CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214070Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: 1/9/23 **Date Consulted:** 11/28/22

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Elaine Sit, Senior Regulatory Project Manager (RPM)
Division of Pulmonology, Allergy and Critical Care (DPACC)

Drug: Airsupra (budesonide/albuterol) Metered Dose Inhaler (MDI)

NDA: 214070

Indication: For the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma

Applicant: Bond Avillion 2 Development LP

Subject: Pregnancy and Lactation Labeling [New Drug Application (NDA), 505(b)(2)]

Materials Reviewed:

- Applicant's submission dated 3/10/22
- (b) (4) .

[1] DPMH consult reviews of budesonide, NDAs (b) (4), 121920, 205636 and 21324 were part of the materials reviewed, but were not relied upon for the purposes of the recommendations.

(b) (4)

- DPMH review of Budesonide, NDA 121920. Christos Mastroyannis, MD. 12/19/18. DARRTS Reference ID # 4366204[1,3].
- DPMH review of Entocort EC (budesonide). NDA 21324. Miriam Dinatale, D.O. 1/25/16. DARRTS Reference ID # 3875179[1,4]
- DPMH review of ProAir (albuterol) NDA 205636. Carol H. Kasten, MD. 4/11/16. DARRTS Reference ID # 3915476[1,5]
- Approved labeling for Ventolin HFA (albuterol sulfate inhalation aerosol) NDA 020983, dated 8/18/21.

Consult Question: We seek maternal health input on a new birth registry included in labeling, as noted above. Is inclusion appropriate and is description accurate?

INTRODUCTION AND BACKGROUND

- On 3/10/22, Bond Avillion 2 Development LP submitted 505 (b)(2) NDA 214070 via the 505 (b)(2) pathway for Airsupra (budesonide/albuterol) MDI to DPACC for the as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma age ≥ 4 years.
- On 11/28/22, DPACC contacted DPMH for a quick turnaround consult to assist with the proposed labeling language for Section 8 for NDA 216951. In particular, to decide whether to include specific publications proposed by the applicant to include in subsection 8.1 under "Human Data".
- Multiple previous DPMH reviews of budesonide products have been conducted, most recently in 2021.[3] Recommended PLLR language has been modeled after that proposed by DPMH for the budesonide product (b) (4) Tarpeyo (NDA 215935).
- This memorandum focuses on the additional paragraph proposed by the applicant under the Human Data subheading in the labeling subsection 8.1 Pregnancy. The new paragraph includes details of a more recent assessment of aggregated data for both drug components, budesonide and albuterol, in the Nordic birth registries.
- One DPMH review of albuterol was identified from 2016[5]. Recommended PLLR language for the albuterol component of Airsupra has been modeled after that used in the revised labeling for the more recently converted Ventolin HFA (NDA 020983).

REVIEW

As noted above, the published literature regarding budesonide use in pregnant and lactating individuals has been previously reviewed by DPMH, most recently in 2021. An information request (IR) was sent to the applicant to confirm the origin of their proposed statements for subsection 8.1 *Pregnancy.* The applicant responded on 12/10/22 with the correct citations

