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APPLICATION NUMBER:

207921Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	505(b)2
Application Number(s)	NDA 207921
Priority or Standard	Standard
Submit Date(s)	October 1, 2016
Received Date(s)	October 1, 2016
PDUFA Goal Date	August 3, 2017
Division/Office	DPARP
Review Completion Date	July 20, 2017
Established Name	Beclomethasone dipropionate
(Proposed) Trade Name	QVAR RediHaler
Pharmacologic Class	Inhaled corticosteroid (ICS)
Applicant	Norton (Waterford) Ltd. – a subsidiary of Teva Pharmaceuticals
Formulation(s)	Inhalation aerosol
Dosing Regimen	40 µg or 80 µg per breath-actuated inhalation Age ≥ 12 years: 40 to 320 µg twice daily Age 4 to 11 years: 40 to 80 µg twice daily
Applicant Proposed Indication(s)/Population(s)	Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.
Recommendation on Regulatory Action	**Approval**

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1 Executive Summary

1.1. Product Introduction

This is a multidisciplinary review of NDA 207921, a 505(b)2 submission for beclomethasone dipropionate, QVAR® RediHaler, administered via a novel tidal breath inhaler. The sponsor is Norton (Waterford) Ltd., which is a fully owned subsidiary of Teva Pharmaceuticals, Inc. (Teva). The product is intended for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Beclomethasone dipropionate via metered dose inhaler (QVAR) has been approved and marketed in the US by Teva since 2000. The QVAR RediHaler is a breath-actuated version of the applicant's QVAR Inhalation Aerosol. QVAR RediHaler is presented in two dosage strengths intended to deliver either 40 mcg per actuation or 80 mg per actuation (ex-actuator) and a minimum of 120 actuations each

The proposed dose is 40 mcg to 320 mcg twice daily (80 mcg to 640 mcg total daily dose) in those age ≥12 years, and 40 mcg to 80 mcg twice daily (80 mcg to 160 mcg total daily dose) in those age 4 to 11 years, with the starting dose based on prior asthma therapy and disease severity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted clinical program is adequate to support the efficacy of QVAR RediHaler at a range of daily doses (divided BID) from 80 mcg to 640 mcg in patients 12 years of age and older, and from 80 to 160 mcg daily in patients 4 to 11 years of age. The submitted clinical program consisted of 4 clinical studies in total, 3 in patients 12 years of and older (Study 301, 304, and 30039), and one study in patients 4 to 11 years of age (Study 302). Study 301 did not meet its primary endpoint, but was included in the safety evaluation.

Study 304 was a randomized, double-blind, parallel-group, placebo-controlled, 12-week, efficacy and safety trial compared QVAR RediHaler 40 and 80 mcg given as 1 inhalation twice daily with placebo in 270 adult and adolescent patients with persistent symptomatic asthma despite low-dose inhaled corticosteroid or non-corticosteroid asthma therapy. The primary endpoint for this trial was the standardized baseline-adjusted trough morning FEV_1 AUC(0-12wk). Patients in both treatment groups had significantly greater improvements in trough FEV_1 compared to placebo (QVAR RediHaler 80 mcg/day, LS mean change of 0.124 L and QVAR RediHaler 160 mcg/day, LS mean change of 0.116 L over 12 weeks). Both doses of QVAR RediHaler were effective in improving asthma control with significantly greater improvements in FEV_1 and morning PEF when compared to placebo. Reduction in asthma symptoms was also supportive of the efficacy of QVAR RediHaler.

Study 30039 was a randomized, double-blind, parallel-group, placebo-controlled, 6-week, efficacy and safety trial compared QVAR RediHaler 40 and 80 mcg given as 4 inhalations twice daily and placebo in 425 adult and adolescent patients with persistent symptomatic asthma despite treatment with non-corticosteroid, inhaled corticosteroids (with or without a long acting

beta agonist [LABA]), or combination asthma therapy. The study also included a reference treatment group, QVAR Inhalation Aerosol (QVAR MDI) 40 mcg, 4 inhalations twice daily. Patients in both treatment groups had significantly greater improvements in trough FEV1 AUC(0-6wk) compared to placebo (QVAR RediHaler 320 mcg/day, LS mean change of 0.144 L and QVAR RediHaler 640 mcg/day, LS mean change of 0.150 L over 12 weeks). In this study, both doses of QVAR RediHaler were effective in improving asthma control with significantly greater improvements in FEV_1, morning PEF, weekly average of daily trough morning FEV_1, reduced rescue medication use and improved asthma symptom scores than with placebo.

Study 302 was a randomized, double-blind, parallel-group, placebo controlled, 12-week, global efficacy and safety trial compared QVAR RediHaler 40 or 80 mcg, QVAR MDI 40 or 80 mcg or placebo given as 1 inhalation twice daily in pediatric patients aged 4 through 11 years old with persistent symptomatic asthma despite treatment with non-corticosteroid or low dose inhaled corticosteroid (with or without a long acting beta agonist [LABA]). 568 pediatric patients with symptomatic asthma of which 410 had previously been treated with low dose inhaled corticosteroids with or without a LABA were randomized to receive either 40 mcg or 80 mcg twice daily of QVAR RediHaler, QVAR MDI or placebo. The primary endpoint was the change from baseline in trough percent predicted FEV1 AUEC (0-12 weeks). While the primary endpoint, was not statistically significant, change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12 week treatment period was 11.3 [95% CI: 5.58, 17.06] and 8.5 [95% CI: 2.71, 14.24] for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, at nominal significance. Similar results were seen with evening PEF.

Given that the efficacy of ICS in general, and beclomethasone dipropionate specifically, have been evaluated in numerous studies, and the PEF is another objective measure of lung function in the pediatric population, despite the failure in the primary endpoint, the statistical issues are noted; however, there is clinical justification for approving QVAR RediHaler in the pediatric age group 4 to 11 years of age.

1.3. Benefit-Risk Assessment

The Applicant has submitted adequate data to support approval of QVAR RediHaler (beclomethasone dipropionate 40 mcg and 80 mcg per inhalation) for treatment of asthma in patients 4 years of age and older.

The overall risk-benefit assessment supports approval of QVAR RediHaler at the two dose strengths and dose range of 80 mcg to 640 mcg total daily dose (divided BID), depending on asthma severity and age. The risk with the use of ICS as a class, and specifically for beclomethasone propionate, for the treatment of asthma are well known. No new safety findings were identified during the clinical development program for this product. The efficacy findings were robust and consistent with products of these classes.

The various reviews of the CMC, Clinical Pharmacology, Pharmacology/Toxicology, and Statistical teams support approval.

The CDTL recommends **Approval** of this application.

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Banu A. Karimi-Shah, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Asthma is a chronic respiratory disease that affects 8% of the population in the United States. Symptoms are caused by inflammation and narrowing of small airways and may include shortness of breath, coughing, wheezing, and chest pain. Disease severity ranges from mild with occasional symptoms to severe with persistent symptoms that impact quality of life. However, even people with mild disease may suffer severe attacks (1).

A sudden worsening of symptoms is known as an exacerbation. These often lead to missed days of work or school, urgent medical appointments, increased therapy, and occasionally hospitalization. US patients miss 10.5 million school days and 14.2 million work days annually from asthma. Each year, asthma causes 1.75 million emergency department visits and 456,000 hospitalizations in the US (2).

Asthma can present in a variety of ways, from early-onset childhood asthma with allergies, to late-onset adult non-allergic asthma associated with obesity. In allergic asthma, exposure of the airway to allergens following sensitization causes mast cell degranulation and initiation of an inflammatory cascade. In non-allergic asthma, epithelial stimulation and initiation of inflammation can occur with viral or bacterial infections or exposure to noxious chemicals (3).

Diagnosis is based on the pattern of symptoms, response to therapy over time, and spirometry. Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate (4).

2.2. Analysis of Current Treatment Options

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agonists (LABAs), leukotriene modifying drugs, methylxanthines, inhaled anticholinergic, anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, and anti-IgE antibody omalizumab. ICSs are considered to be the most effective treatment for persistent asthma, and are used as the first drug when a maintenance treatment is necessary. When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is often added, preferably for a limited time period with the intent of discontinuing the LABA once asthma control is achieved and maintained. Since some patients with asthma use both an ICS and a LABA, these two drugs have been combined together in the same formulation and in the same device and marketed as combination products. There are several such combination products in the market in the United States. Examples include Advair Diskus and Advair HFA Inhalation Aerosol (both are a combination of fluticasone

propionate and salmeterol), Symbicort (a combination of budesonide and formoterol fumarate), Dulera (a combination of mometasone furoate and formoterol fumarate), and Breo Ellipta (a combination of fluticasone furoate and vilanterol).

Corticosteroids administered systemically at large doses have variety of serious adverse effects that are well known. Although ICS do not usually have the typical serious adverse effects associated with systemic corticosteroids because absorption from the inhaled route is limited, ICS can have local adverse effects, such as oral candidiasis, and pneumonia in patients with COPD, particularly at high doses. Also, ICS at high doses have some systemic effects, such as changes in bone mineralization and an effect on linear growth in young growing children.

Table 1. Currently available therapies for the maintenance treatment of asthma

Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI/Respules	Pulmicort
	Fluticasone propionate HFA, DPI	Flovent HFA Flovent Diskus
	Mometasone DPI/HFA	Asmanex
	Ciclesonide HFA	Alvesco
Combination inhaled corticosteroids/long-acting beta agonist (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone propionate/ Salmeterol HFA, Diskus	Advair
	Mometasone/Formoterol HFA	Dulera
	Fluticasone furoate/ Vilanterol	Breo Ellipta
Anti-IgE	Omalizumab	Xolair
Anti-IL5	Mepolizumab	Nucala
	Reslizumab	Cinqair
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	Multiple
Anticholinergics	Tiotropium bromide	Spiriva Respimat

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Beclomethasone dipropionate is not a new molecular entity. Currently it is marketed by Teva as a metered dose inhaler for asthma, QVAR 40 or 80 (NDA 020911), and as a nasal spray, QNASL (NDA 202813) for allergic rhinitis. Previously it was marketed by Schering as Vancenase in a metered aerosol (NDA 018521 and 019589), as a double strength aerosol, Vanceril (NDA 020486) and Vancenase AQ, a nasal spray (NDA 020469). Glaxosmithkline had marketed it as the metered aerosols Beclovent (NDA 018153) and Beconase (NDA 018584), as well as the nasal spray Beconase AQ (NDA 019389).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Division and Teva had typical milestone meetings for QVAR RediHaler for asthma.

- The development program was performed under IND 114865.
- Pediatric Research Equity Act exemption September 30, 2014 - under the 505(b)2 pathway, QVAR RediHaler was deemed exempt because it does not have new active ingredients, indications, dosage forms, dosing regimens or routes of administration.
- End of Phase 2 meeting October 6, 2014 – the Division recommended inclusion of children down to age 4, (b) (4) in study 302. Young children who were unable to perform spirometry could be excluded from efficacy analyses, but included in safety analyses.
- Pre-NDA meeting April 28, 2015 – study 301 failed to demonstrate efficacy for the primary endpoint. The Division recommended that an additional phase 3 study be performed (Study 30039).
- A second pre-NDA meeting July 5, 2016 – The Division agreed with submission of QVAR RediHaler for registration under the 505(b)2 pathway, and noted that evidence to support approval in pediatric patients was weak. Agreement was reached to present the ITT as a sensitivity analysis, since the Division requested it after unblinding and Teva had performed a modified ITT as the primary analysis.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An audit was not necessary and not conducted for this application. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity.

4.2. Product Quality

The QVAR RediHaler is a breath-actuated version of the applicant's QVAR Inhalation Aerosol. It provides beclomethasone dipropionate (BDP) corticosteroid for inhalation for prophylactic therapy of patients, 4 years and older, with asthma, but is not indicated for acute bronchospasm. Relative to a typical press-and-breathe inhalation aerosol, a breath-actuated inhalation aerosol removes the need for patients to coordinate their inhalation breath with the actuation of the device valve to dispense a dose of formulation, with the intent being less variable dose delivery to the patients' lungs. The drug substance for this (solution formulation) inhalation aerosol is beclomethasone dipropionate (BDP), which is a USP monographed compound.

The CMC information for drug substance is referenced to DMF 4871, which was found to be adequate to support the NDA. BDP has eight chiral centers, and it is slightly soluble in water. (b) (4) which is a related degradant of BDP, is the only impurity observed in the active pharmaceutical ingredient (API) at release. All other BDP related substances are considered unspecified impurities and controlled at NMT (b) (4)%. Residual (b) (4) impurities are controlled as per ICH guidance recommendations. Potential mutagenic impurities include (b) (4) a (b) (4) The (b) (4) impurity is controlled at NMT (b) (4)% where the allowed limit based on the maximum daily dose of (b) (4) mcg and the threshold of toxicological concern of (b) (4) mcg is (b) (4)%. Possible (b) (4) from six batches showed (b) (4) ppm or (b) (4) times lower than the permitted amount. The BDP retest period is (b) (4) months and there is also an expiration period of (b) (4) months from the date of receipt or manufacturer's expiration date, whichever is earlier. The drug substance manufacturing facility (b) (4) has received an approval recommendation, as does the API (b) (4) site (b) (4)

QVAR RediHaler, Beclomethasone dipropionate (breath-actuated) inhalation aerosol (BDP BAI) is presented in two dosage strengths intended to deliver either 40 mcg per actuation or 80 mg per actuation (ex-actuator) and a minimum of 120 actuations each, with strengths distinguished by the color of the BAI device. BDP BAI is a solution formulation of beclomethasone dipropionate (BDP) in (b) (4) and 1,1,1,2-tetrafluoroethane (also referred as HFA-134a) as propellant, contained in a (b) (4) aluminum canister closed with a primeless metering valve of 50 microliters (mcL) (b) (4), and fitted into a breath-actuated inhaler (BAI). Inhalers are individually packed with a patient information leaflet and information for use leaflet into a paper carton. The BAI device, constructed of two sub-assemblies, the Force Holding Unit

(FHU) and the Main Body Assembly (MBA), synchronizes the dispensing of metered dose with patient inhalation, eliminating the need for patients to co-ordinate inhalation with the manual actuation of an aerosol canister.

(b) (4)

microorganisms. The drug product manufacturing facility (IVAX Pharmaceuticals Ireland) and (b) (4) have received approval recommendations and the CDRH Office of Compliance has recommended post-approval inspection of the two device-related manufacturing and control facilities (Norton Waterford Ltd. and Teva Branded Pharmaceutical Products R&D Inc.).

Apart from the typical quality control information and data evaluated in support of this drug product, there were several device-related problems that were observed during development, either by analysts during testing, or via patient complaints during the clinical studies. First, the applicant had problems with the device (b) (4) during development. (b) (4) The applicant and (b) (4) manufacturer made changes (b) (4) during development to address this issue, and improvement was realized (b) (4) However, the applicant agrees to monitor the first three commercial scale batches after storage at all ICH Q1A storage conditions, such that there will be additional data available to gauge their corrective action for the (b) (4) manufacturing. In addition, the applicant has revised the drug product test methods to assure analysts perform a thorough examination for any evidence of (b) (4). Second, there were patient complaints (about 1.0% rate) of devices actuating prematurely, and this was traced to variability in placement of the (b) (4) of the device. As a result, the applicant has taken corrective action to orient and inspect for the proper placement of this part during (b) (4) manufacture. Third, there were complaints (about 0.5% rate) of th (b) (4) Fourth, there were some complaints regarding the counter devices, but the same counter mechanism is used in the press-and-breathe QVAR® Inhalation Aerosol, and since the complaint rate is less than 0.002% (over (b) (4) units dispensed), thus no changes to the counter are proposed currently.

In summary, although not desirable, it is not unexpected for there to be some minor changes to these types of devices, based on testing observations and patient complaints during clinical studies. The applicant has been diligent in addressing these to provide greater assurance of the quality of the commercial drug product they plan to market. Nevertheless, during life-cycle management of this application, it will be prudent for the Agency to monitor annual and any field-alert reports for additional quality issues that may only become evident with wide-spread use.

From a risk/benefit perspective, the advantage of a breath-actuated inhalation aerosol to the patient, relative to a typical press-and-breathe inhalation aerosol, i.e., the elimination of the coordination of actuation and inhalation, is likely worth the increased complexity of the former over the latter device, as the applicant has demonstrated a willingness to address and correct human factor-related issues that had been observed with patient use.

The application is recommended to be **approved** from the quality perspective. All sub-disciplines (drug substance, drug product, process, microbiology, and facilities) concur that the quality aspects of the drug product, as manufactured, meet the standards expected for an inhalation drug product for the intended patient population.

Currently, an 18 month expiration dating period is granted for both strengths of the drug product.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

For nonclinical pharmacology and toxicology support of this application, the sponsor relied on previous safety and efficacy findings from BECLOVENT® (NDA 018153, GlaxoSmithKline), QVAR® Inhalation Aerosol (NDA 020911, Teva), QNASL® Nasal Aerosol (NDA 202813, Teva), and published literature. Since no new nonclinical data was submitted, the information below was based on cross-referenced labels of NDA 020911 updated on July 21, 2014. As the maximum dose proposed in this application is identical to that approved for QVAR® Inhalation Aerosol in NDA 020911, we conclude that the application is approvable from the nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA018153, NDA020911, NDA 202813

5.3. Pharmacology

N/A

5.4. ADME/PK

N/A

5.5. Toxicology

5.5.1. General Toxicology

N/A

5.5.2. Genetic Toxicology

From QVAR's approved label (July 2014)
Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese hamster ovary (CHO) cells in vitro. No significant clastogenic effect was seen in cultured CHO cells in vitro or in the mouse micronucleus test in vivo.

5.5.3. Carcinogenicity

From QVAR's approved label (July 2014)
The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment -related increases in the incidence of tumors in this study at the highest dose, which is

approximately 37 and 72 times the MRHDID in adults and children, respectively, on a mg/m^2 basis.

5.5.4. Reproductive and Developmental Toxicology

From QVAR's approved label (July 2014)
Fertility and Early Embryonic Development (Section 13.1)
In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 250 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 25 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 17 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Embryo-Fetal Development (Section 8.1)
In an embryofetal development study in pregnant rats, beclomethasone dipropionate administration during organogenesis from gestation days 6 to 15 at inhaled doses 180 times the MRHDID (0.64 mg/day) in adults and higher (on a mg/m^2 basis at maternal doses of 11.5 and 28.3 mg/kg/day) produced dose-dependent gross injury (characterized by red foci) of the adrenal glands in fetuses. There were no findings in the adrenal glands of rat fetuses at an inhaled dose that was 40 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 2.4 mg/kg/day). There was no evidence of external or skeletal malformations or embryolethality in rat fetuses at inhaled doses up to 440 times the MRHDID (on a mg/m^2 basis at maternal doses up to 28.3 mg/kg/day).

In an embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 18 at subcutaneous doses equal to and greater than 0.75 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 0.1 mg/kg/day and higher) produced teratogenic effects (increased incidence of cleft palate). A no effect dose in mice was not identified. In a second embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 13 at subcutaneous doses equal to and greater than 2.3 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.3 mg/kg/day) produced embryolethal effects (increased fetal resorptions) and decreased pup survival.

In an embryofetal development study in pregnant rabbits, beclomethasone dipropionate administration during organogenesis from gestation days 7 to 16 at subcutaneous doses equal to and greater than 0.75 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 0.025 mg/kg/day and higher) produced teratogenic (external and skeletal malformations) and embryolethal effects (increased fetal resorptions). There were no effects in fetuses of pregnant rabbits administered a subcutaneous dose 0.2 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 0.006 mg/kg/day).

Prenatal and Postnatal Development
N/A

5.5.5. Other Toxicology Studies

N/A

X X

Xiaochun Chen, PhD
Primary Reviewer

Carol Galvis, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The applicant submitted NDA 207-921 to seek approval of beclomethasone dipropionate (BDP) breath actuated inhaler (BAI) for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. The applicant conducted 1 clinical pharmacology study and 4 clinical efficacy and safety studies to support this NDA.

The mean peak plasma concentration (C_{max}) of BDP was 6635 pg/mL at 2 minutes after inhalation of 320 µg BDP through the BAI (4 inhalations of the 80 µg/inhalation strength). The mean peak plasma concentration of the major and most active metabolite, beclomethasone-17-monopropionate (17-BMP), was 1464 pg/mL at the median time of 10 minutes after inhalation of 320 µg BDP through the BAI. Relying on the 17-BMP pharmacokinetic data upon administration of the 320 µg BDP BAI and 320 µg QVAR® MDI (4 inhalations of the 80 µg/inhalation strength), the BDP BAI is bioequivalent to the QVAR® MDI.

Recommendations
The Office of Clinical Pharmacology has reviewed the clinical pharmacology data for NDA 207-921 and finds the data acceptable.

Post Marketing Requirement
None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

BDP is a corticosteroid. BDP is a pro-drug and is converted to 3 metabolites, namely 17-BMP, beclomethasone-21-monopropionate, and beclomethasone, via esterase-catalyzed hydrolysis. Oxidative metabolism via cytochrome P450 3A enzymes also occurs, but the metabolites do not appear to contribute to the pharmacological activity of the drug. 17-BMP is the most pharmacologically active metabolite (Harrison et al. *J Pharm Pharmacol* 1999;51:263-9). In in vitro studies, 17-BMP showed a binding affinity for the human glucocorticoid receptor, whereas beclomethasone dipropionate showed little or no binding ability (Wurthwein and Rohdewald. *Biopharm Drug Dispos* 1990;11:381-94).

The Applicant currently markets BDP as QVAR (BDP hydrofluoroalkane) inhalation aerosol, NDA 20-911. QVAR Inhalation Aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older and for asthma patients who require systemic corticosteroid administration, where adding QVAR inhalation aerosol may reduce or eliminate the need for systemic corticosteroids.

QVAR inhalation aerosol (hereinafter referred to as BDP MDI) delivers BDP through MDI and it has been approved in the United States since September 15, 2000. Although the MDI is a common device to deliver inhaled corticosteroids, MDI requires coordination of actuation and inhalation for effective delivery of the corticosteroids. The Applicant has developed a BAI, which ensures that actuation of the metered-dose valve occurs automatically when the user inhales.

The Applicant provided the results of a single dose, crossover study to characterize and compare the relative bioavailability of 320 µg BDP BAI and 320 µg BDP MDI. The BDP BAI is bioequivalent to the BDP MDI for 17-BMP.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Patient's Previous Therapy	Recommended Starting Dose	Highest Dose Recommended
Patients aged 12 years or older		
Bronchodilators Alone	40 to 80 mcg twice daily	320 mcg twice daily
Inhaled Corticosteroids	40 to 160 mcg twice daily	320 mcg twice daily
Patients aged 4-11 years		
Bronchodilators Alone	40 mcg twice daily	80 mcg twice daily
Inhaled Corticosteroids	40 mcg twice daily	80 mcg twice daily

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review – Question-Based Review

The Applicant submitted NDA 207-921 (BDP BAI) via the 505(b)(2) regulatory pathway referencing QVAR inhalation aerosol (BDP MDI). The Applicant conducted 1 clinical pharmacology study (BDB-AS-101) to support NDA 207-921. The purpose of Study BDB-AS-101 is to assess and compare the pharmacokinetics (PK) of BDP BAI and the reference BDP MDI.

Table 2 summarizes the clinical pharmacology study (BDB-AS-101). Table 8 summarizes the Phase 3 studies for NDA 207-921.

Table 2. Summary of clinical pharmacology study.

