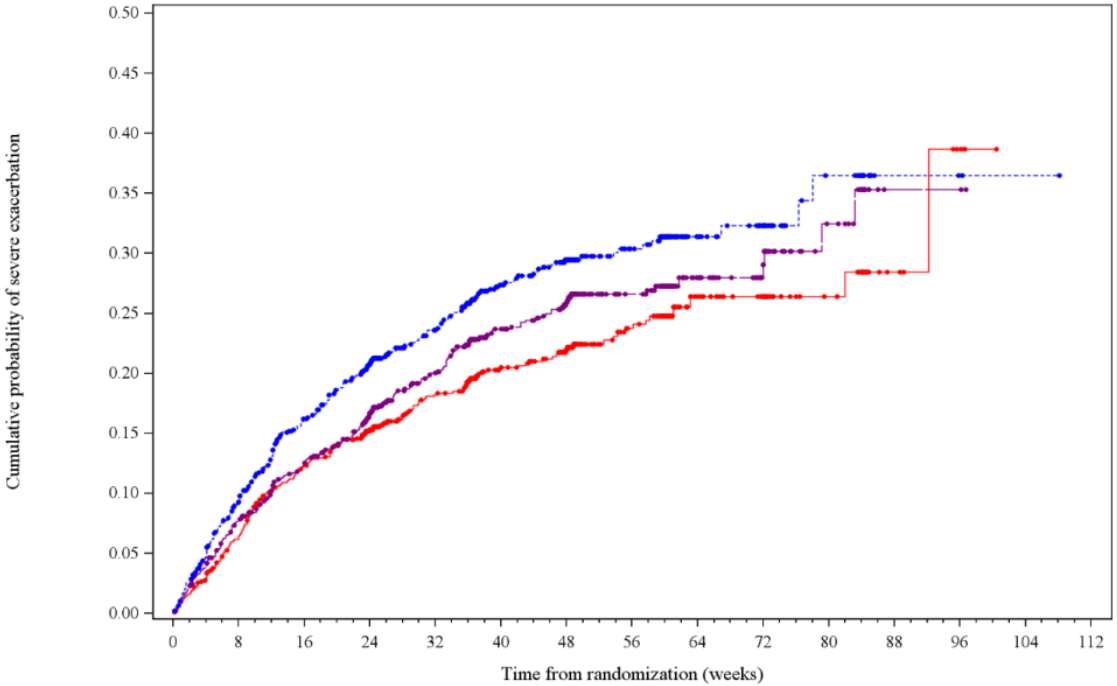
† Included data before discontinuation of randomized treatment or change in maintenance therapy

* Number of children 4 to 11 years

Source: Statistical Reviewer

Primary Endpoint Efficacy Results

Kaplan-Meier Curve for Time to First Severe Exacerbation, Efficacy Estimand (MANDALA, FAS)



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

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

ACQ-5:
Asthma Control Questionnaire-5

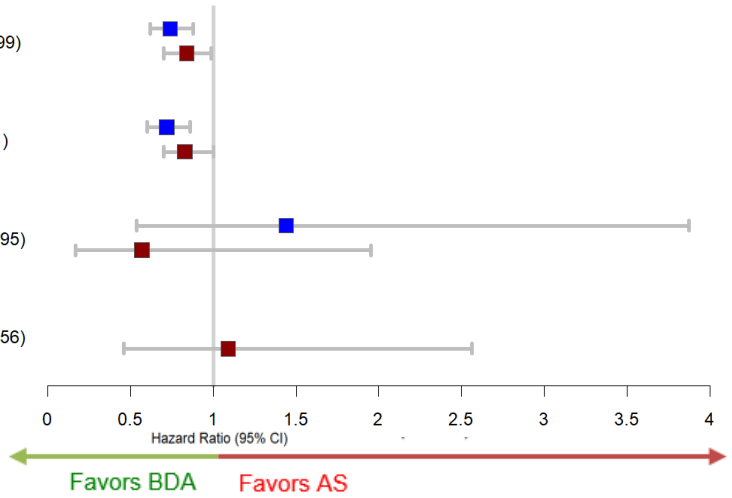
AQLQ-12:
Asthma Quality of Life Questionnaire-12

Source: Statistical Reviewer

Pediatric Efficacy: Age-Based Subgroup Analysis

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

Subgroup	N of Patients BDA 160/180	N of Patients BDA 80/180	N of Patients AS 180	HR (95% CI) BDA 160/180	HR (95% CI) BDA 80/180
Overall	1013	1054	1056	0.74 (0.62, 0.88)	0.84 (0.7, 0.99)
>=18	981	979	980	0.72 (0.6, 0.86)	0.83 (0.7, 1)
>=12 - <18	34	32	34	1.44 (0.54, 3.87)	0.57 (0.17, 1.95)
>= 4 - <12	NA	41	42	NA	1.09 (0.46, 2.56)