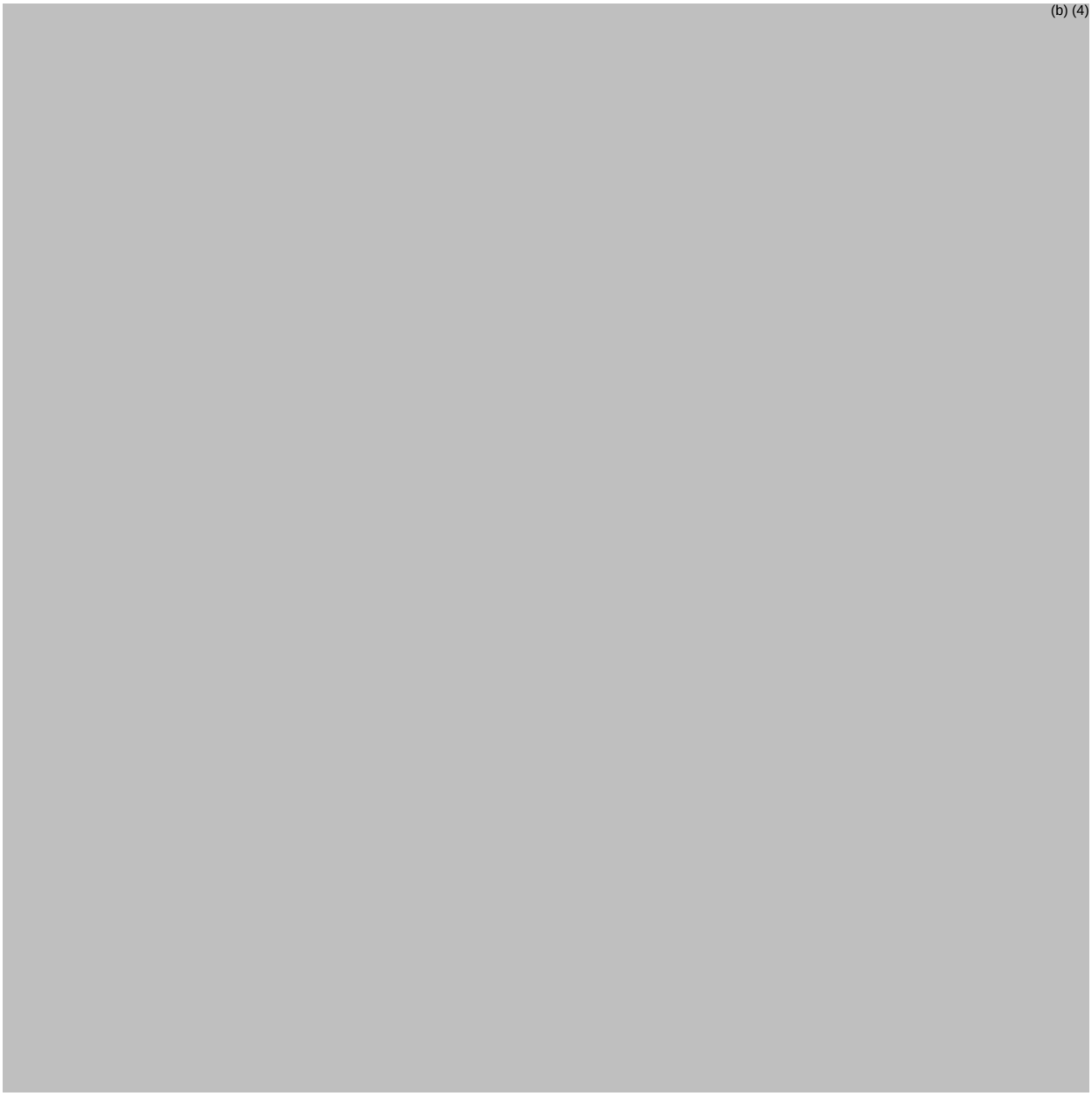
[3] DPMH review of Budesonide, NDA 121920. Christos Mastroyannis, MD. 12/19/18. DARRTS Reference ID # 43662041.
[4] DPMH review of Entocort EC (budesonide). NDA 21324. Miriam Dinatale, D.O. 1/25/16. DARRTS Reference ID # 38751791
[5] DPMH review of ProAir (albuterol) NDA 205636. Carol H. Kasten, MD. 4/11/16. DARRTS Reference ID # 3915476.

and copies of the publications. DPMH held internal discussions and then discussions with the division. DPMH concluded that simplified statements, under the Risk Summary heading of labeling subsection of 8.1, was the best approach to provide concise and understandable labeling language for prescribers. These summary statements noted the lack of a signal for adverse maternal and infant outcomes associated with the use of budesonide and albuterol in the extensive published literature available over many years of use in pregnant women. No new information was identified in the publications proposed by the applicant.

Below is the recommended proposed labeling for Airsupra.

DPMH Proposed Airsupra (budesonide/albuterol) Pregnancy and Lactation Labeling

(b) (4)



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TAMARA N JOHNSON
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 3, 2023
To:	Elaine Sit Senior Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett-Mmagu, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	AIRSUPRA (albuterol and budesonide)
Dosage Form and Route:	inhalation aerosol, for oral inhalation use
Application Type/Number:	NDA 214070
Applicant:	Bond Avillion 2 Development LP

1 INTRODUCTION

On March 10, 2022, Bond Avillion 2 Development LP submitted for the Agency's review New Drug Application (NDA) #214070 AIRSUPRA (albuterol and budensonide) inhalation aersol. The proposed indication for this application is as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonology, Allergy, and Critical Care (DPACC) on March 15, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for AIRSUPRA (albuterol and budesonide) inhalation aersol, for oral inhalation use.