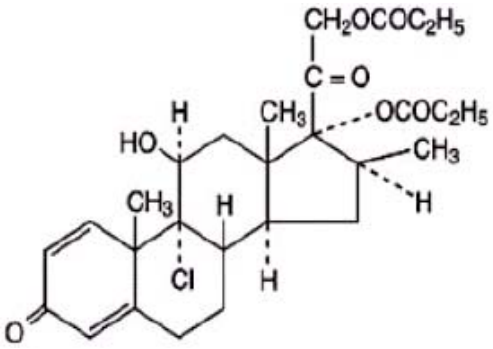
Study identifier (type of study) Total number of centers with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects: Treated Completed study M/F (enrolled) Age range (y) (enrolled)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Phase 1 Pharmacokinetics, Safety, and Tolerability							
BDB-AS-101 (Pharmacokinetics) Single center USA	To compare the relative rate and extent of the systemic availability of 17-BMP administered via BAI and MDI	Randomized, open-label, 3-period crossover, single dose	BDP BAI 40 mcg/inhalation 4 inhalations once daily 160 mcg total BDP BAI 80 mcg/inhalation 4 inhalations once daily 320 mcg total BDP MDI 80 mcg/inhalation 4 inhalations once daily 320 mcg total	Treated: 72 Completed: 65 M: 36/F: 36 18-45 y	Healthy adult subjects	Single doses on 3 days	Completed Final CSR (Module 5.3.3.1)

Source: The Applicant's Section 5.2, Tabular Listing of All Clinical Studies.

6.3.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

BDP has a molecular weight of 521.(b) (4) with the molecular formula of $C_{28}H_{37}ClO_7$. Figure 1 shows the molecular structure of BDP.

Figure 1: Structure of BDP



Source: The sponsor's S.1.2, Figure 1.

6.3.2 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical development program included 1 clinical pharmacology study (Table 2) and 4 clinical efficacy and safety studies (Table 4). Please refer the clinical review section for the design features of the 4 clinical efficacy and safety studies.

Study BDB-AS-101 was a Phase 1, randomized, open-label, 3-period crossover, single-dose study designed to investigate the PK, safety, and tolerability of 320 µg BDP delivered via BAI and MDI as well as 160 µg BDP delivered via BAI in healthy adult participants aged 18 to 45 years, inclusive. Participants received each treatment with at least an 8 hour overnight fast. A 7- to 14-day washout period separated each treatment.

6.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

Yes. The Applicant measured the concentrations of BDP and 17-BMP in plasma samples for Study BDB-AS-101. 17-BMP is the most active metabolite of BDP.

6.3.4 Dose-Exposure/Response

In NDA 207921, the sponsor is relying on the previous findings of efficacy and safety for BDP MDI. The BDP BAI development program does not contain dose-response studies. The Phase 3 studies evaluated the efficacy and safety of BDP administered via BAI at doses previously approved for BDP MDI. For the Phase 3 studies, see the Clinical Section of the review.

General Pharmacology and Pharmacokinetic Characteristics

6.4 What are the PK characteristics of the drug?

6.4.1 What are the PK parameters of BDP and 17-BMP in healthy adult volunteers following single-dose administration of BDP BAI?

Table 3 shows the BDP PK parameters upon administration of BDP BAI and BDP MDI. The mean peak plasma concentration (C_{max}) of BDP was 6635 pg/mL at the median time of 2 minutes after inhalation of 320 µg BDP through the BAI (4 inhalations of the 80 µg/inhalation).

Table 3. BDP BAI and BDP MDI PK Parameters

Parameter Statistics	**Treatment**		
	Beclomethasone dipropionate BAI, 160 µg (N=66)	**Beclomethasone dipropionate BAI, 320 µg (N=65)**	**Beclomethasone dipropionate MDI, 320 µg (N=67)**
AUC_{0-t} (h•pg/mL)			
Mean	277.57	616.33	553.55
SD	92.048	185.373	203.598
Geometric mean	262.86	591.28	514.67
Min, max	126.73, 609.83	255.70, 1165.70	127.02, 1210.64
C_{max} (pg/mL)			
Mean	3103.41	6635.08	5973.73
SD	1481.312	2741.624	2778.989
Geometric mean	2758.68	6080.72	5211.19
Min, max	658.00, 9070.00	2060.00, 12700.00	1220.00, 15600.00
$AUC_{0-\infty}$ (h•pg/mL)			
Mean	283.45[a]	623.58[a]	572.49[b]
SD	95.174	190.302	199.742
Geometric mean	267.98	597.60	538.41
Min, max	129.55, 615.02	259.89, 1171.80	217.28, 1221.77
t_{max} (h)			
Median	0.03	0.03	0.03
Min, max	0.02, 0.06	0.03, 0.05	0.03, 0.09
$t_{½}$ (h)			
Mean	0.57[a]	0.92[a]	0.81[b]
SD	0.284	0.405	0.363
Median	0.52	0.79	0.69
Min, max	0.19, 1.47	0.40, 1.99	0.38, 2.37

Source: The Applicant's Table 4 of Section 2.7.2.

Table 4 shows the 17-BMP PK parameters upon administration of BDP BAI and BDP MDI. The mean C_{max} of 17-BMP was 1464 pg/mL at the median time of 10 minutes after inhalation of 320 µg BDP through the BAI.

Table 4. The PK parameters of 17-BMP for Study BDB-AS-101.

Parameter Statistics	**Treatment**		
	Beclomethasone dipropionate BAI, 160 µg (N=66)	**Beclomethasone dipropionate BAI, 320 µg (N=65)**	**Beclomethasone dipropionate MDI, 320 µg (N=67)**
AUC_{0-t} (h•pg/mL)			
Mean	2107.53	4480.67	4081.99
SD	493.709	921.813	905.728
Geometric mean	2053.21	4388.39	3986.88
Min, max	1151.00, 3759.15	2597.18, 7138.75	1730.20, 7692.22
C_{max} (pg/mL)			
Mean	660.02	1464.40	1268.49
SD	270.700	783.883	503.495
Geometric mean	611.63	1312.15	1168.33
Min, max	270.00, 1430.00	513.00, 4660.00	402.00, 2680.00
$AUC_{0-\infty}$ (h•pg/mL)			
Mean	2201.89	4594.93	4185.06
SD	497.938	928.721	911.917
Geometric mean	2148.70	4503.91	4092.65
Min, max	1202.27, 3845.13	2773.92, 7251.21	1949.66, 7871.18
t_{max} (h)			
Median	0.17	0.17	0.17
Min, max	0.03, 1.00	0.03, 1.00	0.03, 1.50
$t_{½}$ (h)			
Mean	4.15	4.30	4.12
SD	1.031	0.979	0.854
Median	3.99	4.17	4.08
Min, max	2.52, 7.41	2.75, 6.90	2.50, 6.62

Source: The Applicant's Table 1 of Section 2.7.2.

6.4.2 How does the systemic exposure of BDP and 17-BMP compare upon single-dose administration of BDP BAI and BDP MDI?

Table 5 shows the statistical comparisons of 17-BMP PK parameters upon single-dose administration of BDP BAI (160 µg and 320 µg BDP) and BDP MDI (320 µg BDP).

Table 5. Statistical comparisons of 17-BMP PK parameters.

Test (T)	Reference (R)	Parameter	Unit	Ratio, in %, of geometric mean (T/R)	Ratio's 90% confidence interval
A	B	$AUC_{0\text{-}inf}$	pg.hr/mL	47.72	45.94 – 49.57
		$AUC_{0\text{-}t}$	pg.hr/mL	46.79	44.97 – 48.69
		C_{max}	pg/mL	47.24	43.51 – 51.28
A	C	$AUC_{0\text{-}inf}$	pg.hr/mL	52.53	50.58 – 54.56
		$AUC_{0\text{-}t}$	pg.hr/mL	51.53	49.53 – 53.61
		C_{max}	pg/mL	53.37	49.19 – 57.91
B	C	$AUC_{0\text{-}inf}$	pg.hr/mL	110.08	105.98 – 114.33
		$AUC_{0\text{-}t}$	pg.hr/mL	110.12	105.85 – 114.57
		C_{max}	pg/mL	112.99	104.12 – 122.61
A = 160 µg BDP BAI B = 320 µg BDP BAI C = 320 µg BDP MDI					

Source: This reviewer's analyses of the 17-BMP PK parameters via SAS 9.4.

Relying on the 17-BMP PK data upon administration of 320 µg BDP BAI and 320 µg BDP MDI, the BDP BAI is bioequivalent to the BDP MDI.

This reviewer did not assess dose proportionality because the sponsor only studied 2 doses (160 µg and 320 µg) of BDP BAI in Study BDB-AS-101.

Table 6 shows the statistical comparisons of BDP PK parameters upon single-dose administration of BDP BAI (160 µg and 320 µg BDP) and BDP MDI (320 µg BDP).

Table 6. Statistical comparisons of BDP PK parameters.

Test (T)	Reference (R)	Parameter	Unit	Ratio, in %, of geometric mean (T/R)	Ratio's 90% confidence interval
A	B	$AUC_{0\text{-}inf}$	pg.hr/mL	44.34	40.78 – 48.2
		$AUC_{0\text{-}t}$	pg.hr/mL	44.92	41.31 – 48.85
		C_{max}	pg/mL	46.72	41.29 – 52.87
A	C	$AUC_{0\text{-}inf}$	pg.hr/mL	50.63	46.62 – 54.99
		$AUC_{0\text{-}t}$	pg.hr/mL	52.63	48.42 – 57.21
		C_{max}	pg/mL	56.03	49.54 – 63.36
B	C	$AUC_{0\text{-}inf}$	pg.hr/mL	114.2	105.2 – 123.96
		$AUC_{0\text{-}t}$	pg.hr/mL	117.17	107.78 – 127.38
		C_{max}	pg/mL	119.92	106.03 – 135.63

A = 160 µg BDP BAI
B = 320 µg BDP BAI
C = 320 µg BDP MDI

Source: This reviewer's analyses of the BDP PK parameters via SAS 9.4.

Single-dose administration of BDP BAI (320 µg) resulted in 20% higher BDP C_{max} and 14 – 17% higher BDP AUC as compared to BDP MDI (320 µg). This increase in BDP exposure following administration of BDP BAI as compared to BDP MDI is not expected to have any clinically meaningful impact on the efficacy and safety of BDP BAI for the following reasons: For inhaled BDP, the systemic exposure is not directly related to clinical response and does not account for the efficacy of BDP BAI.

The major systemic safety concern for the inhalation steroids is suppression of the endogenous cortisol release [such as the hypothalamic-pituitary-adrenal (HPA) suppression]. Although the systemic exposure of BDP (C_{max} and AUC) upon single-dose administration of BDP BAI (320 µg) was slightly higher than BDP MDI, the systemic exposure of the active metabolite, 17-BMP was comparable in Study BDB-AS-101.

The dose-related effect of multiple doses (BID dosing for 10 days) of BDP MDI (doses ranging from 200 µg to 2800 µg/day) on 24 h urinary free cortisol, a recognized method to assess adrenal function, was studied under NDA 20-911. Relying on the results of this assessment

(https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20-911_QVAR_BioPharmr.pdf), a slight increase in exposure of BDP from BDP BAI, as compared to the approved QVAR MDI, is not expected to have any clinically meaningful impact on safety of BDP BAI.

6.4.3 How is the proposed to-be-marketed formulation linked to the clinical formulation?

The BDP BAI drug product tested in Study BDB-AS-101 is identical to the to-be-marketed BDP BAI drug products. The batch size of the BDP BAI drug product used in Study BDB-AS-101 was (b) (4) which is the same as the to-be-marketed batch size. The reference product used in Study BDB-AS-101 was the QVAR® Inhalation Aerosol (BDP MDI, NDA 20-911) approved and marketed in the United States.

6.5. Bioanalytical Section

6.5.1 How are the parent drug and relevant metabolites identified and what are the bioanalytical methods used to measure them in plasma?

The sponsor used a liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay to determine the 17-BMP and BDP concentrations in plasma samples. Table 7 details the validation of the bioanalytical assay. Validations for the LC/MS/MS bioanalytical assay of 17-BMP and BDP appear acceptable with reasonable precision and accuracy.

Table 7. Validation of the bioanalytical assay to measure 17-BMP and BDP for Study BDB-AS-101.

Analyte	**17-BMP**	**BDP**
Matrix	Plasma	Plasma
Anticoagulant	K_2EDTA	K_2EDTA
Sample volume, mL	0.2	0.2
Lower limit of quantitation, pg/mL	10.0	5.0
Linear range, pg/mL	10.0 – 2500	5.0 – 1250
Average recovery (%)	83.3 (17-BMP) 82.9 (internal standard)	58 (BD) 58.1 (internal standard)
Assay precision (%CV)		
Inter-day calibration standards	3.1 – 7.6	3.5 – 7.7
Inter-day quality controls	3.0 – 6.2	4.2 – 7.9
Assay accuracy (% relative error)		
Inter-day calibration standards	-2.4 – 1.8	-1.3 – 0.9
Inter-day quality controls	-3.9 – 2.6	-7.3 – -0.5
Storage stability	up to 95 days at –80°C±10°C	
Freeze-thaw stability (5 cycles), %	-7.52 – -1.62	-5.55 – -0.699

Source: This reviewer's compilation of the sponsor's Bioanalytical and Validation Reports for Study BDB-AS-101 (DP-2014-049 and LCMSD 333.1).

6.6 Other Clinical Pharmacology Questions

6.6.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Study BDB-AS-101 bridges the systemic exposure BDP and 17-BMP upon single-dose administration of BDP BAI and BDP MDI.

6.6.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of BDP BAI is the same as the approved dosing regimen of QVAR MDI.

6.6.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No.

6.6.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No.

6.6.5 Question on clinically relevant specifications (TBD)?

Not applicable.

X X

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7 Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 8. Relevant clinical studies with QVAR RediHaler (beclomethasone dipropionate) in patients with asthma

ID [Year]	Study Characteristics † - Patient age (years) - Patient characteristics - Study design, objective - Study duration	Treatment groups dose in µg/day ‡	N §	Primary efficacy variables	Regions and Countries
304 [2013-2014]	- ≥ 12, mean 38 years - asthma, low dose ICS - parallel arm, DB - 12 weeks	BD BAI 80 BD BAI 160 Placebo	90 92 91	1°: Trough morning FEV1 AUEC(0-12wk)	US (100%)
301 [2014]	- ≥ 12, mean 46 years - asthma, ICS ± LABA - parallel arm, DB - 12 weeks	BD BAI 320 BD BAI 640 BD MDI 320 BD MDI 640 Placebo	106 106 107 107 106	1°: Trough morning FEV1 AUEC(0-12wk)	Germany, Hungary, Poland, and US (100%)
30039 [2015-2016]	- ≥ 12, mean 42 years - asthma, non ICS, ICS ± LABA - parallel arm, DB - 6 weeks	BD BAI 320 BD BAI 640 BD MDI 320 Placebo	108 105 105 107	1°: Trough morning FEV1 AUEC(0-6wk)	US (100%)
302 [2014-2016]	- 4 to 11, mean 8 years - asthma, ICS ± LABA - parallel arm, DB - 12 weeks	BD BAI 80 BD BAI 160 BD MDI 80 BD MDI 160 Placebo	126 125 125 125 127	1°: Trough morning percent predicted FEV1 AUEC(0-12wk)	Croatia, Mexico, Poland, Ukraine & US (74%)

† DB=double blind
‡ BD=beclomethasone dipropionate, BAI = breath actuated inhaler, MDI = metered dose inhaler
§ Intent to treat

7.1.2. Review Strategy

The clinical review focused on the four core studies in the RediHaler development program: Studies 304, 301, and 30039 targeting an FEV_1 endpoint, and study 302, a pediatric study. Review of the studies was based primarily on this reviewer's independent analysis of the data sets provided by the Applicant, and secondarily on the Applicant's study reports. The tables and analyses presented in this report reflect the independent analysis of the reviewer except where otherwise noted. Narratives of patients with serious adverse events were reviewed; there were no deaths. The Applicant's bibliography was reviewed when relevant.

This portion of the review is completed by the clinical review team, but relies on the efficacy analyses provided by the statistical reviewer. Section 7.2 contains a review of each protocol, and a presentation of patient disposition, protocol violations/deviations, demographic/baseline disease characteristics, concomitant medication use, and treatment compliance. The clinical reviewer will summarize the efficacy data as presented in Section 8 Statistical Evaluation in Section 7.3 Integrated Review of Effectiveness.

Data and Analysis Quality

Data quality and integrity were adequate.

Teva provided adequate attestation that studies 304, 301, 30039 and 302 were conducted in compliance with Good Clinical Practices, in accordance with:

- the protection of human subjects (21 CFR part 50)
- Institutional Review Boards (21 CFR part 56)
- the obligations of clinical investigators (21 CFR 312.50 to 312.70)
- The requirements of 21 CFR 312.120 for foreign clinical studies not conducted under an IND do not apply as all four studies enrolled at least some US patients. The protocols for 30039, 301, 302, and 304 were all submitted to the IND, No. 114865.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

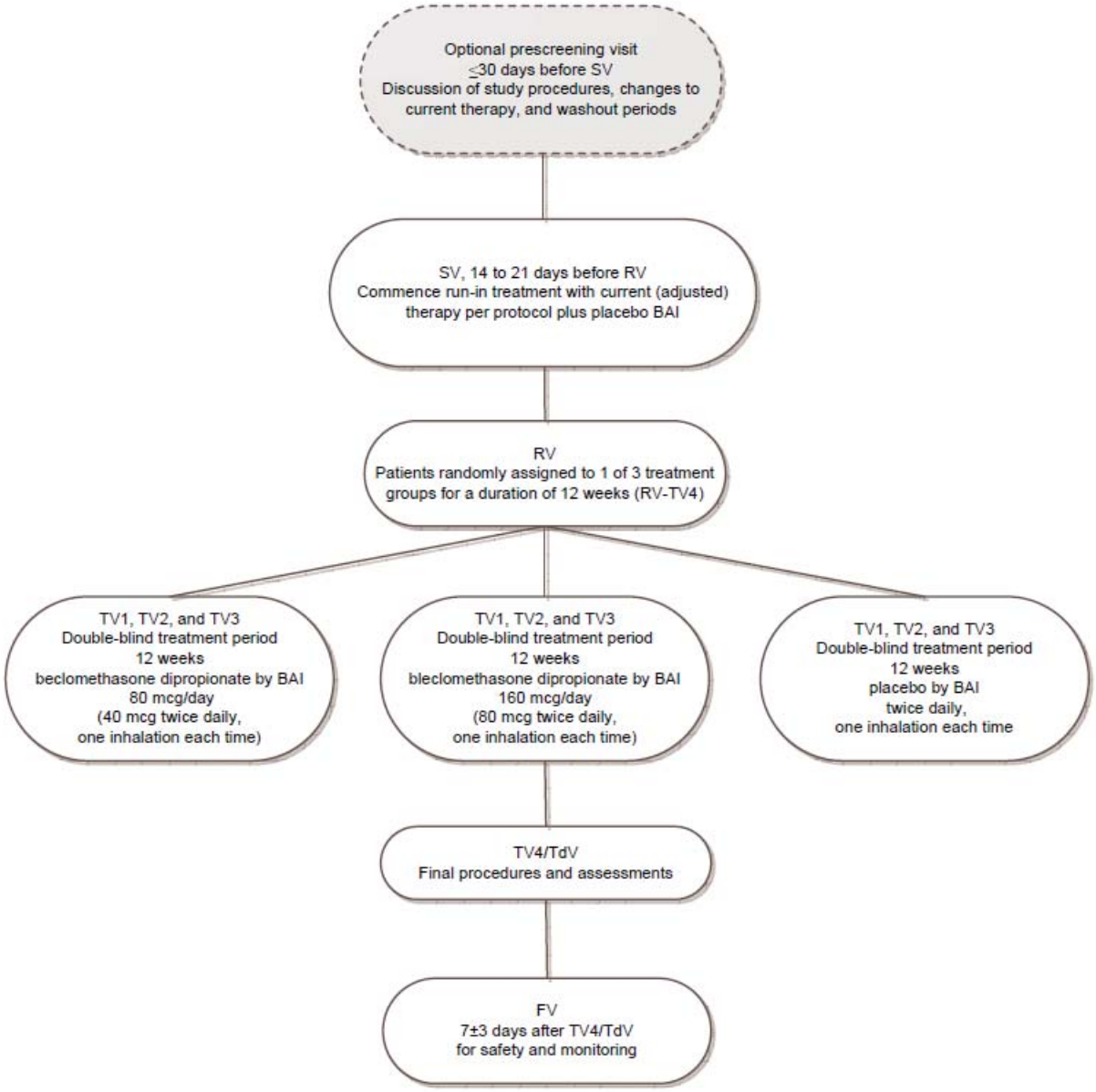
7.2.1. Study 304

Overview and Objective

Study 304 was titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 12-Week Clinical Study to Assess the Efficacy and Safety of Beclomethasone Dipropionate (80 and 160 µg/day) Delivered via Breath-Actuated Inhaler (BAI) in Adolescent and Adult Patients 12 Years of Age and Older with Persistent Asthma." It was conducted at 47 centers in the United States from December 26, 2013 to December 24, 2014. The primary objective was to evaluate the efficacy of beclomethasone dipropionate administered via BAI at doses of 40 and 80 µg per oral inhalation (80 or 160 µg/day) compared with placebo treatment in patients with persistent asthma as assessed by baseline-adjusted trough morning forced expiratory volume in 1 second (FEV1) area under the effect curve from time zero to 12 weeks (AUEC(0-12wk)).

Trial Design

Figure 2: Study 304 schema



Source: Study 304 protocol p. 39
SV=screening visit; ICS= inhaled corticosteroid; RV=randomization visit; BAI=breath-actuated inhaler; TV1=treatment visit 1; TV2=treatment visit 2; TV3=treatment visit 3; TV4=treatment visit 4 (final treatment visit); TdV=treatment discontinuation visit; FV=follow-up visit/telephone call.

This was a Phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of beclomethasone dipropionate treatment administered via BAI at dosages of 80 and 160 µg/day in males and females 12 years of age and older with persistent asthma. Patients treated with a stable dose of ICS in combination with a non-corticosteroid medication were required to discontinue the non-corticosteroid therapy at a prescreening visit if in the investigator's judgment there would be no inherent harm. The study consisted of 4 periods:

- Run-in period: screening to randomization, 2-3 weeks
- Double-blind treatment period: randomization through the final treatment visit, 12 weeks
- Follow-up period: treatment visit four through the follow-up visit/telephone call, 7±3 days

Pertinent Inclusion Criteria:

- at least 12 years of age
- persistent asthma, with an FEV1 40%-85% of the value predicted for age, height, sex, and race
- inhaled corticosteroid (ICS) ≤ 220 µg/day fluticasone propionate via metered-dose inhaler (MDI) or equivalent, or a stable daily dose of non-corticosteroid therapy (including leukotriene modifiers, theophylline, chromones, or short-acting β2 agonists) alone or in combination, both for a minimum of 4 weeks before screening
- 15% reversibility increase from baseline FEV1 at screening

Pertinent Exclusion Criteria:

- history of life-threatening asthma
- known hypersensitivity to any corticosteroid, study drug excipients, or rescue medication
- bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved at least two weeks before screening
- asthma exacerbation requiring oral corticosteroids within one month of screening
- hospitalization for asthma within two months before screening

Prohibited medications (washout time before screening)

- anti-IgE therapy such as omalizumab (90 days)
- any other investigational drug (30 days)
- aspirin (1 day)
- beta-adrenergic receptor blocking agents (30 days)
- bisphosphonates oral or iv (30 days)
- intranasal aerosol corticosteroids (discontinue at screening)
- corticosteroids (oral, iv, intra-articular, intramuscular) (30 days)
- decongestants such as pseudoephedrine, phenylpropanolamine, phenylephrine (discontinue 24 hours before study visits and resume use after the visit)
- immunologically active biologic medications such as anti-TNFα, abatacept (90 days)
- immunosuppressive therapy such as methotrexate, gold, azathioprine (30 days)
- immunotherapy initiation within 90 days or change in dose within 30 days
- inhaled anticholinergic medication such as tiotropium bromide (7 days)
- LABA (7 days)
- monoamine oxidase inhibitors (14 days),

- oral ß2-agonists (7 days)
- oral or nasal antihistamines (discontinue 24 hours before study visit and resume use after visit)
- protocol-allowed non-corticosteroid asthma therapy such as leukotriene modifiers, theophylline, chromones, alone or in combination were permitted at screening, but discontinued at randomization for patients on non-corticosteroid asthma therapy only
- protocol-allowed ICS asthma therapy other than study drug was permitted at screening, but discontinued at randomization for patients on non-corticosteroid asthma therapy only
- strong CYP3A4 inhibitors such as azole antifungals, ritonavir, clarithromycin (30 days)
- topical dermatologic corticosteroids of intermediate to high potency such as fluticasone propionate, mometasone furoate (14 days)
- marijuana (30 days)
- inhaled nicotine such as e-cigarettes (1 day)

Investigational Product: beclomethasone dipropionate, oral inhalation via BAI at the following doses:

- 80 µg/day (one inhalation twice daily, 40 µg/inhalation)
- 160 µg/day (one inhalation twice daily, 80 µg/inhalation)

Placebo: placebo BAI canisters, oral inhalation, one inhalation twice daily

Method of blinding and randomization: Patients were randomly assigned (1:1:1) via the interactive response technology system in a double-blind fashion to receive one of the three treatments over a 12-week period:

- Beclomethasone dipropionate BAI, one inhalation (40 µg/inhalation), twice daily
- Beclomethasone dipropionate BAI, one inhalation (80 µg/inhalation), twice daily
- Placebo BAI, one inhalation, twice daily

Randomization was stratified based on current asthma therapy at screening and run-in.