Source: Statistical Reviewer

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

HR: Hazard Ratio

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

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

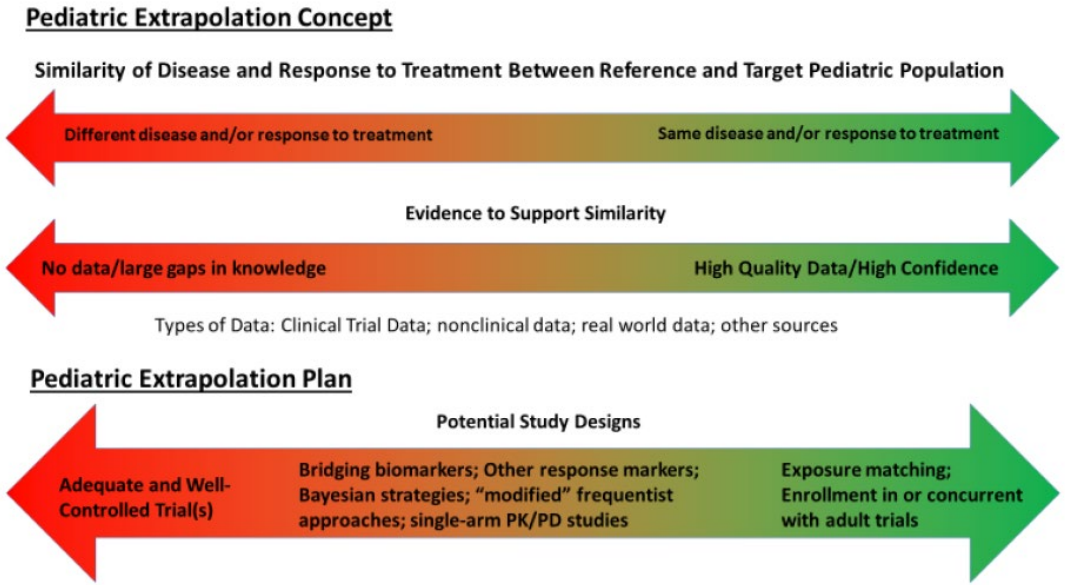
Borrowing Required to Establish Efficacy of *Low Dose* BDA in *Children (4 to <12)*

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 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.

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

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 ICS-Related Adverse Events

- Analyzed both local and systemic ICS-related Adverse Events
- 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

SUMMARY OF EFFICACY AND RESULTS

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
- DENALI
  - Dual-primary efficacy endpoints met
    - Combination rule satisfied

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)

Age Subgroup Analysis: Cox Regression Forest Plot

BDA 160/180 BDA 80/180

	N of Patients			HR (95% CI)	
Subgroup	**BDA 160/180**	**BDA 80/180**	**AS 180**	**BDA 160/180**	**BDA 80/180**
Overall	1013	1054	1056	0.74 (0.62, 0.88)	0.84 (0.7, 0.99)
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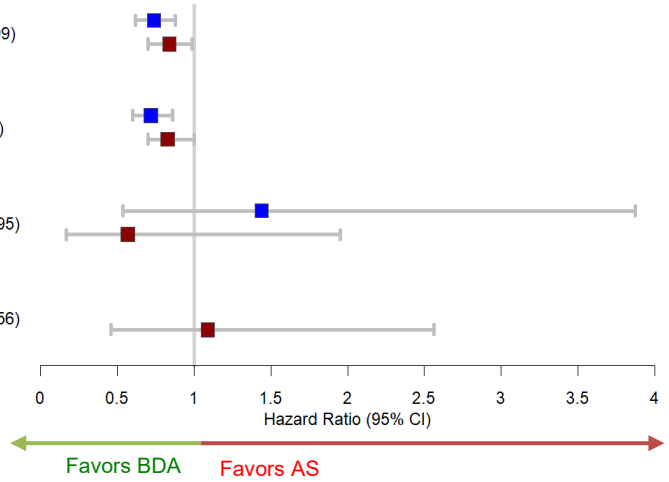

Regulatory Considerations: Pediatric Development

- **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.

FEV1: forced expiratory volume in 1 second

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.
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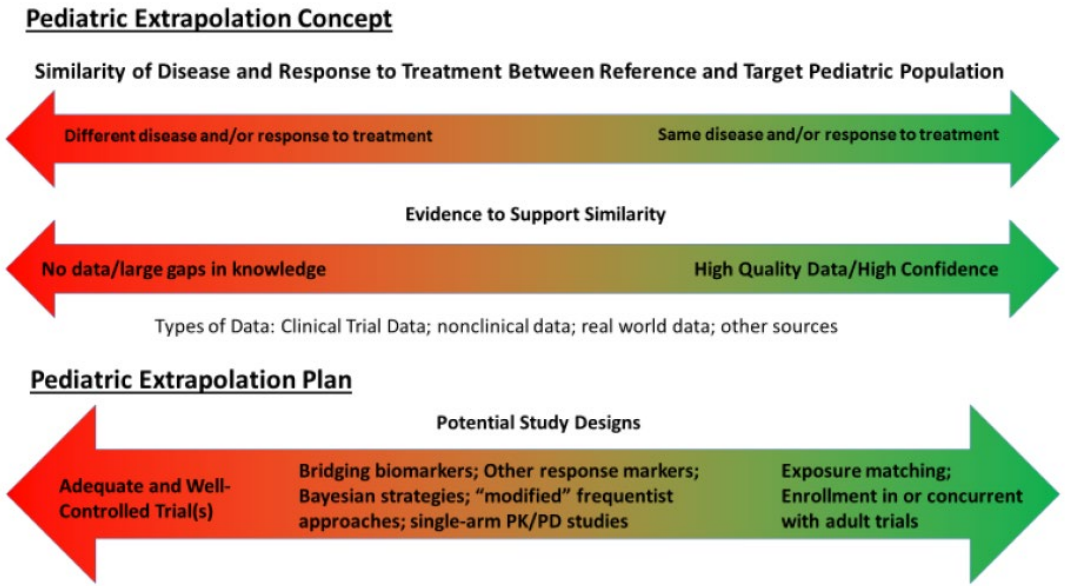
Pediatric Extrapolation



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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

Question 1

DISCUSSION: Discuss the data to support the efficacy of fixed dose combination of budesonide and albuterol sulfate metered dose inhaler (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.

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DISCUSSION: Discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.

Question 3

VOTE: 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?

Question 4

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Question 5

VOTE: 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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