2 MATERIAL REVIEWED

- Draft AIRSUPRA (albuterol and budesonide) PPI and IFU received on March 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 21, 2022.
- Draft AIRSUPRA (albuterol and budesonide) Prescribing Information (PI) received on March 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 21, 2022.
- Approved SYMBICORT comparator labeling dated December 20, 2017.
- Approved PULMICORT FLEXHALER comparator labeling dated September 6, 2019.
- Approved BREZTRI AEROSPHERE comparator labeling dated July 23, 2020.
- Approved PROAIR RESPICLICK and DIGIHALER comparator labeling dated September 29, 2020.
- Approved VENTOLIN HFA comparator labeling dated August 18, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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MARIA T NGUYEN
01/03/2023 11:04:06 AM
DMPP-OPDP review of albuterol and budesonide (AIRSUPRA) NDA 214070 PPI and IFU

TAYLOR B BURNETT MMAGU
01/03/2023 11:15:17 AM

MARCIA B WILLIAMS
01/04/2023 06:11:18 AM

LASHAWN M GRIFFITHS
01/04/2023 08:20:42 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 19, 2022
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214070
Product Name and Strength:	Airsupra (albuterol sulfate and budesonide) inhalation Aerosol, 90 mcg/40 mcg and 90 mcg/80 mcg
Applicant/Sponsor Name:	AstraZeneca
TTT ID #:	2022-2493-01
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 16, 2022 for Airsupra. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Airsupra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant has addressed all of our recommendations and we have no additional recommendations at this time. We note that the Agency is not able to support approval for the pediatric indication for children aged 4 to 11 years old, hence the 90 mcg/40 mcg strength is not to be approved at this time.

[a] Owens, Lissa. Label and Labeling Review for Airsupra (NDA 214070). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 07. TTT ID No.: 2022-2493.

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/s/

IDALIA E RYCHLIK
12/19/2022 02:59:51 PM

VALERIE S VAUGHAN
12/19/2022 03:02:52 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 7, 2022
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214070
Product Name and Strength:	Airsupra (albuterol sulfate and budesonide) Inhalation Aerosol, 90 mcg/40 mcg per inhalation and 90 mcg/80 mcg per inhalation
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca
FDA Received Date:	March 10, 2022
TTT ID #:	2022-2493
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Airsupra (albuterol sulfate and budesonide) Inhalation Aerosol, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Airsupra prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for AstraZeneca.

4 RECOMMEDATIONS FOR DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed name, “Airsupra” is not listed.	The proposed proprietary name “Airsupra” was found conditionally acceptable.	Replace the “Tradename” placeholder with the conditionally acceptable proprietary name “Airsupra”.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The first temperature numerical is missing the degree symbol.	Lack of clarity.	Revise the sentence to read “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].”.

5 RECOMMENDATIONS FOR ASTRAZENECA

Table 3. Identified Issues and Recommendations for AstraZeneca (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
	The proposed name, “Airsupra” is not listed.	The proposed proprietary name “Airsupra” was found conditionally acceptable.	Replace the “Tradename” placeholder with the conditionally acceptable proprietary name “Airsupra”.
1.	(b) (4)		

Table 3. Identified Issues and Recommendations for AstraZeneca (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Airsupra that AstraZeneca submitted on March 10, 2022.

Table 4. Relevant Product Information for Airsupra	
Initial Approval Date	N/A
Active Ingredient	Albuterol sulfate and budesonide
Indication	as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older
Route of Administration	Oral inhalation
Dosage Form	Inhalation Aerosol
Strength	(b) (4) 90 mcg/80 mcg per inhalation
Dose and Frequency	2 inhalations as needed. Do not take more than 6 doses (12 inhalations) in a 24-hour period)
How Supplied	(b) (4) supplied as a pressurized aluminum canister with an attached dose indicator and a white plastic actuator, with a frosted clear plastic dust cap tethered to it
Storage	Store at controlled room temperature 20°C to 25°C (68° F to 77°F); excursions permitted to 15°C to 30°C (59° F to 86°F) [see USP].

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Airsupra labels and labeling submitted by AstraZeneca.