Table 9. Study 304 schedule of procedures and assessments

	Screening	Randomization	Double blind treatment visits						Follow Up
Visit No.	**SV**	**RV**	**TV1**	**TV2**	**TV3**	**TV4**			**FV**
Week No.	**-3 to -2**	**0**	**2**	**4**	**8**	**12**			**13**
Complete H&P	✓								
Oropharyngeal exam	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test	✓	✓	✓			✓	✓	✓	
Adverse event queries	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	
Spirometry	✓	✓	✓	✓	✓	✓	✓	✓	

Source: Adapted from Study 304 Protocol Table 2 Study Procedures and Assessments p. 47
SV = screening visit, RV= randomization visit, TV = treatment visit, FV = follow up visit, H&P = medicalhistory and physical, ECGs = electrocardiograms, CBC w/ diff = complete blood count with differential

Study Endpoints

Primary endpoint: the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV1 AUEC(0-12wk)

Secondary endpoints:

- change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period
- change from baseline in weekly average of daily evening PEF over the 12-week treatment period
- change from baseline in the weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1-12
- change from baseline in the weekly average of the total daily asthma symptom score over weeks 1-12
- time to patient withdrawal due to meeting stopping criteria for worsening asthma during the 12- week treatment period

Exploratory endpoints included change from baseline in:

- albuterol use
- percentage of rescue free days
- daily asthma symptom score
- symptom free days
- asthma control days
- trough morning FEV1 at multiple timepoints
- FEF25-75 at multiple timepoints
- trough morning PEF at multiple timepoints
- AQLQ
- ACT
- comprehension of device instructions for use (in a subset of patients)

Statistical Analysis Plan

The primary variable was analyzed using an analysis of covariance (ANCOVA) model with effects due to baseline trough morning FEV1, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of screening and during the run-in period and treatment. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI dose versus placebo were constructed. The estimated treatment difference between each active treatment group and the placebo group was presented together with the 2-sided 95% confidence interval for the difference and the p-value. The study was to be considered positive if the results from the comparison of the higher beclomethasone dipropionate dose (160 µg/day via BAI) with placebo using the ANCOVA model was positive, regardless of the results from the comparisons of the other beclomethasone dipropionate dose level with placebo.

Protocol Amendments

Amendment 1 was issued April 17, 2014 when 74 patients were enrolled. It allowed investigators to step-down therapy from ICS/LABA to ICS alone for four weeks prior to the screening visit.

7.2.1.1 Study 304 Results

Compliance with Good Clinical Practices

Adequate. See Section 7.1.2 Review Strategy.

Financial Disclosure

Adequate and unlikely to bias study results. See 14.2 Financial Disclosure.

Patient Disposition

A total of 273 subjects were enrolled in Study 304. Twenty-three (8%) subjects stopped medication and discontinued the study prematurely. The most common reason for discontinuation was withdrawal by subject, occurring in 8 (3%) of subjects. Patient disposition for study 304 is shown in the table below.

Table 10. Study 304 disposition

	BAI 160		BAI 80		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Total	92	(100)	90	(100)	91	(100)	273	(100)
Randomized Set	92	(100)	90	(100)	91	(100)	273	(100)
Safety Set	92	(100)	90	(100)	91	(100)	273	(100)
Full Analysis Set	92	(100)	88	(98)	90	(99)	270	(99)
Complete treatment	88	(96)	83	(92)	79	(87)	250	(92)
Reason for discontinuing treatment								
adverse event	0	0	0	0	1	(1)	1	(0)
lack of efficacy	0	0	2	(2)	4	(4)	6	(2)
lost to follow-up	1	(1)	2	(2)	1	(1)	4	(1)
non-compliance	0	0	1	(1)	0	0	1	(0)
protocol violation	0	0	1	(1)	2	(2)	3	(1)
withdrawal by subject	3	(3)	1	(1)	4	(4)	8	(3)
Complete Study	88	(96)	83	(92)	79	(87)	250	(92)
Reason for discontinuing study								
adverse event	0	0	0	0	1	(1)	1	(0)
lack of efficacy	0	0	2	(2)	4	(4)	6	(2)
lost to follow-up	1	(1)	2	(2)	1	(1)	4	(1)
non-compliance	0	0	1	(1)	0	0	1	(0)
protocol violation	0	0	1	(1)	2	(2)	3	(1)
withdrawal by subject	3	(3)	1	(1)	4	(4)	8	(3)

Source: 304 ADSL.xpt

Protocol Violations/Deviations

Sixteen percent of participants had at least one protocol violation. The most common violations were related to Good Clinical Practice guidelines, such as not re-consented at next visit or study medication not returned.

Reviewer comment: The type of protocol violations were comparable across treatment groups, but the number of patients with one or more violations was higher in the low dose and placebo groups compared to the high dose group; theoretically this has the potential to bias the study away from the null, but since the majority of the violations were to good clinical practice guidelines, this seems unlikely.

Table 11. Study 304 protocol violations

	BAI 160		BAI 80		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Patient with at least one violation*	10	(11)	16	(18)	18	(20)	44	(16)
excluded concomitant medication	2	(2)	3	(3)	5	(5)	10	(4)
GCP guidelines	8	(9)	7	(8)	8	(9)	23	(8)
inclusion criteria	0	0	2	(2)	1	(1)	3	(1)
non-compliance to study medication	1	(1)	1	(1)	2	(2)	4	(1)
randomization criteria	0	0	3	(3)	2	(2)	5	(2)

Source: 304 DDDV.xpt
*Patients may have had more than one violation
GCP = good clinical practice

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in Table 12. In Study 304, subject demographics and baseline characteristics were generally balanced among the treatment groups. The majority of subjects were female, white and of non-Hispanic or non-Latino ethnicity. The mean age was 38 years with 30 (11%) subjects less than 18 years old.

Table 12. Study 304 demographics

	BAI 160		BAI 80		Placebo		Total	
Total, n (%)	92	(100)	90	(100)	91	(100)	273	(100)
Sex, n (%)								
Female	56	(61)	54	(60)	46	(51)	156	(57)
Male	36	(39)	36	(40)	45	(49)	117	(43)
Age Group, n (%)								
12 to < 18 years	13	(14)	8	(9)	9	(10)	30	(11)
18 to 65 years	76	(83)	80	(89)	80	(88)	236	(86)
> 65 years	3	(3)	2	(2)	2	(2)	7	(3)
Race, n (%)								
Asian	1	(1)	2	(2)	3	(3)	6	(2)
Black	14	(15)	17	(19)	13	(14)	44	(16)
Other	5	(5)	7	(8)	2	(2)	14	(5)
White	72	(78)	64	(71)	73	(80)	209	(77)
Ethnicity, n (%)								
Hispanic or Latino	9	(10)	11	(12)	10	(11)	30	(11)
Not Hispanic or Latino	83	(90)	79	(88)	81	(89)	243	(89)
Country, n (%)								
USA	92	(100)	90	(100)	91	(100)	273	(100)
Age in years, mean (SD)	37	(16)	39	(15)	37	(15)	38	(15)
Weight in kg, mean (SD)	80	(21)	85	(22)	82	(24)	83	(22)
Height in cm, mean (SD)	169	(9)	171	(10)	169	(9)	170	(10)
BMI in kg/m^2, mean (SD)	28	(7)	29	(8)	28	(7)	29	(7)

Source: 304 ADSL.xpt
SD = standard deviation, BMI = body mass index
BAI = breath actuated inhaler, doses in µg/day

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The distribution of baseline disease characteristics was similar across treatment groups. Lung function, asthma duration, and baseline asthma medication use are described in the tables below.

Table 13. Study 304 disease characteristics

	BAI 160	BAI 80	Placebo	Total
Lung function in L, mean (SD)				
forced exp. flow (25% - 75%)	1.61 (0.67)	1.50 (0.63)	1.63 (0.69)	1.58 (0.66)
forced exp. volume	2.35 (0.56)	2.35 (0.65)	2.44 (0.61)	2.38 (0.61)
forced vital capacity	3.46 (0.92)	3.64 (1.15)	3.60 (0.86)	3.56 (0.98)
Asthma duration, n (%)				
< 10 years	12 (13)	14 (16)	14 (15)	40 (15)
10 to 15 years	18 (20)	16 (18)	12 (13)	46 (17)
> 15 years	62 (67)	60 (67)	65 (71)	187 (68)

Sources: Study 304 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, doses in µg/day

Table 14. Study 304 baseline asthma medication use

	BAI 80 (N=90) n (%)	BAI 160 (N=92) n (%)	Placebo (N=91) n (%)	All (N=273) n (%)
Anticholinergic/SABA			1 (1)	1 (0)
ICS	30 (33)	38 (41)	30 (33)	98 (36)
ICS/LABA	9 (10)	11 (12)	13 (14)	33 (12)
LTRA (leukotriene receptor antagonist)	2 (2)	1 (1)	8 (9)	11 (4)
SABA Only	54 (60)	51 (55)	53 (58)	158 (58)

Sources: Study 304 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, doses in µg/day

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (≥ 96% of participants were at least 80% adherent) in all arms. Concomitant medication use generally was well-balanced between treatment arms, with one exception. Patients in the treatment arms were slightly more likely than those randomized to placebo to use anti-inflammatory and anti-rheumatic products (22% and 17% of those randomized to BAI 80 and 160 µg/day, respectively, vs. 11% randomized to placebo). Rescue medication use of short acting beta agonists was evaluated as a secondary endpoint and is discussed below.

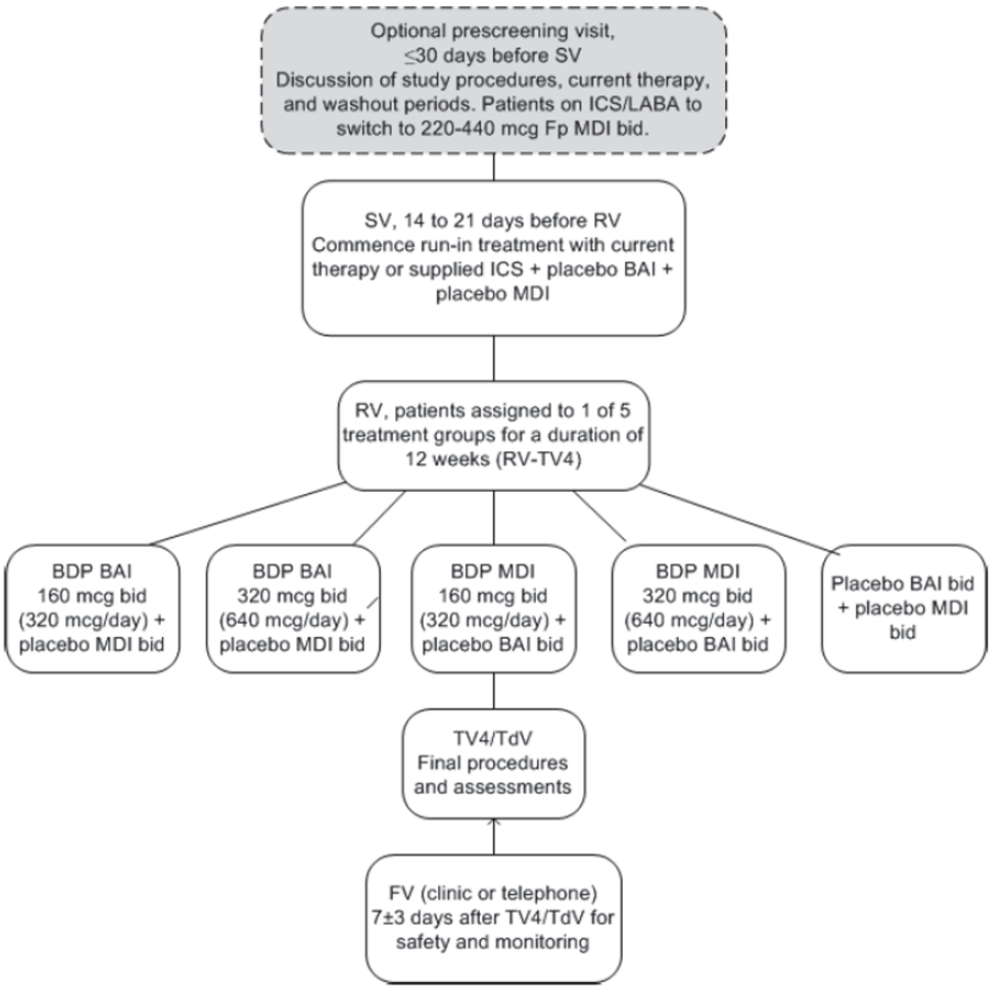
7.2.2. Study 301

Overview and Objective

Study 301 was conducted at 135 centers in the United States, Germany, Hungary, and Poland, from January 2, 2014 to November 20, 2014. The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate (320 or 640 µg/day) administered via BAI and MDI compared with placebo treatment in patients with persistent asthma as assessed by the standardized baseline-adjusted trough morning forced expiratory volume in 1 second (FEV1) area under the effect curve from time 0 to 12 weeks (AUEC(0-12wk)).

Trial Design

Figure 3. Study 301 schema



Source: Study 301 Protocol Figure 1 p. 35
SV=screening visit; ICS=inhaled corticosteroid; LABA=long-acting □₂agonist; Fp=fluticasone propionate; MDI=metered-dose inhaler; RV=randomization visit; BAI=breath-actuated inhaler; BDP=beclomethasone dipropionate; bid=twice daily; TV4=final treatment visit; TdV=treatment discontinuation visit; FV=follow-up visit. Note: Follow-up visit may be in the clinic or by telephone.

This was a Phase 3, 12-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study evaluating the efficacy and safety of beclomethasone dipropionate treatment administered via BAI or MDI at dosages of 320 and 640 µg/day in male and female adolescents and adults 12 years of age and older with persistent asthma. The study consisted of 3 periods:

- placebo run-in period: SV to randomization visit (RV), 14 to 21 days (up to 24 days for patients who required a retest of pulmonary function)
- double-blind treatment period: RV to the final TV (Treatment Visit 1 [TV1] to TV4), 85±3 days (12 weeks)
- follow-up period: TV4 through the follow-up visit/phone call (FV), 7±3 days

Pertinent Inclusion Criteria:

- ≥ 12 years of age
- persistent asthma, with an FEV1 40%-85% of predicted
- 12% reversibility of FEV1 at screening
- stable dose of an ICS of at least 440 µg/day of fluticasone propionate or equivalent, or any ICS/long-acting β2-agonist (LABA) combination, for a minimum of 4 weeks before the prescreening visit
- a diagnosis of asthma as defined by the National Institutes of Health (NIH), present for a minimum of 3 months and stable, defined as no exacerbations and no changes in medication, for at least 30 days

Pertinent Exclusion Criteria:

- history of life-threatening asthma
- known hypersensitivity to any corticosteroid, study drug excipients, or rescue medication
- bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved at least two weeks before screening
- asthma exacerbation requiring oral corticosteroids within one month of screening
- hospitalization for asthma within two months before screening
- initiation or dose escalation of immunotherapy planned during study
- immunosuppressive medications within four weeks of screening

Prohibited medications (washout time before screening)

- anti-IgE therapy such as omalizumab (90 days)
- any other investigational drug (30 days)
- aspirin (1 day)
- beta-adrenergic receptor blocking agents (30 days)
- bisphosphonates oral or iv (30 days)
- intranasal aerosol corticosteroids (discontinue at screening)
- corticosteroids (oral, iv, intra-articular, intramuscular) (30 days)
- decongestants such as pseudoephedrine, phenylpropanolamine, phenylephrine (discontinue 24 hours before study visits and resume use after the visit)
- immunologically active biologic medications such as anti-TNFα, abatacept (90 days)
- immunosuppressive therapy such as methotrexate, gold, azathioprine (30 days)
- immunotherapy initiation within 90 days or change in dose within 30 days

- inhaled anticholinergic medication such as tiotropium bromide (7 days)
- LABA (7 days)
- monoamine oxidase inhibitors (14 days),
- oral ß2-agonists (7 days)
- oral or nasal antihistamines (discontinue 24 hours before study visit and resume use after visit)
- protocol-allowed non-corticosteroid asthma therapy such as leukotriene modifiers, theophylline, chromones, alone or in combination were permitted at screening, but discontinued at randomization for patients on non-corticosteroid asthma therapy only
- protocol-allowed ICS asthma therapy other than study drug was permitted at screening, but discontinued at randomization for patients on non-corticosteroid asthma therapy only
- strong CYP3A4 inhibitors such as azole antifungals, ritonavir, clarithromycin (30 days)
- topical dermatologic corticosteroids of intermediate to high potency such as fluticasone propionate, mometasone furoate (14 days)
- marijuana (30 days)
- inhaled nicotine such as e-cigarettes (1 day)

Investigational Product: beclomethasone dipropionate delivered via breath actuated inhaler totaling 320 µg/day (4 inhalations of 40 µg per inhalation twice daily) or 640 µg/day (4 inhalations of 80 µg per inhalation twice daily).

Placebo: placebo breath actuated inhaler canisters, or placebo metered dose inhaler canisters.

Method of blinding and randomization: Patients were randomly assigned (1:1:1:1:1) within each country via the interactive response technology in a double-blind fashion to receive one of the five treatments over a 12-week period:

- 320 µg/day of beclomethasone dipropionate delivered via BAI
- 640 µg/day of beclomethasone dipropionate delivered via BAI
- 320 µg/day of beclomethasone dipropionate delivered via MDI
- 640 µg/day of beclomethasone dipropionate delivered via MDI
- Placebo (matching each delivery device [BAI and MDI])

Table 15. Study 301 schedule of procedures and assessments

	Screening	Randomization	Double blind treatment visits						Follow Up
Visit No.	**SV**	**RV**	**TV1**	**TV2**	**TV3**	**TV4**			**FV**
Week No.	**-3 to -2**	**0**	**2**	**4**	**8**	**12**			**13**
Complete H&P	✓								
Oropharyngeal exam	✓	✓	✓	✓	✓	✓	✓	✓	
Pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	
Labs	✓							✓	
Adverse event queries	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	
Spirometry	✓	✓	✓	✓	✓	✓	✓	✓	

Source: Adapted from Study 301 Protocol Table 2 Study Procedures and Assessments p. 46
SV = screening visit, RV= randomization visit, TV = treatment visit, FV = follow up visit, H&P = medical history and physical, ECGs = electrocardiograms, CBC w/ diff = complete blood count with differential

Study Endpoints

Primary endpoint: the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV1 AUEC(0-12wk)

Secondary endpoints:

- change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period
- change from baseline in weekly average of daily evening PEF over the 12-week treatment period
- change from baseline in the weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1-12
- change from baseline in the weekly average of the total daily asthma symptom score over weeks 1-12
- time to patient withdrawal due to meeting stopping criteria for worsening asthma during the 12- week treatment period

Exploratory endpoints included change from baseline in:

- albuterol use
- percentage of rescue free days
- daily asthma symptom score
- symptom free days
- asthma control days
- trough morning FEV1 at multiple timepoints
- FEF25-75 at multiple timepoints
- trough morning PEF at multiple timepoints
- AQLQ
- ACT
- comprehension of device instructions for use (in a subset of patients)

Statistical Analysis Plan

Following a Type B meeting with the Food and Drug Administration to address early drop out, the primary efficacy variable was changed. This change was made prior to database lock and is reflected in the final statistical analysis plan. The initial protocol specified that the primary variable was the change from baseline in trough morning FEV1 over the 12 week treatment period, whereas the statistical analysis plan specified that the primary endpoint would be the standardized baseline-adjusted trough morning FEV1 area under the curve from weeks zero to twelve.

The primary variable was analyzed using an analysis of covariance (ANCOVA) model with effects due to baseline trough morning FEV1, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of screening and during the run-in period and treatment. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI dose versus placebo were constructed. The estimated treatment difference between each active treatment group and the placebo group was presented together with the 2-sided 95% confidence interval for the difference and the p-value. The study was to be considered positive if the results from the comparison of the higher beclomethasone dipropionate dose (640 µg/day via BAI) with placebo using the ANCOVA model was positive, regardless of the results from the comparisons of the other beclomethasone dipropionate dose level with placebo.

Protocol Amendments

Amendment 1 was issued April 24, 2014 when 140 patients were enrolled. It specified that patients who experience a clinical asthma exacerbation will be withdrawn from the study, study drug will be stopped, and appropriate treatment (based on the investigator's judgment) should be offered. In addition, it clarified that urgent care/emergency room visits where the treatment is limited to a single dose of nebulized albuterol/salbutamol will not meet the criteria of an asthma exacerbation. The protocol for concomitant medications was changed to allow aqueous formulations of intranasal steroids, but not aerosol formulations, lest they affect efficacy.

7.2.2.1 Study 301 Results

Compliance with Good Clinical Practices

Adequate. See Section 7.1.2 Review Strategy.

Financial Disclosure

Adequate and unlikely to bias study results. See 14.2 Financial Disclosure.

Patient Disposition

A total of 532 subjects were enrolled in Study 301. Forty-nine (9%) subjects stopped medication and discontinued the study prematurely. The most common reason for discontinuation was lack of efficacy, occurring in 26 (5%) subjects. Patient disposition for study 301 is shown in the table below.

Table 16. Study 301 patient disposition

	BAI 320		BAI 640		MDI 320		MDI 640		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total	106	(100)	106	(100)	107	(100)	107	(100)	106	(100)	532	(100)
Randomized Set	106	(100)	106	(100)	107	(100)	107	(100)	106	(100)	532	(100)
Safety Set	106	(100)	106	(100)	107	(100)	107	(100)	106	(100)	532	(100)
Full Analysis Set	104	(98)	106	(100)	106	(99)	107	(100)	106	(100)	529	(99)
Completed Treatment	100	(94)	99	(93)	96	(90)	104	(97)	84	(79)	483	(91)
Reason for discontinuing treatment												
adverse event	0	0	2	(2)	0	0	0	0	0	0	2	(0)
lack of efficacy	3	(3)	2	(2)	5	(5)	1	(1)	14	(13)	25	(5)
lost to follow-up	0	0	0	0	1	(1)	0	0	3	(3)	4	(1)
non-compliance	0	0	1	(1)	1	(1)	0	0	1	(1)	3	(1)
protocol violation	0	0	1	(1)	3	(3)	1	(1)	2	(2)	7	(1)
withdrawal by subject	3	(3)	1	(1)	1	(1)	1	(1)	2	(2)	8	(2)
Completed Study	100	(94)	99	(93)	96	(90)	104	(97)	84	(79)	483	(91)
Reason for discontinuing study												
adverse event	0	0	2	(2)	0	0	0	0	0	0	2	(0)
lack of efficacy	3	(3)	2	(2)	5	(5)	1	(1)	15	(14)	26	(5)
lost to follow-up	0	0	0	0	1	(1)	0	0	3	(3)	4	(1)
non-compliance	0	0	1	(1)	1	(1)	0	0	1	(1)	3	(1)
protocol violation	0	0	1	(1)	3	(3)	1	(1)	1	(1)	6	(1)
withdrawal by subject	3	(3)	1	(1)	1	(1)	1	(1)	2	(2)	8	(2)

Source: 301 ADSL.xpt
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Protocol Violations/Deviations

Nearly one quarter of participants had at least one protocol violation. The most common violations were related to Good Clinical Practice guidelines, such as consent form not signed or study drug not dispensed.

Reviewer comment: The comparatively high proportion of protocol violations may have contributed to the potential for Type II error for this study and the failure to achieve a statistically significant difference between treatment groups for the primary endpoint. At a

minimum, the number of patients with one or more protocol violations and the type of violations were comparable across treatment group such that one need not be concerned about bias away from the null.

Table 17. Study 301 protocol violations

	BAI 320		BAI 640		MDI 320		MDI 640		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients with at least one violation*	23	(22)	27	(25)	18	(17)	28	(26)	24	(23)	120	(23)
excluded concomitant medication	1	(1)	4	(4)	0	0	2	(2)	3	(3)	10	(2)
exclusion criteria	0	0	0	0	1	(1)	0	0	0	0	1	(0)
GCP guidelines	15	(14)	18	(17)	11	(10)	14	(13)	12	(11)	70	(13)
inclusion criteria	2	(2)	3	(3)	3	(3)	5	(5)	2	(2)	15	(3)
non compliance to study medication	2	(2)	2	(2)	2	(2)	5	(5)	4	(4)	15	(3)
primary objective variable	5	(5)	1	(1)	1	(1)	2	(2)	4	(4)	13	(2)
randomization criteria	0	0	2	(2)	1	(1)	0	0	2	(2)	5	(1)

Source: 301 DDDV.xpt
*Patients may have had more than one violation
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses

Table of Demographic Characteristics

Subject demographics generally were balanced among the treatment groups in Study 301. The majority of subjects were female, white and of non-Hispanic or non-Latino ethnicity. The mean age was 46 years, with 26 subjects (5%) less than 18 years old. Subjects were recruited primarily from the US. All participants identifying as black were recruited in the US, and all but one identifying as Hispanic or Latino were recruited in the US.

Table 18. Study 301 demographics

	BAI 320		BAI 640		MDI 320		MDI 640		Placebo		Total	
Total, n (%)	106	(100)	106	(100)	107	(100)	107	(100)	106	(100)	532	(100)
Sex, n (%)												
Female	69	(65)	67	(63)	65	(61)	66	(62)	68	(64)	335	(63)
Male	37	(35)	39	(37)	42	(39)	41	(38)	38	(36)	197	(37)
Age Group, n (%)												
12 to < 18 years	5	(5)	7	(7)	4	(4)	6	(6)	4	(4)	26	(5)
18 to 65 years	90	(85)	94	(89)	96	(90)	94	(88)	95	(90)	469	(88)
> 65 years	11	(10)	5	(5)	7	(7)	7	(7)	7	(7)	37	(7)
Race, n (%)												
American Indian	0	0	1	(1)	0	0	0	0	0	0	1	(0)
Asian	2	(2)	2	(2)	1	(1)	1	(1)	2	(2)	8	(2)
Black	18	(17)	14	(13)	16	(15)	24	(22)	27	(25)	99	(19)
Other	1	(1)	2	(2)	1	(1)	1	(1)	4	(4)	9	(2)
White	85	(80)	87	(82)	89	(83)	81	(76)	73	(69)	415	(78)
Ethnicity, n (%)												
Hispanic or Latino	11	(10)	6	(6)	7	(7)	6	(6)	9	(8)	39	(7)
Not Hispanic or Latino	95	(90)	100	(94)	100	(93)	101	(94)	97	(92)	493	(93)
Country, n (%)												
Germany	11	(10)	9	(8)	10	(9)	9	(8)	7	(7)	46	(9)
Hungary	5	(5)	10	(9)	6	(6)	10	(9)	9	(8)	40	(8)
Poland	8	(8)	8	(8)	4	(4)	5	(5)	6	(6)	31	(6)
USA	82	(77)	79	(75)	87	(81)	83	(78)	84	(79)	415	(78)
Age in years, mean (SD)	48	(16)	46	(15)	47	(15)	46	(15)	44	(15)	46	(15)
Weight in kg, mean (SD)	86	(22)	86	(22)	82	(20)	86	(20)	85	(25)	85	(22)
Height in cm, mean (SD)	169	(9)	168	(9)	167	(9)	169	(11)	168	(9)	168	(10)
BMI in kg/m^2, mean (SD)	30	(7)	30	(7)	29	(6)	30	(6)	30	(9)	30	(7)

Source: 301 ADSL.xpt
SD = standard deviation, BMI = body mass index, BAI = breath actuated inhaler, MDI metered dose inhaler, doses in µg/day

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The majority of patients in all treatment groups had asthma for 15 or more years at enrollment. Baseline disease characteristics such as lung function and asthma duration generally were balanced among the treatment groups in Study 301.

Table 19. Study 301 disease characteristics

	BAI 320	BAI 640	MDI 320	MDI 640	Placebo	Total
Lung function in L, mean (SD)						
forced exp. flow (25% - 75%)	1.28 (0.74)	1.45 (0.66)	1.26 (0.62)	1.34 (0.64)	1.31 (0.56)	1.33 (0.65)
forced exp. volume	2.14 (0.59)	2.25 (0.59)	2.11 (0.55)	2.15 (0.63)	2.13 (0.58)	2.16 (0.59)
forced vital capacity	3.33 (0.91)	3.35 (0.88)	3.29 (0.87)	3.29 (0.97)	3.27 (0.93)	3.31 (0.91)
Asthma duration, n (%)						
< 10 years	16 (15)	29 (27)	24 (22)	15 (14)	18 (17)	102 (19)
10 to 15 years	10 (9)	22 (21)	15 (14)	16 (15)	19 (18)	82 (15)
> 15 years	80 (75)	55 (52)	68 (64)	76 (71)	69 (65)	348 (65)

Sources: Study 301 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Baseline asthma medication use was well-balanced across treatment arms.

Table 20. Study 301 baseline asthma medication use

	BAI 320 (N=106) n (%)	BAI 640 (N=106) n (%)	MDI 320 (N=107) n (%)	MDI 640 (N=107) n (%)	Placebo (N=106) n (%)	All (N=532) n (%)
Anticholinergic/SABA			1 (1)		1 (1)	2 (0)
ICS	42 (40)	46 (43)	42 (39)	33 (31)	44 (42)	207 (39)
ICS/LABA	64 (60)	60 (57)	65 (61)	74 (69)	62 (58)	325 (61)
LABA	1 (1)	3 (3)		2 (2)	2 (2)	8 (2)
LTRA (leukotriene receptor antagonist)	4 (4)	4 (4)	7 (7)	7 (7)	7 (7)	29 (5)
anticholinergic		1 (1)		3 (3)		4 (1)
anticholinergic/LABA		1 (1)	1 (1)	1 (1)		3 (1)
methylxanthines	1 (1)			2 (2)		3 (1)

Sources: Study 301 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (≥ 94% of participants were at least 80% adherent) in all arms. Concomitant medication use generally was well-balanced across treatment arms. Rescue medication use of short acting beta agonists was evaluated as a secondary endpoint and is discussed below.

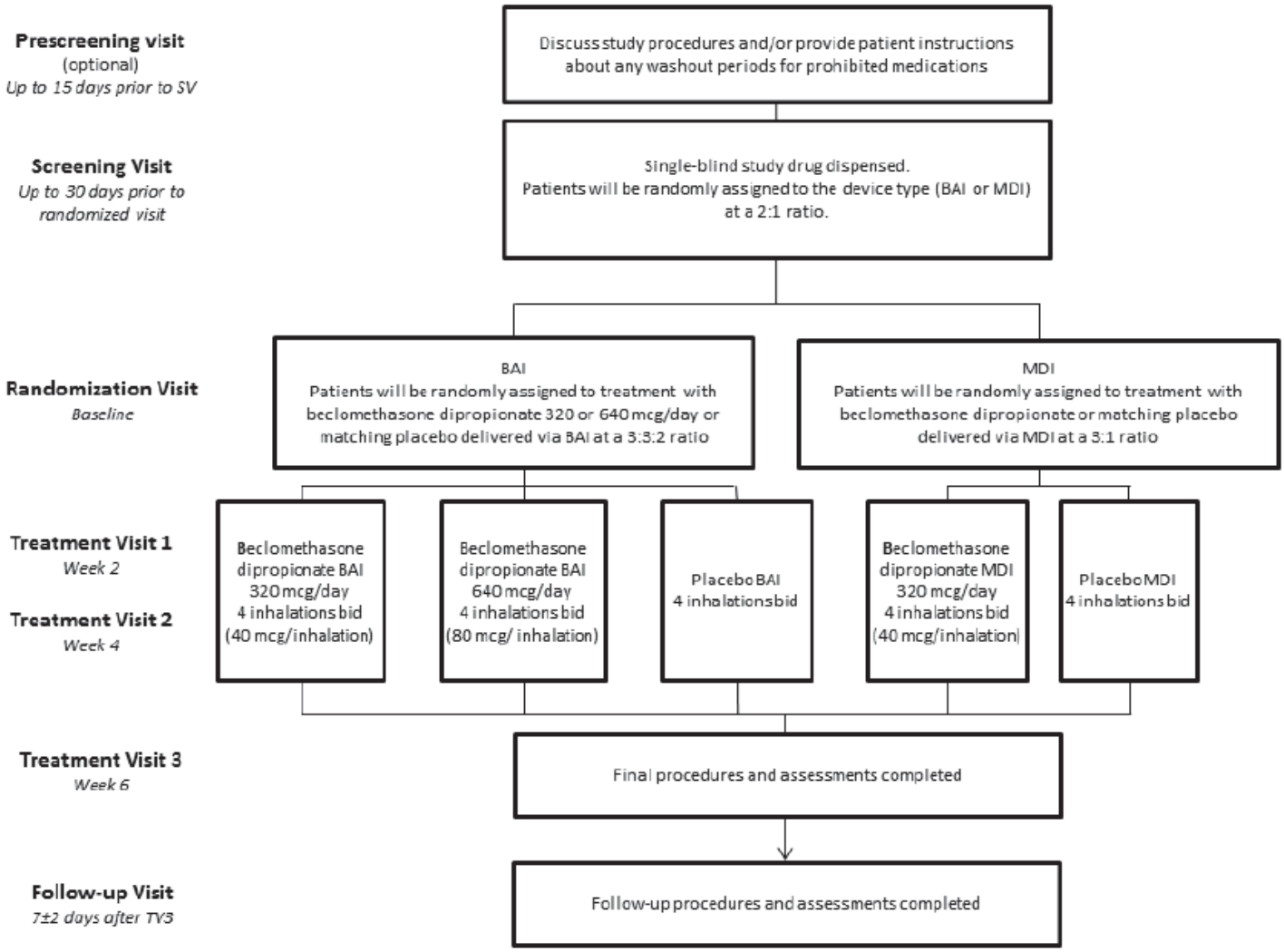
7.2.3. Study 30039

Overview and Objective

The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate administered via BAI at a dose strength of 40 or 80 µg per oral inhalation (320 or 640 µg/day, respectively) compared with placebo treatment in patients with persistent asthma as assessed by the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV1) area under the effect curve from time zero to 6 weeks (AUEC[0-6wk]).

Trial Design

Figure 4. Study 30039 schema



Source: Study 30039 protocol Figure 1 BAI=breath-actuated inhaler; bid=twice daily; MDI=metered-dose inhaler; SV=screening visit; TV3=treatment visit 3.

Pertinent Inclusion Criteria:

- at least 12 years of age
- persistent asthma, with an FEV1 50%-100% of the value predicted for age, height, sex, and race, FEV1 of 40% to 90% at the randomization visit, and an average daily trough morning FEV1 by handheld spirometry of 40 to 85%.
- stable dose of non-corticosteroid therapy, including a short-acting β2-agonist (SABA) alone or in combination with leukotriene modifiers, theophyllines, and/or inhaled cromolyn for a minimum or 30 days or stable dose of ICS therapy with or without a long-acting β2 agonist (LABA) and/or in combination with non-corticosteroid therapy as noted above for a minimum of 30 days
- 15% reversibility, increase from baseline FEV1 after short acting beta agonist at screening

- diagnosis of asthma as defined by the National Institutes of Health, for a minimum of 3 months, with no exacerbations or changes in medication for at least 30 days

Pertinent Exclusion Criteria:

- history of life-threatening asthma
- known hypersensitivity to any corticosteroid, study drug excipients, or rescue medication
- bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved at least two weeks before screening
- asthma exacerbation requiring oral corticosteroids within one month of screening
- hospitalization for asthma within three months before screening

Prohibited medications (washout time before screening)

- anti-IgE therapy such as omalizumab (90 days)
- any other investigational drug (30 days)
- aspirin (1 day)
- inhaled cromolyn (14 days)
- bisphosphonates oral or iv (30 days)
- corticosteroids (oral, iv, intra-articular, intramuscular) (30 days)
- decongestants such as pseudoephedrine, phenylpropanolamine, phenylephrine (discontinue 24 hours before study visits and resume use after the visit)
- immunologically active biologic medications such as anti-TNFα, abatacept (90 days)
- immunosuppressive therapy such as methotrexate, gold, azathioprine (30 days)
- immunotherapy initiation within 90 days or change in dose within 30 days
- inhaled anticholinergic medication such as tiotropium bromide (7 days)
- monoamine oxidase inhibitors (14 days),
- oral ß2-agonists (7 days)
- oral or nasal antihistamines (chronic stable doses allowed)
- strong CYP3A4 inhibitors such as azole antifungals, ritonavir, clarithromycin (30 days)
- topical dermatologic corticosteroids of intermediate to high potency such as fluticasone propionate, mometasone furoate (14 days)
- marijuana (30 days)
- inhaled nicotine such as e-cigarettes (1 day)

Investigational Product: beclomethasone dipropionate, oral inhalation via BAI at the following doses:

- 320 µg/day (four inhalations twice daily, 40 µg/inhalation)
- 640 µg/day (four inhalations twice daily, 80 µg/inhalation)

Placebo: placebo BAI or MDI canisters, four inhalations twice daily

Method of blinding and randomization: patients were randomly allocated via an interactive response technology system to a device type (BAI or MDI), and then randomly assigned to 1 of 3 treatment groups for BAI (study drug at 320 µg/day or 640 µg/day or placebo) or to 1 of 2 treatment groups for MDI (study drug at 320 µg/day or placebo).

Table 21. Study 30039 schedule of procedures and assessments

	Screening	Randomization	Double blind treatment			Follow Up
Visit No.	**SV**	**RV**	**TV1**	**TV2**	**TV3**	**FV**
Week No.	**-3 to -2**	**0**	**2**	**4**	**6**	**7**
Complete H&P	✓					
Oropharyngeal exam	✓	✓	✓	✓	✓	
Urine pregnancy test	✓	✓	✓	✓	✓	
Adverse event queries	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	
Spirometry	✓	✓	✓	✓	✓	

Source: Adapted from Study 30039 Study Report Table 2 Study Procedures and Assessments p. 33
SV = screening visit, RV= randomization visit, TV = treatment visit, FV = follow up visit, H&P = medical history and physical

Study Endpoints

Primary endpoint: the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV1 AUEC (0-6wk)

Secondary endpoints:

- change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 6-week treatment period
- change from baseline in weekly average of daily evening PEF over the 6-week treatment period
- change from baseline in the weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1-6
- change from baseline in the weekly average of the total daily asthma symptom score over weeks 1-6
- time to patient study drug treatment withdrawal due to worsening asthma during the 6-week treatment period

Exploratory endpoints included change from baseline in:

- weekly average of daily evening FEV1 by handheld spirometer
- weekly average of daily evening PEF by handheld spirometer
- albuterol use
- percentage of rescue free days
- daily asthma symptom score
- symptom free days
- asthma control days
- trough morning FEV1 at multiple timepoints
- FEF25-75 at multiple timepoints
- trough morning PEF at multiple timepoints
- AQLQ
- ACT

Statistical Analysis Plan

The primary endpoint was analyzed using an analysis of covariance model with effects due to baseline trough morning FEV1, sex, age, the stratification variable of baseline asthma therapy, and treatment. A fixed-sequence multiple testing procedure was implemented to interpret the results from the primary analysis while controlling the family-wise error rate at 5%. The BAI 640-µg/day dose was tested first. If the comparison to placebo resulted in $p \leq 0.05$, the BAI 320-µg/day dose was then tested. The modified intention to treat analysis set served as the primary population for efficacy analyses. Missing data due to early termination were handled using the modified baseline observation carried forward.

Protocol Amendments

There were no amendments to the protocol for this study.

7.2.3.1 Study 30039 Results

Compliance with Good Clinical Practices

Adequate. See Section 7.1.2 Review Strategy.

Financial Disclosure

Adequate and unlikely to bias study results. See 14.2 Financial Disclosure.

Patient Disposition

A total of 425 subjects were enrolled in Study 30039. Twenty-two (5%) subjects stopped medication and discontinued the study prematurely. The most common reason for discontinuation was lack of efficacy, occurring in 10 (2%) subjects. Patient disposition for study 30039 is shown in the table below.

Table 22. Study 30039 disposition

	BAI 320		BAI 640		BAI Placebo		MDI 320		MDI Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Randomized Set	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Safety Set	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Modified Intent to Treat Set	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Complete treatment	104	(99)	101	(94)	66	(93)	103	(98)	29	(81)	403	(95)
Reason for discontinuing treatment												
adverse event	1	(1)	2	(2)	0	0	0	0	0	0	3	(1)
lack of efficacy	0	0	1	(1)	5	(7)	1	(1)	3	(8)	10	(2)
lost to follow-up	0	0	1	(1)	0	0	0	0	1	(3)	2	(0)
non-compliance	0	0	0	0	0	0	0	0	1	(3)	1	(0)
other	0	0	1	(1)	0	0	0	0	0	0	1	(0)
withdrawal by subject	0	0	2	(2)	0	0	1	(1)	2	(6)	5	(1)
Complete Study	104	(99)	104	(96)	69	(97)	103	(98)	32	(89)	412	(97)
Reason for discontinuing study	104	(99)	104	(96)	69	(97)	103	(98)	32	(89)	412	(97)
lack of efficacy	0	0	0	0	1	(1)	0	0	0	0	1	(0)
lost to follow-up	1	(1)	1	(1)	1	(1)	1	(1)	1	(3)	5	(1)
non-compliance	0	0	0	0	0	0	0	0	1	(3)	1	(0)
other	0	0	1	(1)	0	0	0	0	0	0	1	(0)
withdrawal by subject	0	0	2	(2)	0	0	1	(1)	2	(6)	5	(1)

Source: 30039 ADSL.xpt
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Protocol Violations/Deviations

Eighteen percent of participants had at least one protocol violation. The most common violations were related to receiving an excluded concomitant medication or treatment, failure to meet randomization criteria, and failure to meet exclusion criteria.

Reviewer comment: The type and number of protocol violations were comparable across treatment groups, and unlikely to bias study results.

Table 23. Study 30039 protocol violations

	BAI 320		BAI 640		BAI Placebo		MDI 320		MDI Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients with at least one violation*	5	(5)	2	(2)	5	(7)	3	(3)	3	(8)	18	(4)
excluded concomitant medication	4	(4)	0	0	4	(6)	2	(2)	1	(3)	11	(3)
exclusion criteria	0	0	2	(2)	0	0	0	0	1	(3)	3	(1)
primary objective variable	0	0	0	0	0	0	1	(1)	0	0	1	(0)
randomization criteria	1	(1)	0	0	1	(1)	1	(1)	1	(3)	4	(1)

Source: 30039 DDDV.xpt
*Patients may have had more than one violation
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in Table 24. In Study 30039, subject demographics and baseline characteristics generally were balanced among the treatment groups. The majority of subjects were female, white and of non-Hispanic or non-Latino ethnicity. The mean age was 42 years with 21 (5%) subjects less than 18 years old.

Table 24. Study 30039 demographics

	BAI 320		BAI 640		BAI Placebo		MDI 320		MDI Placebo		Total	
Total, n (%)	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Sex, n (%)												
Female	67	(64)	68	(63)	43	(61)	59	(56)	23	(64)	260	(61)
Male	38	(36)	40	(37)	28	(39)	46	(44)	13	(36)	165	(39)
Age Group, n (%)												
12 to < 18 years	4	(4)	2	(2)	8	(11)	7	(7)	0	0	21	(5)
18 to 65 years	97	(92)	101	(94)	63	(89)	86	(82)	35	(97)	382	(90)
> 65 years	4	(4)	5	(5)	0	0	12	(11)	1	(3)	22	(5)
Race, n (%)												
American Indian	0	0	0	0	1	(1)	0	0	0	0	1	(0)
Asian	0	0	1	(1)	1	(1)	1	(1)	2	(6)	5	(1)
Black	19	(18)	12	(11)	14	(20)	17	(16)	1	(3)	63	(15)
Other	3	(3)	3	(3)	1	(1)	3	(3)	0	0	10	(2)
White	83	(79)	92	(85)	54	(76)	84	(80)	33	(92)	346	(81)
Ethnicity, n (%)												
Hispanic or Latino	12	(11)	18	(17)	11	(15)	17	(16)	7	(19)	65	(15)
Not Hispanic or Latino	93	(89)	90	(83)	60	(85)	88	(84)	29	(81)	360	(85)
Country, n (%)												
USA	105	(100)	108	(100)	71	(100)	105	(100)	36	(100)	425	(100)
Age in years, mean (SD)	43	(14)	42	(14)	38	(13)	43	(16)	42	(14)	42	(15)
Weight in kg, mean (SD)	86	(26)	90	(25)	85	(26)	89	(24)	83	(24)	87	(25)
Height in cm, mean (SD)	168	(9)	169	(9)	168	(11)	169	(9)	167	(9)	168	(9)
BMI in kg/m^2, mean (SD)	30	(8)	31	(8)	30	(9)	31	(8)	30	(8)	31	(8)

Source: 30039 ADSL.xpt
SD = standard deviation, BMI = body mass index
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics such as lung function, asthma duration and baseline asthma medications generally were balanced among the treatment groups, with the exception of long-acting beta agonist use. Fewer patients in the placebo arm were taking long-acting beta agonists, compared to those randomized to one of the three treatment arms (See Table 26).

Reviewer Comment: The imbalance in long-acting beta-agonist use in the treatment arms could bias study results away from the null. However, sensitivity analyses conducted by the Agency's statistical reviewer were reassuring that this was not the case.

Table 25. Study 30039 disease characteristics

	BAI 320		BAI 640		BAI Placebo		MDI 320		MDI Placebo		Total	
Lung function, mean (SD)												
FEF25-75 (L/sec)	1.46	(0.62)	1.49	(0.69)	1.56	(0.71)	1.44	(0.75)	1.40	(0.64)	1.47	(0.69)
FEV1 (ml)	2251	(592)	2289	(650)	2311	(600)	2188	(642)	2154	(626)	2247	(623)
Forced vital capacity (L)	3.38	(0.88)	3.46	(1.07)	3.41	(0.89)	3.32	(0.95)	3.30	(1.04)	3.39	(0.96)
peak flow rate (ml/sec)	359.49	(85.73)	373.69	(93.70)	371.91	(101.08)	356.70	(93.20)	351.42	(98.01)	363.80	(93.25)
Asthma duration, n (%)												
< 10 years	13	(12)	20	(19)	9	(13)	13	(12)	2	(6)	57	(13)
10 to 15 years	8	(8)	7	(6)	10	(14)	12	(11)	2	(6)	39	(9)
> 15 years	84	(80)	81	(75)	52	(73)	80	(76)	32	(89)	329	(77)

Sources: Study 30039 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Table 26. Study 30039 baseline asthma medication use

	BAI 320 (N=108) n (%)	BAI 640 (N=105) n (%)	MDI 320 (N=105) n (%)	Placebo (N=107) n (%)	All (N=425) n (%)
ICS	20 (19)	14 (13)	18 (17)	26 (24)	78 (18)
ICS/LABA	45 (42)	48 (46)	45 (43)	39 (36)	177 (42)
LTRA (leukotriene receptor antagonist)	13 (12)	6 (6)	9 (9)	10 (9)	38 (9)
SABA Only	41 (38)	39 (37)	37 (35)	40 (37)	157 (37)

Sources: Study 30039 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (≥ 98% of participants were at least 80% adherent) in all arms. Concomitant medication use generally was well-balanced across treatment arms. Rescue medication use of short acting beta agonists was evaluated as a secondary endpoint and is discussed below.