- Container label(s) received on March 10, 2022
- Carton labeling received on March 10, 2022
- Professional Sample label received on March 10, 2022
- Professional Sample Carton Labeling received on March 10, 2022
- Instructions for Use received on March 10, 2022, available from \\CDSESUB1\EVSPROD\nda214070\0001\m1\us\draft-labeling-text-ifu-commercial.pdf
- Prescribing Information (Image not shown) received on March 10, 2022, available from \\CDSESUB1\EVSPROD\nda214070\0001\m1\us\draft-labeling-text-pi.pdf

F.2 Label and Labeling Images

Container label(s)

Canister label 90 mcg/80 mcg

(b) (4)

[redacted]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C PRINGLE-OWENS
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IDALIA E RYCHLIK
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Clinical Inspection Summary

Date	September 12, 2022
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Elisabeth Boulos, MD, Clinical Reviewer Kelly Stone, M.D., Ph.D., Clinical Team Leader Elaine Sit, PharmD, Senior Regulatory Project Manager Division of Pulmonary, Allergy, and Critical Care (DPACC)
NDA #	214070
Applicant	Bond Avillion 2 Development LP
Drug	Airsupra (albuterol and budesonide)
NME (Yes/No)	No
Proposed Indication(s)	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
Consultation Request Date	May 5, 2022
Summary Goal Date	September 15, 2022
Action Goal Date	January 10, 2023
PDUFA Date	January 10, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Matthew Doty, Gregg Lucksinger, and Jose Cevallos Yepez were inspected in support of NDA 214070, covering Protocols AV003 (MANDALA) and AV004 (DENALI). Both studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of this NDA.

II. BACKGROUND

Airsupra is a combination product containing the short acting beta agonist (SABA) albuterol and the inhaled corticosteroid (ICS), budesonide, two established asthma medications. The sponsor conducted two studies, Protocols AV003 and AV004, 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. Protocol AV003 evaluates the effect of the investigational product (IP) on the occurrence of severe asthma exacerbations, and Protocol AV004 evaluates the effect of IP in improving lung function. The review division requested three clinical investigator (CI) inspections. The following briefly describes the two protocols:

Protocol # AV003 (MANDALA)

Study Title: "A Long-term, Randomized, Double-blind, Multicenter, Parallel-group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT007 Administered as Needed in Response to Symptoms in Symptomatic Adults and Children 4 Years of Age or Older with Asthma (MANDALA)"

Primary Objective: To compare two doses of budesonide/albuterol sulfate metered dose inhaler (BDA MDI) 80/180 μg and 160/180 μg administered as needed in response to symptoms compared to albuterol metered dose inhaler (AS MDI) 180 μg on the time to first severe asthma exacerbation.

Subjects: First Subject First Visit: (b) (6); Last Subject Last Visit: (b) (6)

Sites: Subjects were enrolled in 296 centers in Argentina, Canada, Czech Republic, Germany, Serbia, Slovakia, South Africa, Spain, United Kingdom, US, and Ukraine.

Number of Subjects: Approximately 3132, including 83 subjects 4 to 11 years of age and 100 subjects 12 to 17 years of age

Primary Efficacy Endpoint: Time to first severe asthma exacerbation

Protocol-definition of asthma exacerbation: The worsening/onset of symptoms must have included at least one of the following symptoms:

- Shortness of breath
- Wheezing
- Chest Tightness
- Cough
- Sputum
- Night-time awakening due to asthma
- Activity limitation due to asthma
- Decreased PEF
- Decreased FEV1

Note - If the asthma exacerbation did not meet the protocol definition, the investigator must have justified the decision for defining the event as an exacerbation and document the reasoning in the eCRF.

An asthma exacerbation was defined as "**severe**" if it fulfilled the above criteria for the protocol definition of an asthma exacerbation and if the asthma exacerbation resulted in at least one of the following:

- A temporary bolus/burst of systemic corticosteroids (SCS) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depot injectable dose of corticosteroids was considered equivalent to a 3-day bolus/burst of SCS.
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) due to asthma that required

SCS (as per the above).
- An in-patient hospitalization (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

All screening and post randomization severe asthma exacerbations (including investigator justified asthma exacerbations) were captured using the Severe Asthma Exacerbation eCRF. The time to first severe asthma exacerbation was calculated as the time from randomization (Visit 2) until the start date of the first severe asthma exacerbation. Events not meeting the SEE definition were queried and if confirmed not a SEE removed by the CRO or sponsor personnel; an event not meeting the definition was not permitted to be reported as a SEE. Some events identified during medical listing and data reviews (e.g., 3-day course of systemic steroid prescribed for respiratory issue other than SEE), which were considered to be potentially unreported SEEs, were referred to the independent adjudication committee (note: only one additional event was considered as a SEE by the adjudication committee). Source records supporting the SEE data were available at clinical investigator sites, and copies of the eCRF data were sent to sites either as a download from a secured portal or as a password protected CD.