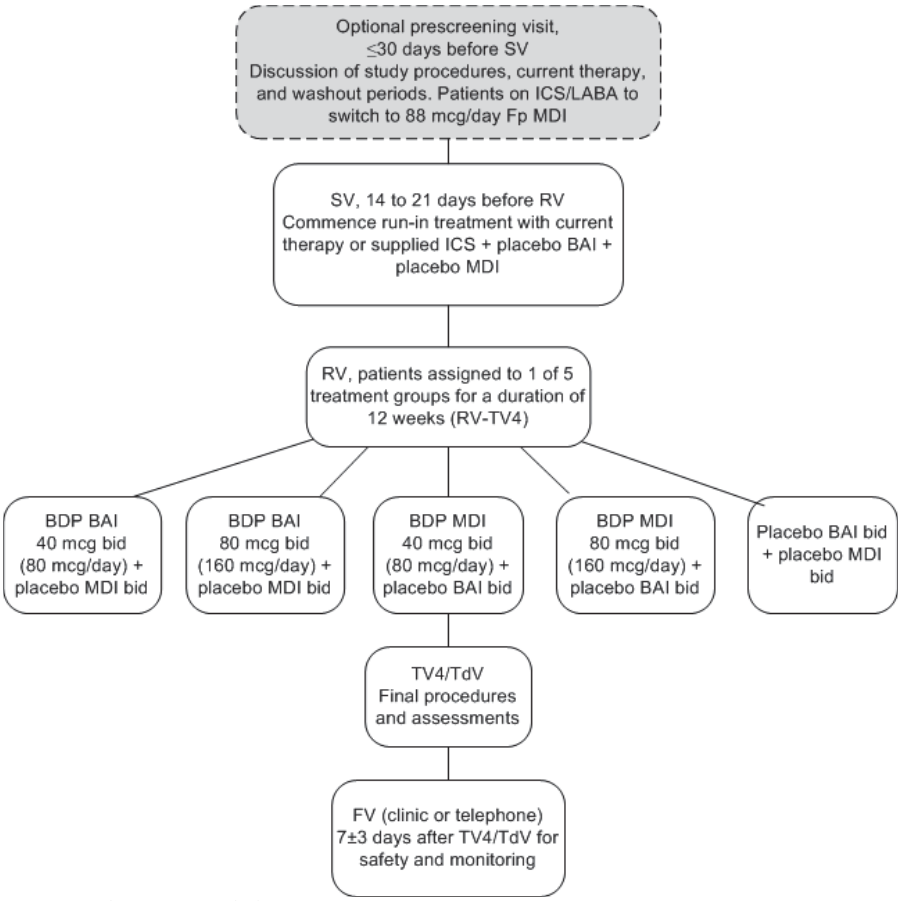
7.2.4. Study 302

Overview and Objective

The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate administered via BAI and MDI (80 or 160 µg/day) compared with placebo treatment in pediatric patients 4 through 11 years of age with persistent asthma as assessed by the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) percent predicted FEV1 area under the effect curve from time 0 to 12 weeks (FEV1 AUEC[0-12wk]).

Trial Design

Figure 5. Study 302 schema



Source: Study 302 Protocol Figure 1 p. 37
SV=screening visit; ICS= inhaled corticosteroid; LABA=long-acting B2-agonist; Fp=fluticasone propionate; MDI=metered-dose inhaler; RV=randomization visit; BAI=breath-actuated inhaler; BDP=beclomethasone dipropionate; bid=twice daily; TV4=final treatment visit; TdV=treatment discontinuation visit; FV=follow-up visit. Note: Follow-up visit may be in the clinic or by telephone.

Pertinent Inclusion Criteria:

- 4 to 11 years of age
- persistent asthma, FEV1 40%-90 predicted
- stable daily dosage of ICS in the range of 88 to 176 µg/day of fluticasone propionate (or equivalent) for a minimum of 4 weeks before screening; a stable daily dosage of non-corticosteroid therapy; a daily dose of ICS plus a long-acting β2-agonist could have been allowed but the patient was required to discontinue this therapy and start fluticasone propionate MDI for at least 7 days to no more than 30 days before screening.
- 12% reversibility, increase from baseline FEV1 after short acting beta agonist at screening, or a documented historical 12% reversibility within the prior year for patients treated with ICS at baseline

Pertinent Exclusion Criteria:

- history of life-threatening asthma
- known hypersensitivity to any corticosteroid, study drug excipients, or rescue medication
- bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved at least two weeks before screening
- asthma exacerbation requiring oral corticosteroids within one month of screening
- hospitalization for asthma within two months before screening

Prohibited medications (washout time before screening)

- anti-IgE therapy such as omalizumab (90 days)
- any other investigational drug (30 days)
- aspirin (1 day)
- beta adrenergic blocking agents (30 days)
- bisphosphonates oral or iv (30 days)
- intranasal corticosteroids (discontinue at screening)
- corticosteroids (oral, iv, intra-articular, intramuscular) (30 days)
- decongestants such as pseudoephedrine, phenylpropanolamine, phenylephrine (discontinue 24 hours before study visits and resume use after the visit)
- immunologically active biologic medications such as anti-TNFα, abatacept (90 days)
- immunosuppressive therapy such as methotrexate, gold, azathioprine (30 days)
- immunotherapy initiation within 90 days or change in dose within 30 days
- inhaled anticholinergic medication such as tiotropium bromide (7 days)
- inhaled long-acting beta agonist (7 days)
- monoamine oxidase inhibitors (14 days)
- oral ß2-agonists (7 days)
- oral or nasal antihistamines (discontinue 24 hours before screening, resume after completion of study visits)
- Protocol-allowed non-corticosteroid asthma therapy (including leukotriene modifiers, theophylline, chromones, alone or in combination) Permitted at screening, but discontinue at randomization per protocol for patients on non-corticosteroid asthma therapy only. Prohibited for other patients throughout the study.
- Protocol-allowed ICS asthma therapy (other than study drug) permitted at screening, but discontinue at randomization per protocol for patients on ICS asthma therapy only. Prohibited for other patients throughout the study.

- strong CYP3A4 inhibitors such as azole antifungals, ritonavir, clarithromycin (30 days)
- topical dermatologic corticosteroids of intermediate to high potency such as fluticasone propionate, mometasone furoate (14 days)
- marijuana (30 days)
- inhaled nicotine such as e-cigarettes (1 day)

Investigational Product: beclomethasone dipropionate: 40 µg of beclomethasone dipropionate per inhalation delivered via BAI totaling 80 µg/day (1 inhalation twice daily) or 80 µg of beclomethasone dipropionate per inhalation delivered via BAI totaling 160 µg/day (1 inhalation twice daily).

Placebo: Placebo BAI or MDI canisters

Reference Therapy: beclomethasone dipropionate: 40 µg of beclomethasone dipropionate per inhalation delivered via MDI totaling 80 µg/day (1 inhalation twice daily) or 80 µg of beclomethasone dipropionate per inhalation delivered via MDI totaling 160 µg/day (1 inhalation twice daily).

Method of Blinding: Patients were randomly stratified via the interactive response technology system based on their current asthma therapy (ICS or non-corticosteroid) at screening and during the run-in period. Patients were randomly assigned (1:1:1:1:1) within each country via the interactive response technology in a double-blind fashion to receive 1 of the 5 treatments over a 12-week period:

- 80 µg/day of beclomethasone dipropionate delivered via BAI
- 160 µg/day of beclomethasone dipropionate delivered via BAI
- 80 µg/day of beclomethasone dipropionate delivered via MDI
- 160 µg/day of beclomethasone dipropionate delivered via MDI
- Placebo (matching each delivery device [BAI and MDI])

Table 27. Study 302 schedule of procedures and assessments

	Screening	Randomization	Double blind treatment				Follow Up
Visit No.	SV	RV	TV1	TV2	TV3	TV	FV
Week No.	-3 to -2	0	2	4	8	12	13
Complete H&P	✓						
Oropharyngeal exam	✓	✓	✓	✓	✓	✓	
Urine pregnancy test	✓	✓	✓	✓	✓	✓	
Adverse event queries	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	
Spirometry	✓	✓	✓	✓	✓	✓	

Source: Adapted from Study 302 Study Report Table 3 Study Procedures and Assessments p. 37
SV = screening visit, RV= randomization visit, TV = treatment visit, FV = follow up visit, H&P = medical history and physical

Study Endpoints

Primary endpoint: the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) % predicted FEV1 AUEC (0-12wk)

Secondary endpoints:

- change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period
- change from baseline in weekly average of daily evening PEF over the 12-week treatment period
- change from baseline in the weekly average of the total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1-12
- change from baseline in the weekly average of the total daily asthma symptom score over weeks 1-12
- time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period

Exploratory endpoints included change from baseline in:

- albuterol use
- percentage of rescue free days
- daily asthma symptom score
- symptom free days
- asthma control days
- trough morning FEV1 at multiple timepoints
- FEF25-75 at multiple timepoints
- trough morning PEF at multiple timepoints
- BAI device instructions for use (IFU) comprehension evaluations (subset of patients)
- BAI device use demonstration (subset of patients)

Statistical Analysis Plan

The primary variable was analyzed using an analysis of covariance model with effects due to baseline trough morning percent predicted FEV1, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at screening, during run-in, and during treatment. The study was to be considered positive if the result from the comparison of the higher beclomethasone dipropionate dose (160 mcg/day via BAI) with placebo using the primary ANCOVA model was statistically significant in favor of beclomethasone dipropionate BAI, regardless of the results from the comparisons of all the other beclomethasone dipropionate dose-by-device levels with placebo. Missing data due to early termination was handled using the modified baseline observation carried forward analysis. Patients who discontinued study medication prior to week 12 were assigned a score of zero for change from baseline in trough morning percent predicted FEV1 . Discontinued patients who had a negative change from baseline at the last available time point in percent predicted FEV1 did not have their results adjusted and the last available observation was used since their scores were already poor (and more extreme than an assignment to zero). No adjustments were made to the results for patients who completed the study.

Protocol Amendments

The protocol was amended twice. Amendment 1, dated 21 May 2014, removed some prohibited medications and clarified study procedures regarding training for spirometry and allowed nebulized medications. Amendment 2, dated 18 December 2014, changed the primary efficacy variable, lowered the minimum age for eligibility to participate in the study, added the option to rescreen patients who failed to qualify for the study based on spirometry criteria, and permitted younger patients who were unable to perform spirometry to participate in the study on the basis of PEF criteria in place of spirometry criteria.

7.2.4.1 Study 302 Results

Compliance with Good Clinical Practices

Adequate. See Section 7.1.2 Review Strategy.

Financial Disclosure

Adequate and unlikely to bias study results. See 14.2 Financial Disclosure.

Patient Disposition

A total of 628 subjects were enrolled in Study 302. Sixty-six (11%) subjects stopped medication and discontinued the study prematurely. The most common reason for discontinuation was lack of efficacy, occurring in 24 (4%) subjects. Patient disposition for Study 302 is shown in the table below.

Table 28. Study 302 disposition

	BAI 160		BAI 80		MDI 160		MDI 80		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total	125	(100)	126	(100)	125	(100)	125	(100)	127	(100)	628	(100)
Randomized Set	125	(100)	126	(100)	125	(100)	125	(100)	127	(100)	628	(100)
Safety Set	125	(100)	126	(100)	125	(100)	125	(100)	127	(100)	628	(100)
Full Analysis Set	122	(98)	124	(98)	123	(98)	121	(97)	124	(98)	614	(98)
Complete treatment	113	(90)	116	(92)	112	(90)	112	(90)	109	(86)	562	(89)
Reason for discontinuing treatment												
adverse event	1	(1)	1	(1)	2	(2)	0	0	1	(1)	5	(1)
lack of efficacy	4	(3)	3	(2)	5	(4)	6	(5)	6	(5)	24	(4)
lost to follow-up	3	(2)	1	(1)	4	(3)	1	(1)	4	(3)	13	(2)
non-compliance	0	0	1	(1)	0	0	0	0	0	0	1	(0)
other	0	0	0	0	0	0	0	0	1	(1)	1	(0)
protocol violation	2	(2)	1	(1)	0	0	3	(2)	2	(2)	8	(1)
withdrawal by subject	2	(2)	3	(2)	2	(2)	3	(2)	4	(3)	14	(2)
Complete Study	113	(90)	116	(92)	111	(89)	112	(90)	109	(86)	561	(89)
Reason for discontinuing study												
adverse event	1	(1)	1	(1)	2	(2)	0	0	1	(1)	5	(1)
lack of efficacy	4	(3)	3	(2)	5	(4)	6	(5)	6	(5)	24	(4)
lost to follow-up	3	(2)	1	(1)	5	(4)	2	(2)	4	(3)	15	(2)
non-compliance	0	0	1	(1)	0	0	0	0	0	0	1	(0)
other	0	0	0	0	0	0	0	0	1	(1)	1	(0)
protocol violation	2	(2)	1	(1)	0	0	2	(2)	2	(2)	7	(1)
withdrawal by subject	2	(2)	3	(2)	2	(2)	3	(2)	4	(3)	14	(2)

Source: 302 ADSL.xpt
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Protocol Violations/Deviations

Fifteen percent of participants had at least one protocol violation. The most common violations were related to good clinical practice guidelines, receiving an excluded medication or treatment, failure to meet inclusion criteria, failure to meet randomization criteria, and non-compliance to study medication.

Reviewer comment: The type and number of protocol violations were comparable across treatment groups, and unlikely to bias study results.

Table 29. Study 302 protocol violations

	BAI 160		BAI 80		MDI 160		MDI 80		Placebo		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients with at least one violation*	27	(22)	13	(10)	17	(14)	19	(15)	19	(15)	95	(15)
excluded concomitant medication	6	(5)	3	(2)	4	(3)	4	(3)	5	(4)	22	(3)
exclusion criteria	2	(2)	1	(1)	0	0	0	0	2	(1)	5	(1)
GCP guidelines	11	(8)	4	(3)	7	(5)	2	(2)	12	(9)	36	(5)
inclusion criteria	4	(3)	4	(3)	5	(4)	2	(2)	4	(3)	19	(3)
non-compliance	2	(2)	2	(2)	1	(1)	7	(6)	1	(1)	13	(2)
primary objective variable	1	(1)	0	0	4	(3)	2	(2)	2	(1)	9	(1)
randomization criteria	6	(5)	2	(2)	3	(2)	4	(3)	3	(2)	18	(3)

Source: 302 DDDV.xpt
*Patients may have had more than one violation
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day, GCP = good clinical practice

Table of Demographic Characteristics

Selected demographic features for all randomized patients are shown in Table 302. In Study 302, subject demographics and baseline characteristics generally were balanced among the treatment groups. The majority of subjects were male, white and of non-Hispanic or non-Latino ethnicity. The mean age was 8 years.

Table 30. Study 302 demographics

	BAI 160		BAI 80		MDI 160		MDI 80		Placebo		Total	
Total, n (%)	125	(100)	126	(100)	125	(100)	125	(100)	127	(100)	628	(100)
Sex, n (%)												
Female	46	(37)	52	(41)	50	(40)	49	(39)	41	(32)	238	(38)
Male	79	(63)	74	(59)	75	(60)	76	(61)	86	(68)	390	(62)
Age Group, n (%)												
4 to 5 years	10	(8)	16	(13)	13	(10)	11	(9)	18	(14)	68	(11)
6 to 8 years	47	(38)	41	(33)	48	(38)	54	(43)	45	(35)	235	(37)
9 to 11 year	68	(54)	69	(55)	64	(51)	60	(48)	64	(50)	325	(52)
Race, n (%)												
American Indian	4	(3)	4	(3)	1	(1)	3	(2)	3	(2)	15	(2)
Asian	2	(2)	2	(2)	0	0	0	0	0	0	4	(1)
Black	33	(26)	34	(27)	49	(39)	37	(30)	42	(33)	195	(31)
Other	17	(14)	17	(13)	12	(10)	9	(7)	11	(9)	66	(11)
White	69	(55)	69	(55)	63	(50)	76	(61)	71	(56)	348	(55)
Ethnicity, n (%)												
Hispanic or Latino	33	(26)	37	(29)	22	(18)	25	(20)	27	(21)	144	(23)
Not Hispanic or Latino	92	(74)	89	(71)	103	(82)	100	(80)	100	(79)	484	(77)
Country, n (%)												
Croatia	1	(1)	1	(1)	3	(2)	2	(2)	0	0	7	(1)
Mexico	17	(14)	20	(16)	9	(7)	9	(7)	12	(9)	67	(11)
Poland	13	(10)	15	(12)	11	(9)	13	(10)	13	(10)	65	(10)
Ukraine	3	(2)	7	(6)	4	(3)	3	(2)	6	(5)	23	(4)
USA	91	(73)	83	(66)	98	(78)	98	(78)	96	(76)	466	(74)
Age in years, mean (SD)	8	(2)	8	(2)	8	(2)	8	(2)	8	(2)	8	(2)
Weight in kg, mean (SD)	35	(13)	35	(12)	35	(12)	34	(12)	34	(12)	35	(12)
Height in cm, mean (SD)	136	(12)	136	(14)	135	(13)	136	(12)	134	(13)	135	(13)
BMI in kg/m^2, mean (SD)	19	(4)	18	(4)	19	(4)	18	(4)	19	(4)	19	(4)

Source: 302 ADSL.xpt
SD = standard deviation, BMI = body mass index
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics such as lung function, asthma duration and baseline asthma medications generally were balanced among the treatment groups.

Table 31. Study 302 disease characteristics

	BAI 160		BAI 80		MDI 160		MDI 80		Placebo		Total	
Lung function in L, mean (SD)												
FEF 25-75	1.27	(0.51)	1.37	(0.59)	1.29	(0.47)	1.30	(0.54)	1.22	(0.51)	1.29	(0.53)
FEV1	1.48	(0.40)	1.52	(0.41)	1.48	(0.37)	1.47	(0.35)	1.48	(0.42)	1.49	(0.39)
FVC	1.94	(0.53)	1.95	(0.52)	1.92	(0.48)	1.91	(0.48)	1.99	(0.57)	1.94	(0.51)
percent predicted FEV1	72.86	(10.76)	72.42	(11.58)	72.96	(10.34)	71.98	(11.10)	73.67	(10.24)	72.78	(10.79)
Asthma duration, n (%)												
< 1 year	11	(9)	9	(7)	5	(4)	8	(6)	6	(5)	39	(6)
1 to < 5 years	42	(34)	51	(40)	47	(38)	60	(48)	62	(49)	262	(42)
> 5 years	72	(58)	66	(52)	73	(58)	57	(46)	59	(46)	327	(52)

Sources: Study 302 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/day

Table 32. Study 302 baseline asthma medication use

	BAI 80 (N=126) n (%)	BAI 160 (N=125) n (%)	MDI 80 (N=125) n (%)	MDI 160 (N=125) n (%)	Placebo (N=127) n (%)	All (N=628) n (%)
Anticholinergic/SABA				1 (1)		1 (0)
ICS	79 (63)	84 (67)	73 (58)	81 (65)	81 (64)	398 (63)
ICS/LABA	11 (9)	8 (6)	15 (12)	12 (10)	7 (6)	53 (8)
LABA		1 (1)			2 (2)	3 (0)
LTRA (leukotriene receptor antagonist)	21 (17)	22 (18)	31 (25)	28 (22)	21 (17)	123 (20)
SABA Only	29 (23)	22 (18)	23 (18)	26 (21)	30 (24)	130 (21)
Systemic corticosteroid		1 (1)		1 (1)	1 (1)	3 (0)

Sources: Study 302 ADSPI.XPT, ADSL.XPT
BAI = breath actuated inhaler, MDI = metered dose inhaler, doses in µg/d

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was excellent (≥ 94% of participants were at least 80% adherent) in all arms. Concomitant medication use generally was well-balanced across treatment arms. Rescue medication use of short acting beta agonists was evaluated as a secondary endpoint and is discussed below.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy and Section 8.2 Review of Relevant Individual Trials Used to Support Efficacy.

Secondary and Other Endpoints

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy and Section 8.2 Review of Relevant Individual Trials Used to Support Efficacy.

Subpopulations

Section 8.2 Review of Relevant Individual Trials Used to Support Efficacy.

7.3.2. Integrated Assessment of Effectiveness

Efficacy for the individual trials is presented in tabular format in Section 8.2 Review of Relevant Individual Trials Used to Support Efficacy. The following is clinical summary of the results, placing the statistical analyses and recommendations into clinical context.

The submitted clinical program is adequate to support efficacy of QVAR RediHaler at a range of daily doses (divided BID) from 80 mcg to 640 mcg in patients 12 years of age and older, and from 80 to 160 mcg daily in patients 4 to 11 years of age.

Study 304 was a randomized, double-blind, parallel-group, placebo-controlled, 12-week, efficacy and safety trial compared QVAR RediHaler 40 and 80 mcg given as 1 inhalation twice daily with placebo in 270 adult and adolescent patients with persistent symptomatic asthma despite low-dose inhaled corticosteroid or non-corticosteroid asthma therapy. The primary endpoint for this trial was the standardized baseline-adjusted trough morning forced expiratory volume in 1 second (FEV_1) area under the effect curve from time zero to 12 weeks [FEV_1 AUEC(0-12wk)]. Patients in both treatment groups had significantly greater improvements in trough FEV_1 compared to placebo (QVAR RediHaler 80 mcg/day, LS mean change of 0.124 L and QVAR RediHaler 160 mcg/day, LS mean change of 0.116 L over 12 weeks). Both doses of QVAR RediHaler were effective in improving asthma control with significantly greater improvements in FEV_1 and morning PEF when compared to placebo. Reduction in asthma symptoms was also supportive of the efficacy of QVAR RediHaler.

Study 30039 was a randomized, double-blind, parallel-group, placebo-controlled, 6-week, efficacy and safety trial compared QVAR RediHaler 40 and 80 mcg given as 4 inhalations twice daily and placebo in 425 adult and adolescent patients with persistent symptomatic asthma despite treatment with non-corticosteroid, inhaled corticosteroids (with or without a long acting

beta agonist [LABA]), or combination asthma therapy. The study also included a reference treatment group, QVAR Inhalation Aerosol (QVAR MDI) 40 mcg, 4 inhalations twice daily. Patients in both treatment groups had significantly greater improvements in trough FEV1 AUC(0-6wk) compared to placebo (QVAR RediHaler 320 mcg/day, LS mean change of 0.144 L and QVAR RediHaler 640 mcg/day, LS mean change of 0.150 L over 12 weeks). In this study, both doses of QVAR RediHaler were effective in improving asthma control with significantly greater improvements in FEV_1, morning PEF, weekly average of daily trough morning FEV_1, reduced rescue medication use and improved asthma symptom scores than with placebo.

Study 302 was a randomized, double-blind, parallel-group, placebo controlled, 12-week, global efficacy and safety trial compared QVAR RediHaler 40 or 80 mcg, QVAR MDI 40 or 80 mcg or placebo given as 1 inhalation twice daily in pediatric patients aged 4 through 11 years old with persistent symptomatic asthma despite treatment with non-corticosteroid or low dose inhaled corticosteroid (with or without a long acting beta agonist [LABA]). 568 pediatric patients with symptomatic asthma of which 410 had previously been treated with low dose inhaled corticosteroids with or without a LABA were randomized to receive either 40 mcg or 80 mcg twice daily of QVAR RediHaler, QVAR MDI or placebo. The primary endpoint was the change from baseline in trough percent predicted FEV1 AUEC (0-12 weeks). While the primary endpoint, was not statistically significant, change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12 week treatment period was 11.3 [95% CI: 5.58, 17.06] and 8.5 [95% CI: 2.71, 14.24] for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, at nominal significance. Similar results were seen with evening PEF. Given that the efficacy of ICS in general, and beclomethasone dipropionate specifically, have been evaluated in numerous studies, and the PEF is another objective measure of lung function in the pediatric population, despite the failure in the primary endpoint, there is clinical justification for approving QVAR RediHaler in the pediatric age group 4 to 11 years of age.

The efficacy of QVAR RediHaler at the proposed doses is supported. The clinical review team recommends **Approval** of this application.

7.4. Review of Safety

The safety assessment of QVAR RediHaler is based on studies shown in Table 8. The safety database was adequate. The Applicant conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events, common adverse events, and assessment of adverse events of interest, including oropharyngeal exams and asthma exacerbations. There were no deaths in the clinical program. Serious adverse events were reported in eight subjects across treatment groups. The most frequent serious adverse event was asthma exacerbation. The serious adverse events generally were balanced across treatment groups and do not raise any specific concerns. The most common adverse events were oral candidiasis, upper respiratory infection, headache, and nasopharyngitis. There were no clinically meaningful changes in laboratory parameters or vital signs.

In the clinical studies submitted with this application no new safety signals were seen. Serious adverse events[1] and withdrawals due to adverse events were rare and were typical of events seen in similar asthma development programs. Common adverse events were also typical of such a program. Laboratory parameters, ECGs, and other assessment of safety variables also did not raise any safety concerns. The overall safety findings were consistent with the profiles typical of ICS drug products.

7.4.1. Review of the Safety Database

Overall Exposure

Overall, 607 patients were exposed to at least one dose of QVAR RediHaler via BAI in the phase 3 safety population that included participants from Studies 301, 304 and 30039. The mean duration of exposure was 66 days. Exposure averaged 63 days in the placebo group, and 67 days each in the combined BAI and MDI groups. The distribution of the total numbers of patients exposed to study treatment by category of duration was bimodal because Study 30039 was a 6-week study and Studies 301 and 304 were 12-week studies. The duration category with the greatest number of patients exposed was >8 to ≤12 weeks (552 [45%] patients) followed by >4 to ≤6 weeks (340 [28%] patients). Overall compliance with study drug was high (96%) and similar across the treatment groups.

Relevant characteristics of the safety population:

The safety population was comprised of the patients in the studies presented in Table 8.

See Table 12, Table 18, Table 24,and Table 30 for the patient demographics of the safety database. The safety of QVAR RediHaler was evaluated in 3 clinical trials in patients 12 years of age and older (Studies 301, 304, and 30039). In these 3 studies, 607 patients were treated with QVAR RediHaler 80 mcg, 160 mcg, 320 mcg, or 640 mcg, versus 304 patients in the placebo group. There was also an active control group treated with QVAR MDI (n=319). In Study 302, the safety database included total of 628 patients 4 to 11 years of age randomized to QVAR RediHaler 80 mcg (n=126), QVAR RediHaler 160 mcg (n = 125), QVAR MDI 80 mcg (n = 125), QVAR MDI 160 mcg (n = 125), or placebo (n=127).

[1] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Adequacy of the safety database:

The safety database was adequate to review the safety of QVAR, a well-known, and well characterized ICS, delivered via a novel breath-actuated inhaler.

7.4.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Adequate. See 7.1.2 Review Strategy.

Categorization of Adverse Events

Adverse events were recorded from the time the clinical study patient/subject provided written informed consent/assent and through the end of the follow-up period. Events that occurred during the run-in period before randomization were considered non–treatment-emergent adverse events, and those that occurred after randomization were considered treatment-emergent adverse events. The version of the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 was used for each study and for the pooled analyses. An adverse event was defined as any untoward medical occurrence in a patient/subject administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment. Serious adverse events were defined according to the standard regulatory definition.

Routine Clinical Tests

The standard battery of routine clinical tests, including physical exam, vital signs, and clinical laboratory testing (in study 301) were conducted as part of this development program.

7.4.3. Safety Results

Deaths

There were no deaths in the clinical development program.

Serious Adverse Events

In studies 301, 304, and 30039, serious adverse events were reported in eight subjects across treatment groups. The most frequent serious adverse event was asthma exacerbation (n=2). The serious adverse events do not raise any specific concerns, and all patients recovered. Of the eight patients who had serious adverse events, four were in the BAI 640 group, and four in other arms of the study. In the placebo group, a 56 year old woman had pneumonia and asthma. In the MDI 320 group, a 42 year old woman had acute pancreatitis, cholelithiasis and abdominal pain. In the BAI 320 group, a 47 year old man had gastroenteritis, hypokalemia and renal failure. In the MDI 640 group, a 38 year old woman had pharyngeal abscess. Four patients in the BAI 640 group had serious adverse events: including a 37 year old woman with asthma, a 57 year old woman with

diverticular perforation, a 41 year old woman with positional vertigo, and a 58 year old woman who attempted suicide with alprazolam overdose.

In Study 302 (4 to 11 years old), one patient experienced an SAE of an asthma exacerbation during the placebo run-in period before receiving randomized study drug. No other SAEs were reported during study 302.

Dropouts and/or Discontinuations Due to Adverse Effects

In studies 301, 304 and 30039, adverse events leading to discontinuation generally were well-balanced between the treatment and placebo arms. One patient in the placebo arm had drug withdrawn due to pneumonia and an asthma exacerbation. Two patients in the BAI 320 arm had drug withdrawn, one for upper respiratory tract infection and another for gastroesophageal reflux. Three patients in the BAI 640 arm had drug withdrawn, one for upper respiratory tract infection, another for asthma exacerbation, and the third for tremor.

In study 302, two patients who received beclomethasone dipropionate BAI were discontinued from the study due to an adverse event: one in the BAI 80-µg group (allergic rhinitis) and one in the BAI 160-µg group (cough).

Treatment Emergent Adverse Events and Adverse Reactions

Common adverse events were typical of an ICS development program and are listed in the two tables below.

Table 33. Adverse Reactions Experienced by at Least 3% of Adult and Adolescent Patients in the QVAR REDIHALER or QVAR MDI Groups and Greater Than Placebo

Preferred Term	Number (%) of patients						
	QVAR REDIHALER				QVAR MDI		Placebo
	80 mcg N=90	160 mcg N=92	320 mcg N=214	640 mcg N=211	320 mcg N=212	640 mcg N=107	N=304
Oral Candidiasis	0	2 (2)	7 (3)	15 (7)	6 (3)	9 (8)	1 (<1)
Upper Respiratory Tract Infection	3 (3)	3 (3)	9 (4)	6 (3)	17 (8)	4 (4)	6 (2)
Nasopharyngitis	4 (4)	2 (2)	3 (1)	3 (1)	6 (3)	4 (4)	4 (1)
Oropharyngeal Pain	2 (2)	2 (2)	1 (<1)	3 (1)	6 (3)	4 (4)	2 (<1)
Viral Upper Respiratory Tract Infection	3 (3)	0	1 (<1)	3 (1)	4 (2)	2 (<1)	4 (1)
Sinusitis	3 (3)	0	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)
Rhinitis Allergic	0	3 (3)	0	2 (<1)	0	1 (<1)	0

Source: QVAR RediHaler package insert

Table 34. Adverse Reactions Experienced by at Least 3% of Patients 4 to 11 Years of Age in the QVAR REDIHALER or QVAR MDI Groups and Greater Than Placebo

Preferred Term	Number (%) of patients				
	QVAR REDIHALER		QVAR MDI		Placebo
	80 mcg N=126	160 mcg N=125	80 mcg N=125	160 mcg N=125	N=127
Upper Respiratory Tract Infection	3 (2.4)	1 (0.8)	6 (4.8)	5 (4.0)	5 (3.9)
Nasopharyngitis	5 (4.0)	11 (8.8)	6 (4.8)	6 (4.8)	4 (3.1)
Viral Upper Respiratory Tract Infection	5 (4.0)	5 (4.0)	3 (2.4)	1 (0.8)	4 (3.1)
Pharyngitis	4 (3.2)	4 (3.2)	4 (3.2)	4 (3.2)	2 (1.6)
Cough	1 (0.8)	3 (2.4)	9 (7.2)	6 (4.8)	4 (3.1)
Vomiting	2 (1.6)	2 (1.6)	4 (3.2)	0	2 (1.6)
Headache	2 (1.6)	5 (4.0)	0	4 (3.2)	5 (3.9)
Pyrexia	1 (0.8)	4 (3.2)	4 (3.2)	3 (2.4)	3 (2.4)

Source: QVAR RediHaler package insert

Other adverse reactions that occurred in clinical trials with QVAR RediHaler with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were influenza, gastroenteritis viral, ear infection, oral candidiasis, diarrhea, and myalgia.

Laboratory Findings

Clinical laboratory evaluations were conducted only in study 301, at screening and the last treatment visit. Studies with the reference product, QVAR Inhalation Aerosol, found little effect on most laboratory parameters, and the test and reference products were found to be equivalent in their systemic exposure. There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory variable from screening to the final treatment visit.

Vital Signs

The criteria used to identify potentially clinically significant vital signs were acceptable. No clinically significant differences between treatment groups are seen for sitting pulse, systolic and diastolic blood pressures, as analyzed by absolute change, mean change from baseline, and shift tables.

7.4.4. Additional Safety Explorations

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reported incidences of overdose in the clinical studies. A Controlled Substance Staff review was not indicated, as QVAR RediHaler is not anticipated to be a drug with abuse potential. This assessment was based on QVAR RediHaler's route of administration, mechanism of action, and lack of penetration of the blood-brain barrier. Review of the adverse event data during the post-treatment follow-up period does not indicate any evidence of withdrawal or rebound effects.

SUMMARY AND CONCLUSIONS

7.5. Conclusions and Recommendations

The Applicant has demonstrated the efficacy of QVAR RediHaler at doses ranging from 80 mcg to 640 mcg depending on age and asthma severity for patients 4 years of age and older. The development program included 2 confirmatory trials of 12 weeks duration (Studies 301 and 304) and 1 confirmatory trial of 6 weeks duration in patients 12 years of age and older (Study 30039), and 1 confirmatory trial of 12 weeks duration in patients 4 to 11 years of age (Study 302). The efficacy of QVAR RediHaler was demonstrated using a lung function endpoints. In patients 12 years of age and older, the primary endpoint was FEV1 AUC, while for the pediatric study, we relied on the data with respect to peak expiratory flow.

The overall risk-benefit assessment supports approval of QVAR RediHaler at the two strengths and four dosing regimens (40 mcg BID, 80 mcg BID, 160 mcg BID, or 320 mcg BID) depending on age and asthma severity for patients 4 years of age and older. The risk with the use of ICS as a class, and specifically for beclomethasone dipropionate for the treatment of asthma are well-known. No new safety findings were identified during the clinical development program for these two products. The efficacy findings were robust and consistent with products of these classes. There were no issues identified with the usability of the new device. The clinical team therefore recommends **Approval** of QVAR RediHaler at the proposed doses for the treatment of asthma in patients 4 years of age and older.

X X

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8 Statistical Evaluation

8.1. Sources of Clinical Data and Review Strategy

8.1.1. Table of Clinical Studies

See Table 8. Relevant clinical studies with QVAR RediHaler (beclomethasone dipropionate) in patients with asthma

8.1.2. Review Strategy

Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, and study reports were accessed under the network path \\CDSESUB1\evsprod\NDA207921\207921.enx

Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We were able to reproduce the results of all key primary and secondary analyses.

8.2. Review of Relevant Individual Trials Used to Support Efficacy

Study 304

Trial Design and Endpoints

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Statistical Analysis Plan

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Patient Disposition

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Table of Demographic Characteristics

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

- **Efficacy Results – Primary Endpoint**

For Study 304, both the QVAR REDIHALER 80 mcg and 160 mcg doses produced statistically significant improvements in trough $FEV_1AUEC_{(0\text{-}12wk)}$. The primary endpoint analysis for study 304 is shown in the table below.

Table 35. Study 304 Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV_1 Area Under the Effect Curve From Week 0 to Week 12 (FAS)

P 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	0.048	0.171	0.164
Difference of LS mean from PBO: (95% CI)		0.124 (0.054, 0.193)	0.116 (0.048, 0.185)
p-value		0.0005	0.0010

Efficacy Results – Secondary and other relevant endpoints

For the secondary endpoints of change from baseline in weekly average of daily evening PEF over the 12-week treatment period, change from baseline in weekly average of total daily use of rescue medication over the treatment period, change from baseline in the total daily asthma symptom score over the treatment period, and time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma there were no statistically significant benefits of QVAR REDIHALER over the placebo. Results of the secondary endpoints analysis for study 304 are shown in the tables below.

Table 36. Study 304 Analysis of Change From Baseline in Weekly Average of Daily Trough Morning PEF (L/min) Over the 12-week Treatment Period (FAS)

S1 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	-0.795	12.849	7.116
Difference of LS mean from PBO: (95% CI)		13.645 (5.843, 21.446)	7.911 (0.202, 15.621)
p-value		0.0007	0.0443

Table 37. Study 304 Analysis of Change From Baseline in Weekly Average of Daily Evening PEF (L/min) Over the 12-Week Treatment Period (FAS)

S2 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	-0.797	10.105	4.608
Difference of LS mean from PBO: (95% CI)		10.902 (2.500, 19.303)	5.405 (-2.905, 13.715)
p-value		0.0112	0.2014

Table 38. Study 304 Analysis of Change From Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 (FAS)

S3 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	-0.010	-0.368	-0.398
Difference of LS mean from PBO: (95% CI)		-0.358 (-0.678, -0.038)	-0.388 (-0.708, -0.068)
p-value		0.0285	0.0175

Table 39. Study 304 Analysis of Change From Baseline in Weekly Average of Total Daily Asthma Symptom Scores Over Weeks 1-12 (FAS)

S4 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	-0.166	-0.293	-0.304
Difference of LS mean from PBO: (95% CI)		-0.127 (-0.255, 0.001)	-0.137 (-0.263, -0.011)
p-value		0.0509	0.0335

Table 40. Study 304 Analysis of Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S5 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
Number of patients withdrawn due to meeting stopping criteria	5 (6)	2 (2)	0
Number of patients censored	85 (94)	86 (98)	92 (100)
Log-rank test p-value compared to placebo		0.2384	0.0208

Additional Analyses Conducted on the Individual Trial

For the primary endpoint, subgroup analyses were performed for the following factors: sex (F, M), age (12-17, 18-64, >=65), and race (White, Black, and Other). The subgroup analysis for Study 304 is shown in the figures below.

Figure 6. Subgroup Analysis of Primary Endpoint of 80 mcg Arm Compare to Placebo in Study 304 on Sex, Age and Race

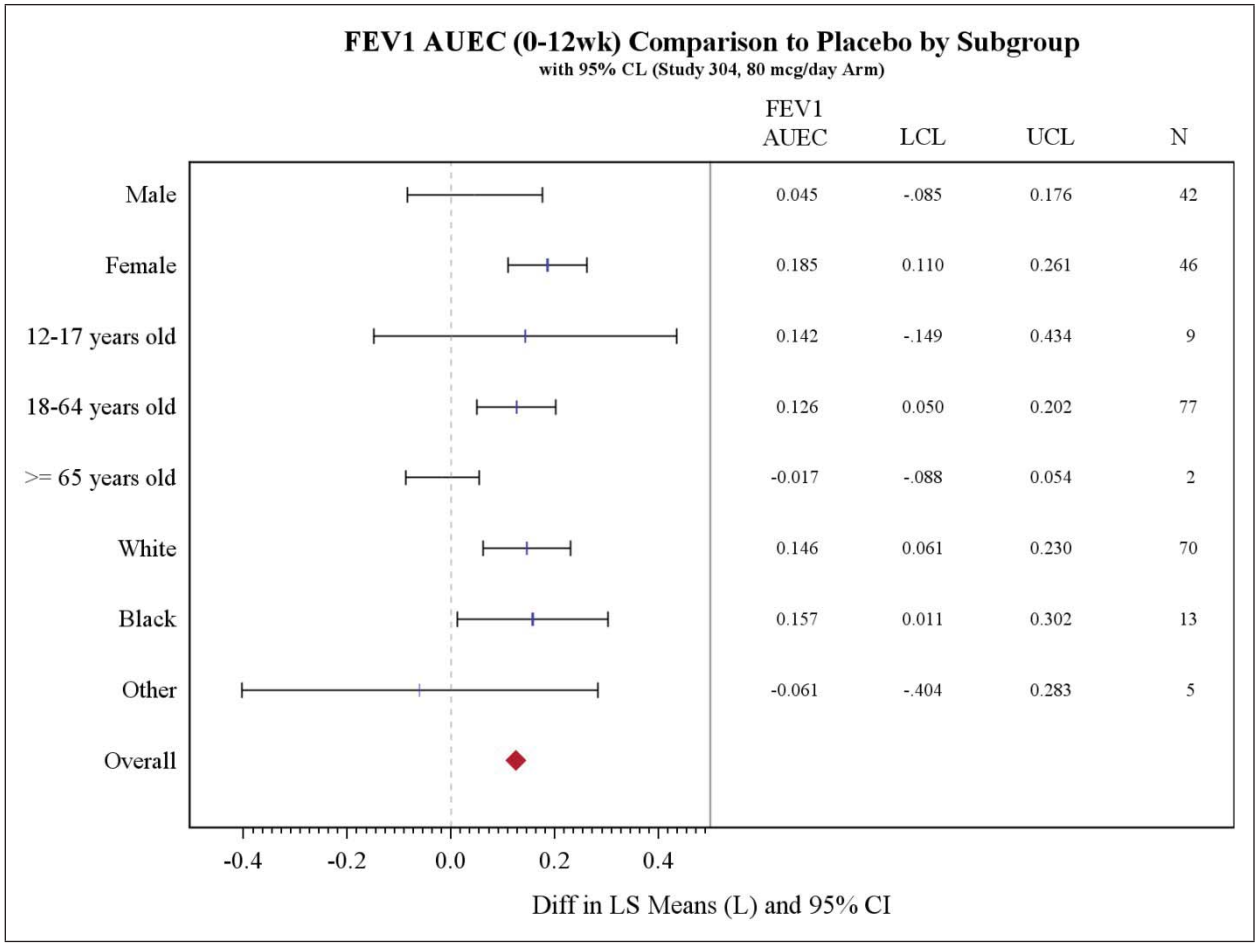
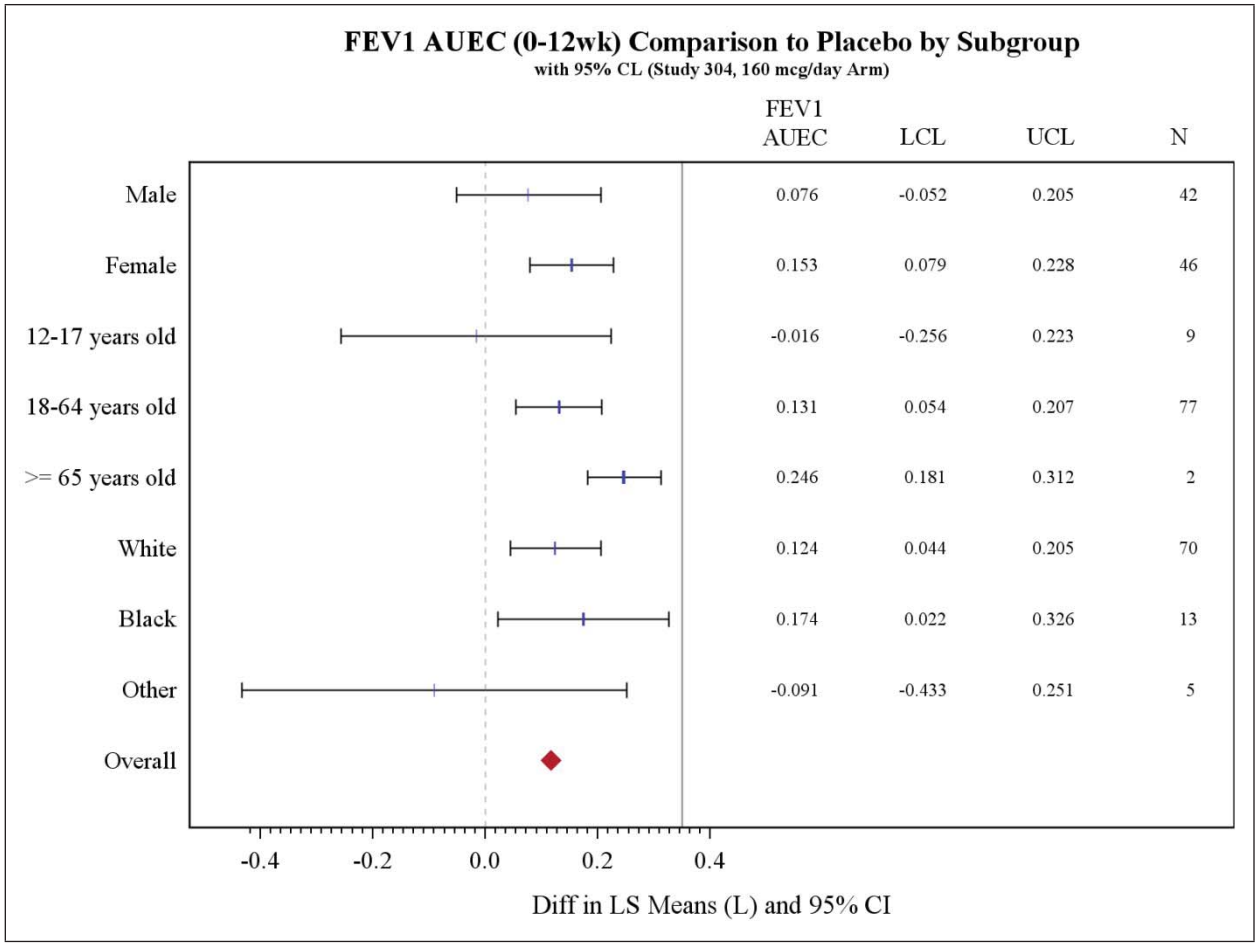


Figure 7. Subgroup Analysis of Primary Endpoint of 160 mcg Arm Compare to Placebo in Study 304 on Sex, Age and Race



8.2.2. Study 301

Trial Design and Endpoints

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Statistical Analysis Plan

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Patient Disposition

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Table of Demographic Characteristics

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Efficacy Results – Primary Endpoint

For study 301, the trial failed on the primary endpoint. The primary endpoint analysis for study 301 is shown in the table below.

Table 41. Study 301 Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV_1 Area Under the Effect Curve From Week 0 to Week 12 (FAS)

P 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.056	0.090	0.101	0.041	0.096
Difference of LS mean from PBO: (95% CI)		0.034 (-0.027, 0.095)	0.045 (-0.015, 0.106)	-0.015 (-0.075, 0.046)	0.040 (-0.020, 0.100)
p-value		0.2720	0.1415	0.6356	0.1932

Efficacy Results – Secondary and other relevant endpoints

According to the predefined testing procedure, it automatically failed on all the secondary endpoints since the primary analysis was failed. Results of the secondary endpoints analysis for study 301 are shown in the tables below.