The study was to consist of three periods:

- *Screening/Run-in period (Visit 1, 14-28 days):* Subjects who met all entry criteria at the screening visit (Visit 1) entered a 14- to 28-day screening and run-in period. Subjects continued to take their regular asthma maintenance therapy throughout the study (from screening through the treatment period). At Visit 1, eligible subjects discontinued their usual as needed short-acting β2-agonist (SABA) used as needed and began sponsor-provided Ventolin (albuterol sulfate) to be used as needed in response to symptoms and prior to exercise during the screening period.

- *Double-Blind Treatment Period of at least 24 week (Visits 2-6):* Adult and adolescent subjects (≥ 12 years of age) were randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio administered as needed on top of their regular asthma maintenance therapy:
    - BDA MDI 80/180 μg (given as 2 inhalations of BDA MDI 40/90 μg) as needed
    - BDA MDI 160/180 μg (given as 2 inhalations of BDA MDI 80/90 μg) as needed
    - AS MDI 180 μg (given as 2 inhalations of AS MDI 90 μg) as needed

    Eligible children (4 to 11 years of age) were randomly assigned to receive either
    - low dose BDA MDI 80/180 μg
    - AS MDI 180 μg

    Subjects self-administered randomized IP as needed in response to their symptoms and may have used it prior to exercise. During this time, subjects continued to take their regular asthma maintenance therapy throughout the study from screening to through the treatment period. The treatment period was to be at least 24 weeks. This period would continue into an extension phase until at least 570 first severe exacerbation events had occurred, and the last adult subject reached 24 weeks of treatment.

- *Safety Follow-up via telephone contact:* 2 weeks (± 4 days) after the subject's last dose

of treatment.

Main Eligibility Criteria: Male and female subjects ≥ 4 years of age with a diagnosis of moderate to severe asthma and at least 1 severe asthma exacerbation within the previous 12 months prior to the screening visit (Visit 1). Subjects must have been regularly taking asthma maintenance therapy with inhaled corticosteroids (ICS), with or without other controllers, for at least 3 months with stable dosing for at least 4 weeks prior to the screening visit (Visit 1). Subjects had to be symptomatic and regularly using SABA as needed due to asthma symptoms.

Protocol # AV004 (DENALI)

Study Title: "A 12-week, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT008 and PT007 Administered QID in Adults and Children 4 Years of Age or Older with Asthma (DENALI)"

Primary Objective: To compare two dose levels of budesonide/albuterol pressurized metered-dose inhaler (BDA MDI) 80/180 μg and 160/180 μg administered four times a day (QID) to its constituent components budesonide pressurized metered-dose inhaler [BD MDI] 160 μg and albuterol pressurized metered-dose inhaler [AS MDI] 180 μg), and placebo on improvement in lung function and asthma symptoms after 12 weeks of treatment with symptomatic asthma being treated with short/rapid-acting β2- adrenoreceptor agonist (SABA; e.g., Ventolin) as needed (prn) alone or with low-dose ICS maintenance therapy plus SABA prn.

Subjects: First Subject First Visit: (b) (6); Last Subject Last Visit: (b) (6)

Sites: Subjects were enrolled in 110 centers in Argentina, Czech Republic, Germany, Serbia, Slovakia, Ukraine, and the United States.

Number of Subjects: Approximately 1001 subjects, including 964 adults, 25 adolescents, and 10 children.

Co-Primary Endpoints:

1. Change from baseline in FEV1 area under the curve from 0 to 6 hours (AUC_{0-6}) over 12 weeks
2. Change from baseline in trough FEV1 at Week 12

The general definition of baseline is defined as the most recent non-missing measurement before the first dose of the randomized treatment on the day of randomization. Both the FEV1 area under the curve from 0 to 6 hours and trough FEV1 are derived values. The FEV1 area under the curve from 0 to 6 hours is calculated using the 10 post-dose FEV1 measurements (at 5 min, 15 min, 30 min, 45 min, 60 min, 120 min, 180 min, 240 min, 300 min, and 360 min) on Day 1 and during the Week 12 visit. The trough FEV1 is calculated using the 30- and 60-min pre-dose FEV1 on Day 1 and during the Week 12 visit.

Pulmonary function test assessments were to be performed by the clinical investigator using a Masterscope device. Spirometry data were electronically transmitted by the clinical investigator to the spirometry vendor, (b) (4), where a centralized reading of spirometric data was performed by an independent spirometric specialist. If the (b) (4) spirometric specialist were to suggest changing to a different effort as the best effort, then the clinical investigator was to be informed and provided the rationale for the proposed deselection. CIs were permitted to reject the result of the best-effort review from central QC and reinstate the initial measurement. The sponsor was not involved in the best-effort review, and there was no adjudication committee involved in the spirometry assessments. Source data for spirometry assessments generated on the Masterscope and all associated reports were to be retained at the sites.

The study was to consist of three periods:

- *Screening Visit /Run-in period (Visit 1, 14-28 days):* At the screening visit (Visit 1), subjects who met all entry criteria were to enter a 14- to 28-day screening/run-in period where subjects were to self-administer a single-blind placebo MDI QID and Ventolin as needed in response to asthma symptoms.

- *Treatment Period of 12 weeks (Visits 2-6):* Adult and adolescent subjects (≥ 12 years of age) were to be randomized to 1 of the following 5 treatment groups in a 1:1:1:1: ratio:
    - BDA MDI 80/180 μg QID (given as 2 inhalations of BDA MDI 40/90 μg)
    - BDA MDI 160/180 μg QID (given as 2 inhalations of BDA MDI 80/90 μg)
    - BD MDI 160 μg QID (given as 2 inhalations of BD MDI 80 μg)
    - AS MDI 180 μg QID (given as 2 inhalations of AS MDI 90 μg)
    - Placebo MDI QID (given as 2 inhalations)

  Children aged 4 to 11 years were to be randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:
    - BDA MDI 80/180 μg QID (given as 2 inhalations of BDA MDI 40/90 μg)
    - AS MDI 180 μg QID
    - Placebo MDI QID

- *Safety Follow-up via telephone contact:* 2 weeks (± 4 days) after the subject's last dose of treatment.

Main Eligibility Criteria: Male and female subjects ≥ 4 years of age with a diagnosis of asthma as defined by Global Initiative for Asthma (GINA) criteria with prebronchodilator forced expiratory volume in 1 second (FEV1) of ≥ 50 to < 85% predicted normal value (subjects ≥ 18 years of age) and ≥ 50 predicted normal value (subjects 4 to 17 years of age) with demonstrated in-clinic FEV1 bronchodilator responsiveness (reversibility of airflow defined as ≥ 15% increase in FEV1 relative to baseline) after administration of sponsor-provided SABA. Subjects must have taken Ventolin on ≥ 2days out of 7 days prior to Visit 2. Subjects must have been taking stable doses of asthma therapies (as-needed SABA alone or stable low-dose ICS in addition to as-needed SABA) for at least the last 30 days before the screening visit (Visit 1).

Rationale for Site Selection

The clinical investigators Drs. Matthew Doty, Gregg Lucksinger, and Jose Cevallos Yepez were selected for GCP inspections using a risk-based approach that considered numbers of enrolled subjects, treatment effect, and prior inspectional history.

III. RESULTS (by site):

1. **Dr. Matthew Doty**
   Site #1469
   Care Research Center Inc.
   11760 Bird Road Suite 511
   Miami, FL 33175-8100
   Clinical Inspection Dates: June 27 – July 1, 2022

For Protocol AV003, 29 subjects were screened, and 25 subjects were randomized. All 25 randomized subjects completed the study.

Records were reviewed for all 25 randomized subjects. Records reviewed included, but were not limited to, informed consents, protocol versions, site training activities, case report forms, Form FDA 1572s, schedule of assessments, subject discontinuations, adverse event reporting, concomitant medications, protocol deviations, study test article accountability, sponsor monitoring activities, and efficacy endpoint source records. All source documents were in paper format.

The primary endpoint data for the date of first severe asthma exacerbation in the clinical investigator's source documents were compared with the data listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

Subject (b) (6) was erroneously enrolled into Study AV003 as they had failed exclusion criteria #5 for current smokers, former smokers with >10 pack-years history, or former smokers who stopped smoking <6 months before Visit 1 (including all forms of tobacco, e-cigarettes, and marijuana). Progress notes documented that the subject was a former smoker with a 15 pack-years smoking history.