Table 42. Study 301 Analysis of Change From Baseline in Weekly Average of Daily Trough Morning PEF (L/min) Over the 12-week Treatment Period (FAS)

S1 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.056	0.090	0.101	0.041	0.096
Difference of LS mean from PBO: (95% CI)		10.616 (3.489, 17.744)	8.419 (1.309, 15.530)	6.004 (-1.121, 13.129)	12.512 (5.435, 19.589)
p-value		0.0036	0.0204	0.0984	0.0006

Table 43. Study 30 Analysis of Change From Baseline in Weekly Average of Daily Evening PEF (L/min) Over the 12-Week Treatment Period (FAS)

S2 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	-4.708	4.439	4.462	-0.620	5.594
Difference of LS mean from PBO: (95% CI)		9.147 (1.866, 16.429)	9.170 (1.914, 16.425)	4.088 (-3.191, 11.367)	10.301 (3.073, 17.530)
p-value		0.0139	0.0133	0.2704	0.0053

Table 44. Study 301 Analysis of Change From Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 (FAS)

S3 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.478	-0.226	-0.213	-0.173	-0.323
Difference of LS mean from PBO: (95% CI)		-0.703 (-1.044, -0.363)	-0.691 (-1.029, -0.352)	-0.651 (-0.994, -0.309)	-0.801 (-1.138, -0.464)
p-value		<0.0001	<0.0001	0.0002	<0.0001

Table 45. Study 301 Analysis of Change From Baseline in Weekly Average of Total Daily Asthma Symptom Scores Over Weeks 1-12 (FAS)

S4 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	-0.058	-0.207	-0.159	-0.247	-0.274
Difference of LS mean from PBO: (95% CI)		-0.149 (-0.265, -0.033)	-0.102 (-0.217, 0.014)	-0.189 (-0.306, -0.072)	-0.216 (-0.332, -0.101)
p-value		0.0119	0.0854	0.0016	0.0003

Table 46. Study 301 Analysis of Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S5 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
Number of patients withdrawn due to meeting stopping criteria	15 (15)	3 (3)	3 (3)	5 (5)	1 (1)
Number of patients censored	91 (86)	101 (97)	103 (97)	101 (95)	106 (99)
Log-rank test p-value (compared to placebo)		0.0030	0.0030	0.0195	0.0002

8.2.3. Study 30039

Trial Design and Endpoints

Refer to the clinical section 7.2.

Statistical Analysis Plan

Refer to the clinical section 7.2.

Patient Disposition

Refer to the clinical section 7.2.

Table of Demographic Characteristics

Refer to the clinical section 7.2.

Efficacy Results – Primary Endpoint

For Study 30039, both the QVAR REDIHALER 320 mcg and 640 mcg doses produced statistically significant improvements in trough $FEV_1AUEC_{(0\text{-}6\ wk)}$. The primary endpoint analysis for study 30039 is shown in the table below.

Table 47. Study 30039 Primary Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV1 Area Under the Effect Curve from Time Zero to 6 Weeks by Actual Treatment Received (mITT)

P 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.062	0.205	0.212	0.210
Difference of LS mean from PBO: (95% CI)		0.144 (0.0807, 0.2066)	0.150 (0.0868, 0.2132)	0.148 (0.0847, 0.2114)
p-value		< 0.0001	< 0.0001	< 0.0001

Efficacy Results – Secondary and other relevant endpoints

Both doses of QVAR REDIHALER produced statistically significant improvements in all secondary endpoints: 1) Change from baseline in weekly average of daily trough morning PEF over the 6-week treatment period. 2) Change from baseline in weekly average daily trough morning FEV1 by handheld spirometer over the 6-week treatment period. 3) Change from baseline in weekly average of total daily rescue medication use over the 6-week treatment period. 4) Change from baseline in the weekly average of the total daily asthma symptom score over the 6-week treatment period. 5) Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma. Results of the secondary endpoints analysis for study 30039 are shown in the tables below.

Table 48. Study 30039 Analysis of Change from Baseline in Weekly Average of Daily Trough Morning PEF Rate (L/min) by Handheld Spirometer over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S1 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	-10.0	20.1	11.9	10.9
Difference of LS mean from PBO: (95% CI)		30.1 (18.33, 41.90)	21.9 (10.11, 33.71)	21.0 (9.14, 32.83)
p-value		<0.0001	0.0003	0.0006

Table 49. Study 30039 Analysis of Change from Baseline in Weekly Average of Daily Trough Morning FEV1 (L) by Handheld Spirometer over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S2 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	-0.008	0.162	0.135	0.125
Difference of LS mean from PBO: (95% CI)		0.17 (0.0985, 0.241)	0.143 (0.0717, 0.214)	0.133 (0.0613, 0.204)
p-value		<0.0001	<0.0001	0.0003

Table 50. Study 30039 Analysis of Change from Baseline in Weekly Average of Total Daily (24-hour) Rescue Medication Use (Number of Inhalations) over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S3 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.37	-0.73	-0.66	-0.66
Difference of LS mean from PBO: (95% CI)		-1.10 (-1.482, -0.717)	-1.02 (-1.408, -0.640)	-1.03 (-1.415, -0.643)
p-value		<0.0001	<0.0001	<0.0001

Table 51. Study 30039 Analysis of Change from Baseline in Weekly Average of Total Daily Asthma Symptom Scores over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S4 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.06	-0.18	-0.26	-0.24
Difference of LS mean from PBO: (95% CI)		-0.25 (-0.365, -0.128)	-0.32 (-0.440, -0.203)	-0.30 (-0.423, -0.185)
p-value		<0.0001	<0.0001	<0.0001

Table 52. Study 30039 Analysis of Time to Patient Study Drug Treatment Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma during the 6-Week Treatment Period by Actual Treatment Received (mITT)

S5 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
Number of patients withdrawn from study drug treatment due to meeting stopping criteria	10 (9)	1 (1)	0 (0)	1 (1)
Number of patients censored	97 (91)	107 (99)	105 (100)	104 (99)
Log-rank test p-value (compared to placebo)		0.0058	0.0014	0.0062

Additional Analyses Conducted on the Individual Trial

For the primary endpoint, subgroup analyses were performed for the following factors: sex (F, M), age (12-17, 18-64, >=65), and race (White, Black, and Other). The subgroup analysis for study 30039 is shown in the figures below.

Figure 8. Subgroup Analysis of Primary Endpoint of 320 mcg Arm Compare to Placebo in Study 30039 on Sex, Age and Race

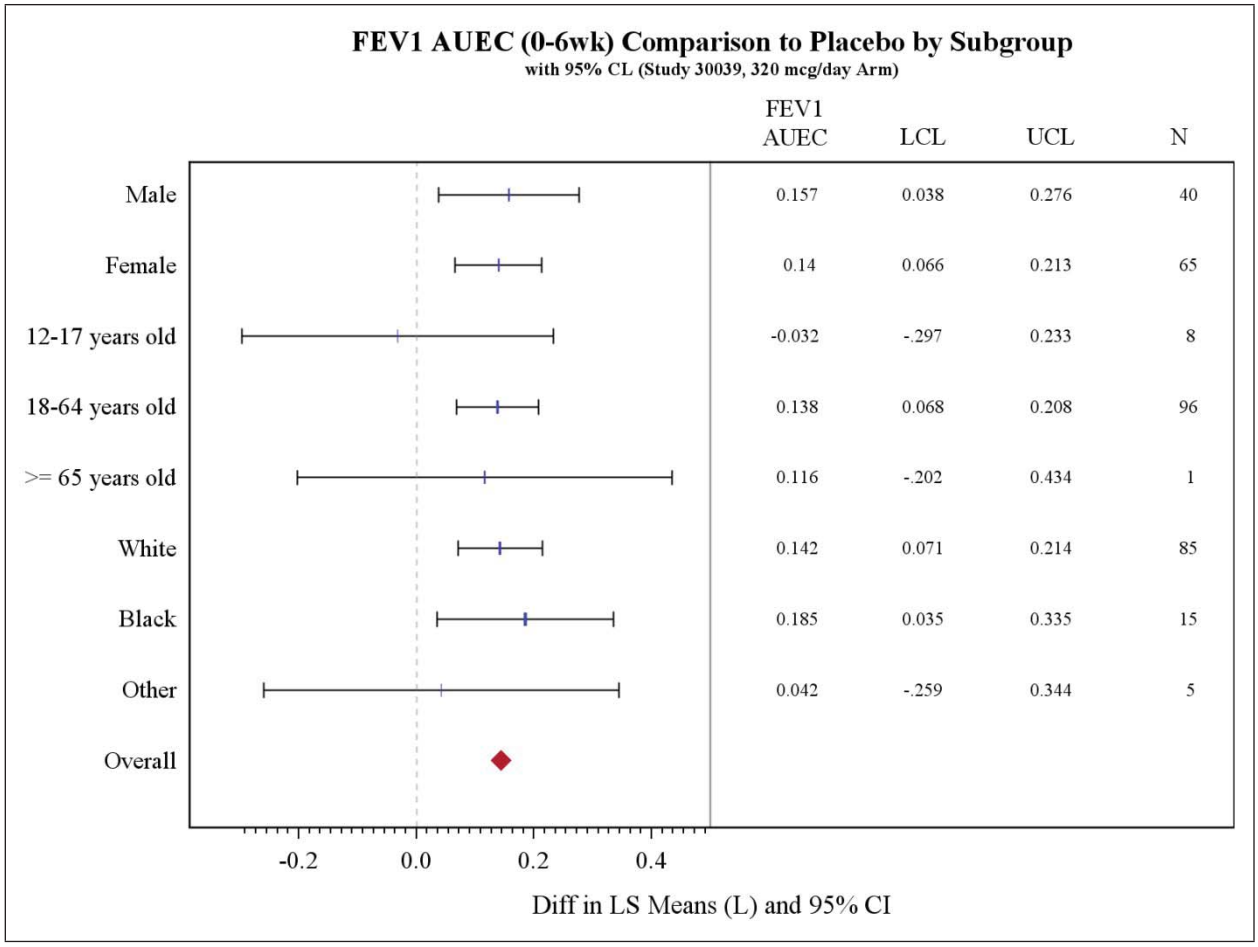
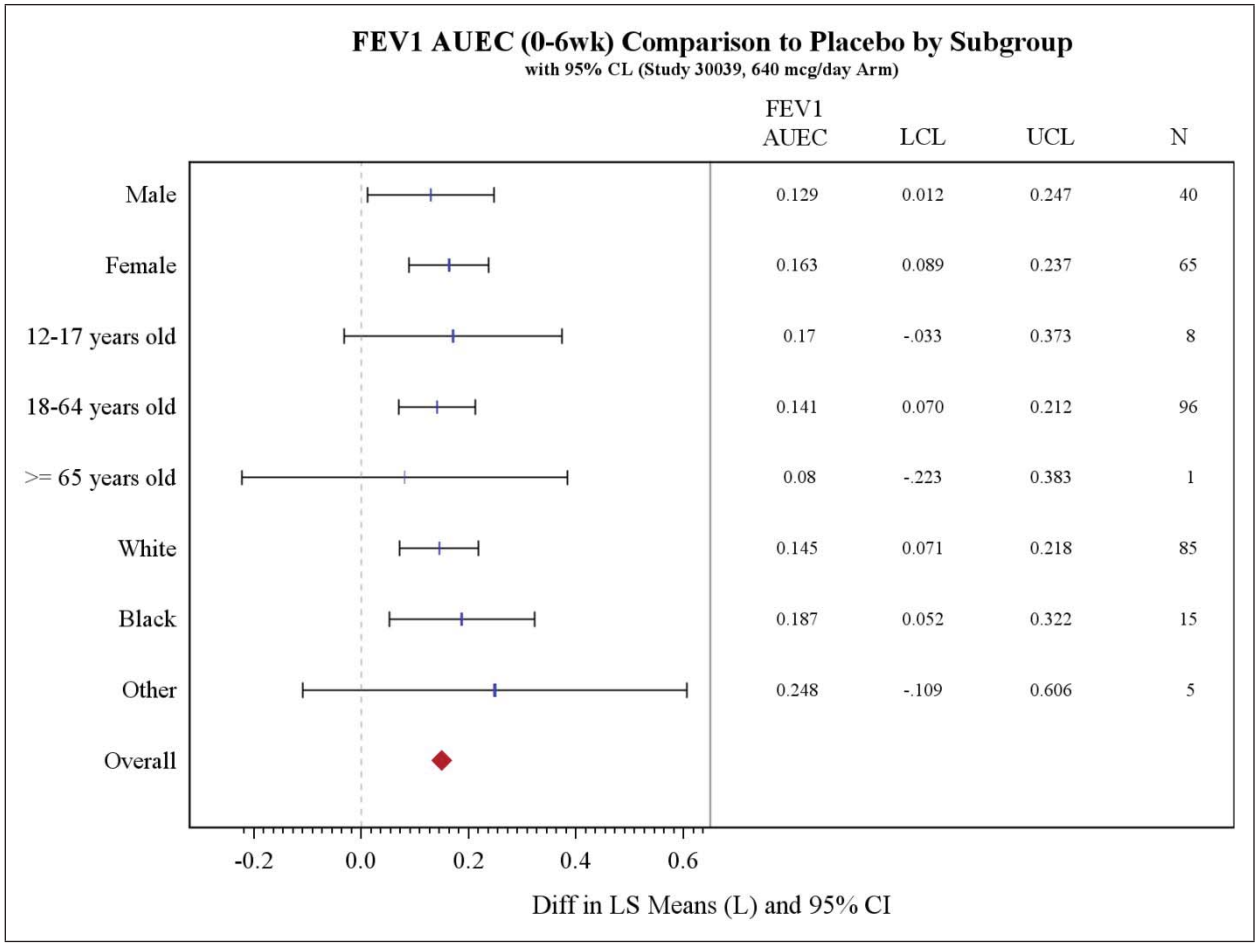


Figure 9. Subgroup Analysis of Primary Endpoint of 640 mcg Arm Compare to Placebo in Study 30039 on Sex, Age and Race



8.2.4. Study 302

Trial Design and Endpoints

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Statistical Analysis Plan

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Patient Disposition

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Table of Demographic Characteristics

Refer to Section 7.2 Review of Relevant Individual Trials Used to Support Efficacy

Efficacy Results – Primary Endpoint

For pediatric study 302, the trial failed on the primary endpoint. The primary endpoint analysis for study 302 is shown in the table below.

Table 53. Study 302 Primary Analysis of Standardized Baseline-Adjusted Trough Morning Percent Predicted FEV1 Area Under the Effect Curve from Time Zero to 12 Weeks (FAS)

P 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 113	N = 111	N = 116	N = 114	N = 114
LS mean	2.62	5.43	3.25	3.54	3.71
Difference of LS mean from PBO: (95% CI)		2.81 (0.796, 4.821)	0.63 (–1.354, 2.614)	0.92 (–1.077, 2.924)	1.09 (–0.902, 3.088)
p-value		0.0063	0.5332	0.3649	0.2823

Efficacy Results – Secondary and other relevant endpoints

According to the predefined testing procedure, it automatically failed on all the secondary endpoints since the primary analysis was failed. Results of the secondary endpoints analysis for study 302 are shown in the tables below.

Table 54. Study 302 Analysis of Change from Baseline in Weekly Average of Daily Trough Morning PEF (L/min) over the 12-Week Treatment Period (FAS)

S1 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	4.3	15.6	12.8	11.9	10.8
Difference of LS mean from PBO: (95% CI)		11.3 (5.58, 17.06)	8.5 (2.71, 14.24)	7.6 (1.79, 13.35)	6.5 (0.71, 12.23)
p-value		0.0001	0.0041	0.0103	0.0278

Table 55. Study 302 Analysis of Change from Baseline in Weekly Average of Daily Evening Peak Expiratory Flow (L/min) over the 12-Week Treatment Period (FAS)

S2 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	1.4	13.1	11.4	11.3	10.1
Difference of LS mean from PBO: (95% CI)		11.7 (5.96, 17.45)	10.0 (4.20, 15.76)	9.9 (4.11, 15.68)	8.7 (2.95, 14.49)
p-value		<0.0001	0.0007	0.0008	0.0031

Table 56. Study 302 Analysis of Change From Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 (FAS)

S3 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	-0.36	-0.72	-0.5	-0.41	-0.54
Difference of LS mean from PBO: (95% CI)		-0.36 (–0.548, -0.174)	-0.14 (–0.331, 0.044)	-0.05 (–0.240, 0.136)	-0.18 (–0.369, 0.007)
p-value		0.0002	0.132	0.5866	0.0587

Table 57. Study 302 Analysis of Change From Baseline in Weekly Average of Total Daily Asthma Symptom Scores Over Weeks 1-12 (FAS)

S4 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	-0.27	-0.44	-0.36	-0.31	-0.36
Difference of LS mean from PBO: (95% CI)		-0.16 (–0.261, -0.065)	-0.09 (–0.185, 0.013)	-0.04 (–0.138, 0.060)	-0.08 (–0.180, 0.017)
p-value		0.0011	0.0869	0.4388	0.1041

Table 58. Study 302 Analysis of Change from Baseline in Trough Morning FEV1 (L) over the 12- Week Treatment Period (FAS)

S5 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	0.067	0.132	0.092	0.091	0.091
Difference of LS mean from PBO: (95% CI)		0.065 (0.0174, 0.1123)	0.025 (–0.0218, 0.0721)	0.024 (–0.0228, 0.0715)	0.025 (–0.0226, 0.0719)
p-value		0.0075	0.2928	0.3112	0.3060

Table 59. Study 302 Analysis of Time to Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S6 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
Number (%) of patients withdrawn due to meeting stopping criteria	6 (5)	3 (2)	4 (3)	6 (5)	5 (4)
Number (%) of patients censored	118 (95)	121 (98)	118 (97)	115 (95)	118 (96)
Log-rank test p-value compared to placebo		0.2870	0.5257	0.9982	0.7633

8.3. Baseline LABA Use

For study 30039, the clinical team asked sponsor to clean up the data about patient's baseline ICS/LABA use information (yes or no). Based on this newly available variable, we have conducted additional analyses to assess the baseline ICS/LABA use to the treatment effect. We conducted analyses on the ITT population on the primary endpoint standardized baseline-adjusted trough morning FEV1 area under the effect curve from time zero to 6 weeks. Due to reversal dose of 320 mcg/day and 640 mcg/day, the analyses were conducted on the data where the dosage actually received.

Following are the two analyses approaches:

1. We stratified the data into two sets, the first set includes all the subjects who did not use ICS/LABA at baseline, the second set patients used ICS/LABA at baseline. Then we used the same original ANOVA model to conduct analyses on these two sets.

2. We added baseline ICS/LABA use (yes, no) in the ANCOVA model as a covariate, in addition to baseline trough morning FEV1, sex, age, current protocol allowed asthma therapy to conduct the analyses use all data without stratification. We also include the interaction term of baseline ICS/LABA use and treatment group.

Figure 10 illustrates the analyses results using Approach 1.

Figure 11 illustrates the analyses results using Approach 2.

Figure 10 showed that patients used ICS/LABA at baseline has larger confidence interval than those who did not use ICS/LABA at baseline, but the mean values are very close to each other. Baseline ICS/LABA use or not does not cause significant differences in treatment effects.

Figure 11 showed that adding or not adding baseline ICS/LABA in the analyses model the results are very similar. Baseline ICS/LABA use is not a significant factor.

Conclusions from two approaches are consistent.

Figure 10: Comparison of Differences of FEV1 AUEC(0-6wk) From Placebo in Each Dosage Arm W/ or W/O Stratification on Baseline ICS/LABA Use

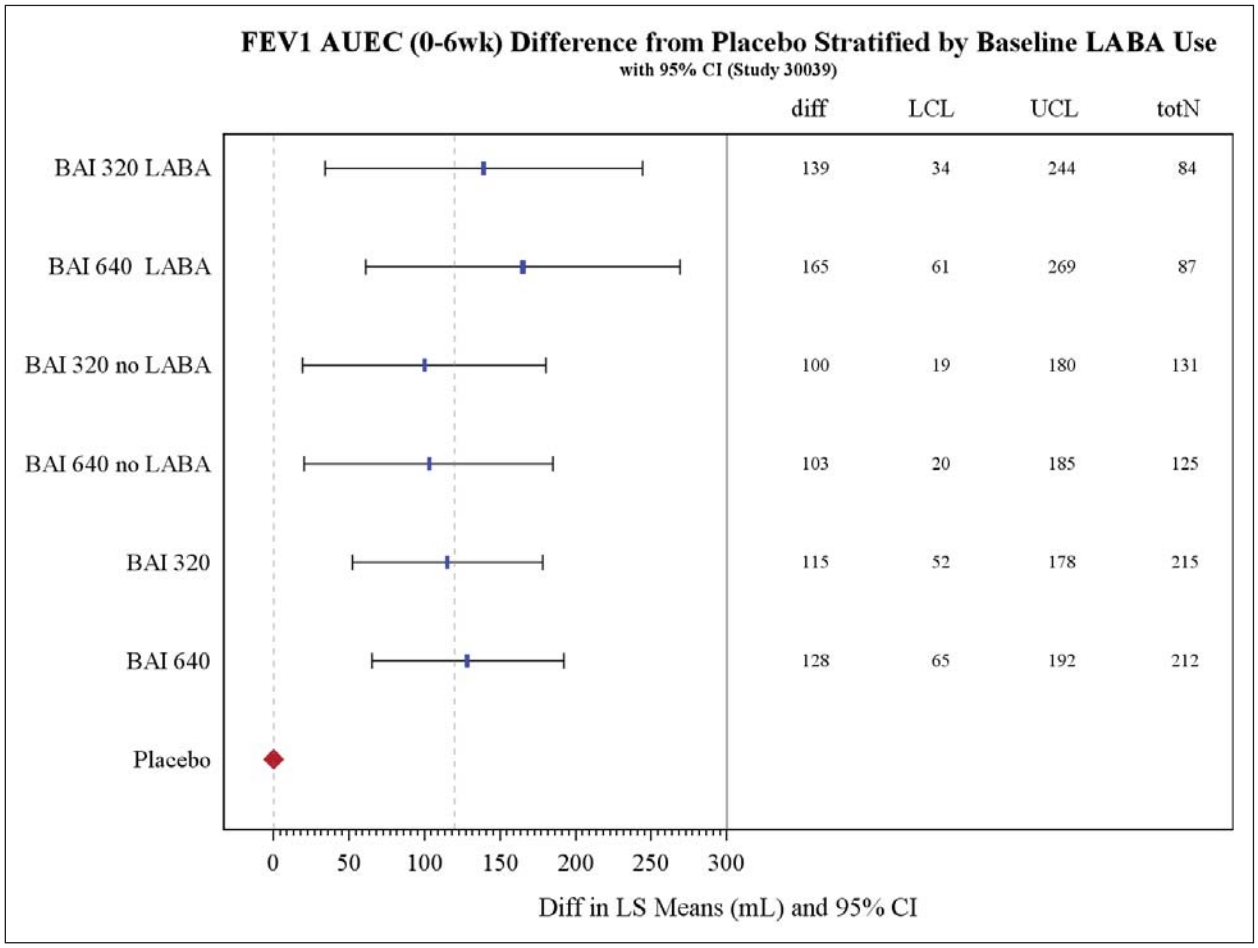
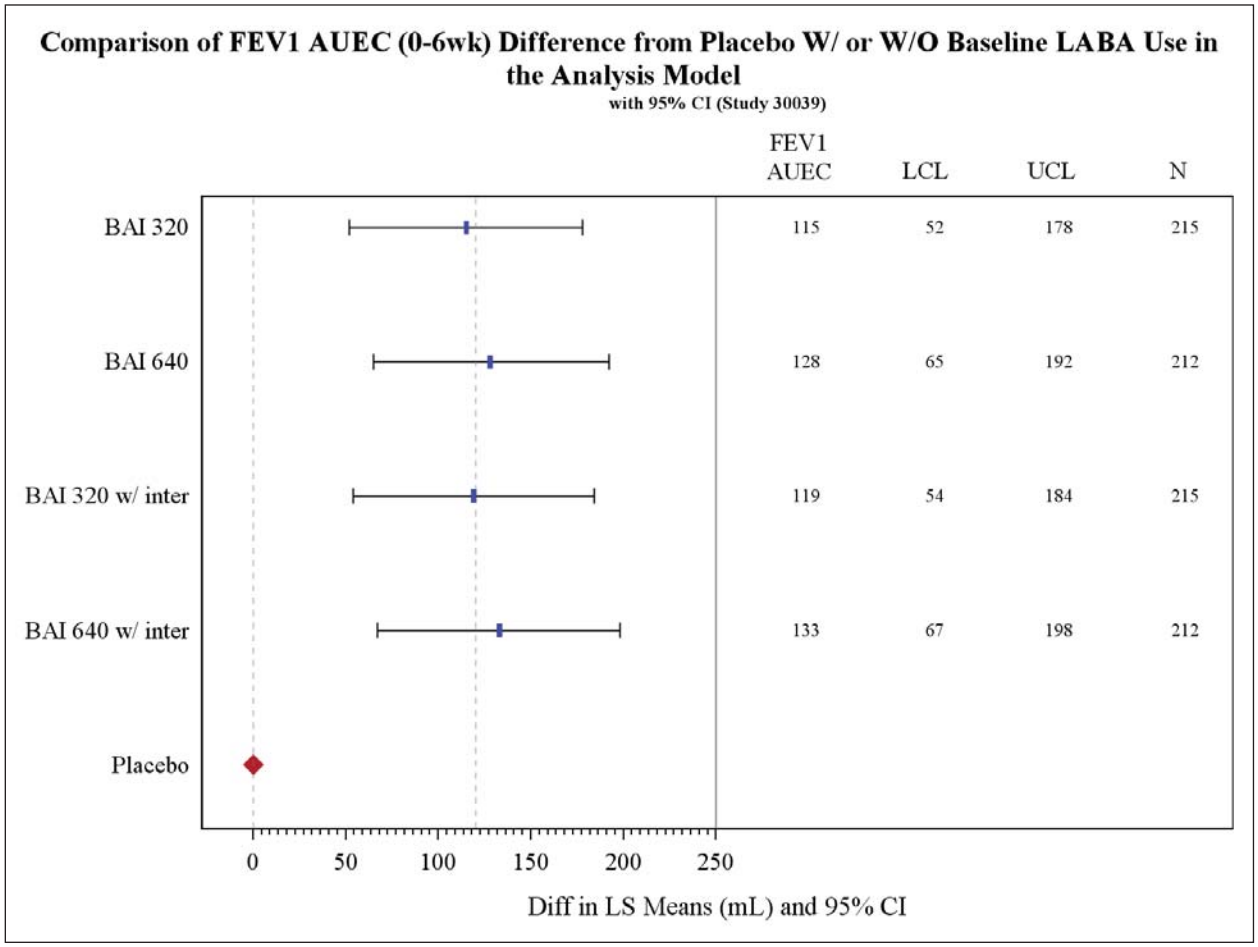


Figure 11: Comparison of Differences of FEV1 AUEC(0-6wk) from Placebo Using Different Model



8.4. Statistical Issues

There were some discussions on "substantial evidence of efficacy" within the stat team and with the clinical team about this application. Although we did not reach a firm conclusion on it, we reasoned with the following findings:

1. This application is an application of drug and device combination and seeks 505(b)(2) pathway approval. The drug is Beclomethasone Dipropionate and the device is Breathe Actuated Inhaler. Same drug with metered inhaler (MDI) from same company has been approved in US since September 2000.