Reviewer's comment: This protocol deviation was not documented during routine monitoring visits or in the protocol deviation listing reported to FDA. This subject was randomized under the previous clinical investigator, Dr. Malankar. Dr. Doty acknowledged the error and stated he would practice due diligence in the future when inspecting medical records. Enrolling a single ineligible subject is unlikely to affect the overall efficacy or safety results of the study.

2. **Dr. Gregg Lucksinger**
   Site #1406
   H Velocity Clinical Research
   1900 Cypress Creek Road
   Cedar Park, TX 78613
   Clinical Inspection dates: June 28 – May 7, 2022

For study AV003, 5 subjects were screened and randomized, and 2 subjects completed the study. Two subjects discontinued due to withdrawal of consent, and a third Subject (b) (6) (randomized to AS MDI 180) discontinued due to a severe asthma exacerbation lasting more than 20 days. Records were reviewed for all 5 randomized subjects.

For study AV004, 38 subjects were screened, 30 subjects were randomized, and 27 subjects completed the study. Two subjects discontinued due to withdrawal of consent and a third Subject (b) (6) (randomized to AS MDI 180) discontinued after an asthma exacerbation that required starting additional asthma medications. The source documents for the primary efficacy endpoints (where applicable) and AEs were reviewed for all 38subjects. Complete study records (see below) were reviewed for 10 randomized subjects.

Records reviewed for the two protocols (AV003 and AV004) included informed consent forms, assent forms, eligibility, randomization, protocol deviations, case report forms, medical records, laboratory reports, ECG reports, eDiary reports, PFT reports, drug accountability, concomitant medications, site correspondence with the sponsor, monitoring reports, financial disclosures, FDA 1572s., primary efficacy endpoints, and adverse events. The site's documentation for this study was maintained via paper records.

For Study AV003, the primary efficacy endpoint data for the date of first severe asthma exacerbation in the clinical investigator's paper source documents were compared with the data line listings submitted by the sponsor; no discrepancies were noted. For Study AV004, the FEV1 measurements documented in the (b) (4) printed paper reports were compared with the data line listings submitted by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse event for either study.

For Study AV004, during the treatment period, there was one unreported AE and associated concomitant medication documented in the subject's source record. Specifically, Subject (b) (6) (BD MDI 160 group) had a URI, treated with Dayquil, between Visits 4 and 5.

Reviewer's comment: The unreported adverse event of URI should not have an impact on the safety profile of albuterol and budesonide which have been established. The unreported concomitant medication of Dayquil is not restricted per the protocol.

3. **Dr. Jose G. Cevallos Yepez**
   Site #1404
   Finlay Medical Research Corp,
   6803 Lake Worth Road, Ste. 315
   Greenacres, FL 33467
   Clinical Inspection dates: July 18-22, 2022

For study AV003, 29 subjects were screened, 17 randomized, and 14 subjects completed the study. Two subjects discontinued due to withdrawal of consent and a third Subject (b) (6) (randomized to AS MDI 180) discontinued after meeting the study specific discontinuation criteria per the data line listings. The records were reviewed for 10 subjects (7 randomized and 3 screen failures).

For study AV004, 52 subjects were screened, 33 randomized, and 29 subjects completed the study. Four subjects discontinued due to withdrawal of consent per the data line listings. The records were reviewed for 15 subjects (12 randomized and 3 screen failures).

Records reviewed for the two protocols (AV003 and AV004) included activities and records related to the authority and administration of the clinical trial, the Institutional Review Board (IRB) documentation, subjects' source records, financial disclosures, adverse event reporting, CI's oversight of the studies, site training activities and implementation of study procedures, adherence to and documentation of protocol required visits, case report forms, Form FDA 1572s, subject discontinuations, adverse event (AE) reporting, concomitant medications, protocol deviations, study test article accountability, and sponsor monitoring activities.

For study AV003, the paper source documents for the primary efficacy endpoint data of the date of first severe asthma exacerbation were compared with the data line listings provided by the sponsor for 7 randomized subjects; no discrepancies were noted. For study AV004, the FEV1 measurements documented in the (b) (4) printed paper reports were compared with the data line listings provided by the sponsor for 12 randomized subjects; no discrepancies were noted. There was no evidence of underreporting of adverse events for both studies.

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OSI/DCCE/Team Leader
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/s/

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