2. This application seeks approval of four dosages QVAR BAI 80, 160, 320, or 640 mcg/day. Originally two pivotal studies were planned with study 304 to support approval of 80 and 160 mcg/day, and study 301 to support approval of 320 and 640 mcg/day. When

study 301 was completed, the sponsor found it failed on the primary endpoint. After the applicant discussed the results with the Agency, both agreed that the applicant conducts another study of 320 and 640 mcg/day dosage, which is study 30039. The treatment duration of study 30039 is 6 weeks while study 301 is 12 weeks. Study 301, 304 and 30039 are of patients of 12 years of age or older. The pediatric study 302 is of patients of 4 to 11 years of age.

3. Study 304 won on the primary endpoint and first of secondary endpoints, and study 30039 won on both primary endpoint and all secondary endpoints. Study 301 failed on the primary endpoint and pediatric study 302 failed on the primary endpoint.

4. In terms of "substantial evidence of efficacy", FDA usually requires two independent efficacy trials for approval. There were two successful adult studies, one failed adult study and one failed pediatric study. When considering adult population, two successful studies might provide substantial evidence. This is further supported by the fact that the failed adult study lacked assay sensitivity from the fact that active control of approved drug also failed.

5. The statistical team raised the question of whether single study is sufficient to support each dose in the filing, mid-cycle, labeling and the wrap-up meetings because none of the proposed doses were studied in more than one study. During these meetings, the clinical team repeatedly expressed that the drug was around in US market for many years and its efficacy was well-proven. Although b(2) regulatory pathway for this application still requires usual standard for substantial evidence for each dose, considering clinical team's experience with this drug, we lean toward a conclusion that there is sufficient evidence for approval.

In regard of failed pediatric study, we suggest the Approval of patients of 12 years of age or older.

X X

Mingyu Xi, PhD
Primary Statistical Reviewer

Yongman Kim, PhD
Statistical Team Leader

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy for inhaled corticosteroids are well understood. There were no unique findings in the QVAR RediHaler program that would warrant a discussion at an Advisory Committee meeting.

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply to this application, the application was exempted from PREA requirements.

While not triggered by PREA, the Applicant conducted a study in 4 to 11 year old patients (Study 302) to obtain a pediatric indication. The primary endpoint was the change from baseline in trough percent predicted FEV1 AUEC (0-12 weeks). While the primary endpoint was not statistically significant, change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12 week treatment period was 11.3 [95% CI: 5.58, 17.06] and 8.5 [95% CI: 2.71, 14.24] for the 80 mcg/day and 160 mcg/day doses of QVAR REDIHALER, respectively, at nominal significance. Similar results were seen with evening PEF. Studies with ICS in asthma often are equivocal, especially in pediatric patients who cannot reliably perform spirometry. As PEF is an objective measure of lung function often used in young children, and the efficacy of QVAR MDI is known in this age group, QVAR RediHaler is recommended for approval in patients 4 to 11 years of age.

11 Labeling Recommendations

11.1. Prescribing Information

- The proprietary name of QVAR RediHaler was proposed by the Applicant, and accepted by DMEPA.
- The Applicant submitted the label in Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Revisions were made to various sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and the Applicant have agreed on the final label language.
- The carton and immediate container were also reviewed by various disciplines of this Division and DMEPA, and found to be acceptable. DMEPA had some comments

regarding updating the carton and container labeling and the corresponding IFU which were deemed not to be approvability issues, and will be communicated to the Applicant as part of the approval letter.

11.2. Patient Labeling

The Division and Applicant have agreed upon a Patient Information sheet and Instructions for Use. QVAR RediHaler will carry safety information/warnings typical of this class.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary as the labeling will be sufficient to communicate safe use of the product.

13 Postmarketing Requirements and Commitments

None.

14 Appendices

14.1. References

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4. Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention. 2013 Accessed October 26, 2015]. Available from: http://www.ginasthma.org.
5. Fanta CH. Asthma. *N Engl J Med* 2009; 360: 1002-1014.

14.2. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Three investigators received speaking and consulting fees from Teva. The number of subjects enrolled by each investigator was not large enough to alter the outcome of the studies. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased these studies.

Table 60. Number of patients randomized per study by investigator with financial interest

Investigator	Fees	Study (b) (6) (n (b) (6)) (n (b) (6)) (n (b) (6))
(b) (6)	$91,498	
	$90,700	
	$51,250	

Covered Clinical Study (Name and/or Number): NDA 207921

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 149		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 140		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15 Division Director (DPARP)

The submitted clinical program is adequate to support the efficacy and safety of QVAR RediHaler at a range of daily doses (divided BID) from 80 mcg to 640 mcg in patients 12 years of age and older, and from 80 to 160 mcg daily in patients 4 to 11 years of age. The submitted clinical program consisted of 4 clinical studies in total, 3 in patients 12 years of and older (Study 301, 304, and 30039), and one study in patients 4 to 11 years of age (Study 302). Study 301 did not meet its primary endpoint, but was included in the safety evaluation. These studies demonstrate efficacy and safety of QVAR at the proposed doses. The product quality data is also adequate. There are no outstanding issues from any review disciplines. I concur with the content of various discipline assessments and the recommendation of approval. The Agency and the Sponsor have also agreed upon final labeling language. The action on this application will be **Approval.**

X

Badrul Chowdhury, MD, PhD
Division Director, DPARP

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/s/

BADRUL A CHOWDHURY
08/03/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 6, 2017

TO: File for NDA 207921

FROM: Carol M. Galvis, PhD, Pharmacology/Toxicology Acting Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

SUBJECT: Pharmacology/Toxicology Secondary Review

APPLICATION/DRUG: NDA 207921/ QVAR RediHaler (beclomethasone dipropionate)

Norton Waterford Limited (with Teva Branded Pharmaceutical Products R&D as US agent) submitted NDA 207921 via the 505(b)(2) regulatory pathway to develop beclomethasone dipropionate as a breath-actuated inhalation (BAI) aerosol product (QVAR Redihaler). There were no nonclinical studies submitted for review in this submission. The sponsor referenced the nonclinical toxicology data for Beclovent (developed under NDA 018153) and QVAR Inhalation Aerosol (developed under NDA 020911).

For the prescribing information, Section 8 of the drug label was updated according to the Pregnancy and Lactation Labeling Rule (PLLR). I agree with Dr. Xiaochun Chen's evaluation that the application should be approved from the nonclinical Pharmacology and Toxicology perspective. Refer to the Multi-disciplinary Review and Evaluation that will be uploaded into DARRTS for additional details.

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/s/

CAROL M GALVIS
07/06/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 29, 2017

TO: File for NDA 207921

FROM: Banu A. Karimi-Shah, M.D.

SUBJECT: Clinical Primary Review

APPLICATION/DRUG: NDA 207921/ QVAR RediHaler (beclomethasone dipropionate)

Executive Summary

The Applicant submitted a 505(b)(2) new drug application for use of QVAR RediHaler (beclomethasone dipropionate) for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. The two reference listed drugs are Beclovent (NDA 018153, no longer marketed) and QVAR (NDA 20911). While beclomethasone dipropionate (BDP) has been approved and marketed as a press-and-breathe metered-dose inhaler in the U.S. since 2000, QVAR RediHaler proposes to deliver BDP via a novel tidal breath-actuated inhaler (RediHaler). The proposed dosing regimen for patients 12 years of age and older (based on prior asthma therapy and severity) is 40, 80, 160, or 320 mcg twice daily. For patients 4 to 11 years of age, the dosing regimen is 40 or 80 mcg twice daily.

The safety and efficacy of QVAR RediHaler was evaluated in 1,858 patients with asthma. The clinical development program included two confirmatory trials of 12 weeks duration and one confirmatory trial of 6 weeks duration in patients 12 years of age and older, and one confirmatory trial of 12 weeks duration in patients 4 to 11 years of age. The reviewed clinical data support the efficacy/safety of QVAR RediHaler.

The clinical review of safety and efficacy is complete and has been added to the NDA Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical reviewers recommend Approval of QVAR RediHaler for the treatment of asthma in patients 4 years of age and older, pending finalization of the labeling language with the Applicant.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

BANU A KARIMI SHAH
06/29/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 06/29/2017

TO: File for NDA 207921

THROUGH: Carol M. Galvis, PhD, Acting Pharmacology/Toxicology Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

FROM: Xiaochun Chen, PhD, Pharmacology/Toxicology Reviewer, DPARP

SUBJECT: Pharmacology and Toxicology Primary Review

APPLICATION/DRUG: NDA 207921/ QVAR RediHaler (beclomethasone dipropionate)

Executive Summary

Teva Branded Pharmaceutical Products R&D Inc. (Teva) on behalf of Norton (Waterford) Limited submitted NDA 207,921 via the 505(b)(2) pathway, for beclomethasone dipropionate (BDP) hydrofluoroalkane (HFA) breath-actuated inhalation (BAI) aerosol (QVAR® REDIHALER™). The proposed indication is for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older (b) (4) . BDP, a diester of beclomethasone, is a synthetic corticosteroid that was first approved in United States in 1976, and therefore, has a long history of clinical use. There are no new nonclinical pharmacology and toxicology data submitted to support this application. The applicant relied on previous nonclinical safety findings from BECLOVENT® (NDA 018153, GlaxoSmithKline), QVAR® Inhalation Aerosol (NDA 020911, Teva), QNASL® Nasal Aerosol (NDA 202813, Teva) and published literature.

Recommendation

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

XIAOCHUN CHEN
06/29/2017

CAROL M GALVIS
06/29/2017
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	NDA 207-921
Drug Name:	QVAR REDIHALER (Beclomethasone Dipropionate Inhalation Aerosol HFA Breathe Actuated Inhaler[BAI]) 80, 160, 320, or 640 mcg/day
Indication(s):	Beclomethasone dipropionate BAI is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (b) (4)
Applicant:	Teva Branded Pharmaceutical Products R&D Inc.
Date(s):	Stamp Date: 10/4/2016, PDUFA due date: 8/3/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Mingyu Xi, Ph.D.
Concurring Reviewers:	Yongman Kim, Ph.D. (Acting Team Lead, DB II)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Erika Torjusen, M.D., Banu Karimi-Shah, M.D.
Project Manager:	Laura Musse

Keywords: double-blind, longitudinal data analysis, mixed models, NDA review, repeated measure AN(C)OVA & subgroup analyses

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1 EXECUTIVE SUMMARY

Teva Branded Pharmaceutical Products R&D Inc. has proposed QVAR REDIHALER (Beclomethasone Dipropionate Inhalation Aerosol HFA Breathe Actuated Inhaler) 80, 160, 320, or 640 mcg/day for the maintenance treatment of asthma as a prophylactic therapy in patients 4 years of age and older. (b) (4)

Effectiveness and safety of four different dosages of QVAR REDIHALER were examined with this submission: 40 mcg twice daily (BID), 80 mcg BID, 160 mcg BID, or 320 mcg BID. The review focused on four phase 3 studies to investigate the efficacy of QVAR REDIHALER in terms of standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)}$ or FEV_1 $AUEC_{(0\text{-}6wk)}$, change from baseline in weekly average of daily trough morning PEF over the treatment period, change from baseline in weekly average of daily evening PEF over the treatment period, change from baseline in weekly average of total daily use of rescue medication over the treatment period, change from baseline in the total daily asthma symptom score over the treatment period, and time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma.

In study BDB-AS-304 (304), statistical evidence of benefit was shown for QVAR REDIHALER 80 mcg and 160 mcg with respect to the primary endpoint, standardized baseline-adjusted trough morning $FEV_1AUEC_{(0\text{-}12\ wk)}$, with improvement over placebo of 0.124 L (95% confidence interval[CI]: 0.054, 0.193) and 0.116 L (95% CI: 0.048, 0.185); with respect to the secondary endpoint change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period with improvement over placebo of 13.645 L/min (95% CI: 5.843, 21.446) and 7.911 L/min (95% CI: 0.202, 15.621). However, statistical significance was not reached in the other clinical endpoints.

In study BDB-AS-30039 (30039), statistical evidence of benefit shown for QVAR REDIHALER 320 mcg and 640 mcg with respect to the primary endpoint, standardized baseline-adjusted trough morning $FEV_1AUEC_{(0\text{-}6\ wk)}$, with improvement over placebo of 0.144 L (95% CL: 0.081, 0.207) and 0.150 L (95% CI: 0.087, 0.213); with respect to the secondary endpoint change from baseline in weekly average of daily trough morning PEF over the 6-week treatment period with improvement over placebo of 30.1 L/min (95% CI: 18.33, 41.90) and 21.8 L/min (95% CI: 10.11, 33.71); with respect to the secondary endpoint change from baseline in weekly average of daily trough morning FEV_1 over the 6-week treatment period with improvement over placebo of 0.17 L (95% CI: 0.099, 0.241) and 0.143 L (95% CI: 0.072, 0.214); with respect to the secondary endpoint change from baseline in weekly average of total daily rescue medication use (number of inhalation) over the 6-week treatment period with improvement over placebo of -1.10 (95% CI: (-1.482, -0.717) and -1.02 (95% CI: -1.408, -0.640); with respect to the secondary endpoint change from baseline in weekly average of total daily asthma symptom scores over the 6-week treatment period with improvement over placebo of -0.25 (95% CI: -0.365, -0.128) and -0.32 (95% CI: -0.440, -0.203); with respect to the secondary endpoint of time to patient study drug treatment withdrawal due to meeting stopping criteria for worsening asthma during the 6-week treatment period with improvement over placebo (the p-value of Log-rank test were both less than 0.05).

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors of age, sex, race, and baseline disease characteristics of baseline LABA use. The results were consistent to the primary analysis results.

However, one phase 3 study BDB-AS-301 (301) failed on primary endpoint and the pediatric study BDB-AS-302 (302) also failed on primary endpoint.

This submission supports effectiveness of QVAR REDIHALER in treatment of patients with asthma of 12 years of age or older in terms of standardized baseline-adjusted trough morning FEV_1AUEC over treatment period and change from baseline weekly average of daily trough morning PEF over the treatment period. However, no statistically significant benefits in terms of other endpoints were found.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Asthma is a chronic disease involving the airways in the lungs; it leads to bronchoconstriction, airway hyper responsiveness and eventually airway edema and remodeling. The symptoms of asthma are coughing, wheezing, shortness of breath and/or chest tightness.

Corticosteroids exhibit multiple anti-inflammatory effects. Beclomethasone dipropionate is an anti-inflammatory corticosteroid currently marketed in the United States (US) by Teva Branded Pharmaceutical Products R & D, Inc. (Teva) as QVAR. QVAR Inhalation Aerosol delivers beclomethasone dipropionate through a metered-dose inhaler (MDI) and has been approved in the US since September 2000. Although MDI is a commonly used device for the delivery of inhaled corticosteroids (ICSs), it requires coordination of actuation and inhalation for effective delivery of the therapeutic agent. In this application Teva is developing a breath-actuated inhaler (BAI), which ensures that actuation occurs automatically when the subject inhales.

This review considers QVAR BAI for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (b) (4) We often omit the mcg unit when referring to the dose of QVAR in this review.

2.1.2 History of Drug Development

During IND 114865 development, statistical advice regarding the design and analysis of the phase 3 trials was given to the applicant. Advice and comments from the Division were delivered

through one Type B pre-IND meeting, one Type C teleconference, one end-of-phase 2 meeting, one Type B meeting, and one Type C written response. Table 1 summarizes these interactions.

Table 1: List of Key Correspondences and Meeting Minutes

Document	Meeting Date/ Document Date	Topic	Reference Number
Type B pre-IND Meeting	28 Sept 2012/ 26 Oct 2012	505(b)(2) NDA pathway	IND 114865
Type C Teleconference Minutes	15 Apr 2014/ 27 May 2014	FDA recommended the use of a landmark assessment for the primary efficacy measure	IND 114865
EOP II Meeting Minutes	10 Oct 2014/ 23 Oct 2014	FDA encouraged the inclusion of patients aged 4 and 5 years old in study BDB-AS-302. FDA confirmed the use of the landmark primary efficacy endpoint was appropriate.	IND 114865
Type B Meeting	28 Apr 2015	Discussed results of studies BDB-AS-301 and BDB-AS-304. Discussed the third phase 3 study BDB-AS-30039 of 6-week treatment duration due to insignificant results of study BDB-AS-301.	IND 114865
Type C Written Response	5 July 2016	Agreed that primary analysis of the primary endpoint was performed on the mITT population, and included the sensitivity analysis evaluating the ITT population.	IND 114865

Several topics have been discussed during the development of the program:

1. The agency recommended the use of a landmark assessment for the primary efficacy measure in the clinical studies. After discussion, the Agency and the applicant reached an agreement that dropouts should be considered as having bad outcomes.

2. The agency encouraged the inclusion of patients aged 4 and 5 years old in the study BDB-AS-302.

3. The agency agreed on treatment duration of 6-weeks for the third phase 3 study BDB-AS-30039.

4. The agency agreed on primary analysis of the primary endpoint that was performed on the mITT population, and including the sensitivity analysis evaluating the ITT population.

2.1.3 Specific Studies Reviewed

The Applicant has submitted the results of four phase 3 studies: BDB-AS-301, BDB-AS-304, BDB-AS-30039, and BDB-AS-302. We reviewed all of four phase 3 studies.

In this review, we will omit suffix BDB-AS- whenever referring to the studies.

Table 2: List of Key Phase 3 Studies in the Clinical Development Program

Study	Treatment Period	# of Randomized Subjects per Arm	Study Objectives
BDB-AS-301	12 weeks	PBO/320BAI/640BAI/320MDI/640MDI 106/104/106/106/107	Safety and efficacy
BDB-AS-304	12 weeks	PBO/80BAI/160BAI 90/88/92	Safety and efficacy
BDB-AS-30039	6 weeks	PBO/320BAI/640BAI/320MDI 107/108/105/105	Safety and efficacy
BDB-AS-302	12 weeks	PBO/80BAI/160BAI/80MDI/160MDI 124/124/122/121/123	Safety and efficacy

2.1.4 Statistical Issues

There were some discussions on "substantial evidence of efficacy" within the stat team and with the clinical team about this application. Although we did not reach a firm conclusion on it, we reasoned with the following findings:

1. This application is an application of drug and device combination and seeks 505(b)(2) pathway approval. The drug is Beclomethasone Dipropionate and the device is Breathe Actuated Inhaler. Same drug with metered inhaler (MDI) from same company has been approved in US since September 2000.

2. This application seeks approval of four dosages QVAR BAI 80, 160, 320, or 640 mcg/day. Originally two pivotal studies were planned with study 304 to support approval of 80 and 160 mcg/day, and study 301 to support approval of 320 and 640 mcg/day. When study 301 was completed, the sponsor found it failed on the primary endpoint. After the applicant discussed the results with the Agency, both agreed that the applicant conducts another study of 320 and 640 mcg/day dosage, which is study 30039. The treatment duration of study 30039 is 6 weeks while study 301 is 12 weeks. Study 301, 304 and 30039 are of patients of 12 years of age or older. The pediatric study 302 is of patients of 4 to 11 years of age.

3. Study 304 won on the primary endpoint and first of secondary endpoints, and study 30039 won on both primary endpoint and all secondary endpoints. Study 301 failed on the primary endpoint and pediatric study 302 failed on the primary endpoint.

4. In terms of "substantial evidence of efficacy", FDA usually requires two independent efficacy trials for approval. There were two successful adult studies, one failed adult study and one failed pediatric study. When considering adult population, two successful studies might provide substantial evidence. This is further supported by the fact that the failed adult study lacked assay sensitivity from the fact that active control of approved drug also failed.

5. We stat raised the question of whether single study is sufficient to support each dose in the filing, mid-cycle, labeling and the wrap-up meetings because none of the proposed doses were studied more than one study. During these meetings, the clinical team repeatedly expressed that the drug was around in US market for many years and its efficacy was well proven. Although b(2) regulatory pathway for this application still requires usual standard for substantial evidence for each dose, considering clinical team's experience with this drug, we lean toward a conclusion that there is sufficient evidence for approval.

In regard of failed pediatric study, we suggest the Approval of patients of 12 years of age or older.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, and study reports were accessed under the network path \\CDSESUB1\evsprod\NDA207921\207921.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We were able to reproduce the results of all key primary and secondary analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study BDB-AS-301

Study BDB-AS-301was a 12-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to evaluate the efficacy and safety of beclomethasone dipropionate treatment administered via BAI or MDI at dosages of 320 and 640 mcg/day in patients 12 years of age and older with persistent asthma.

The study consisted of a 14- to 21-day run-in period, during which time patients continued their current ICS and took 4 inhalations twice a day of a single-blinded placebo BAI device and 4 inhalations twice a day of a single-blinded placebo MDI device. Patients who were being treated with combination ICS and LABA therapy discontinued this therapy at a prescreening visit and were placed on study-supplied fluticasone propionate at a dose of 440 or 880 mcg/day, based on the dose of prior ICS therapy. Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned to 1 of 5 treatment groups:

- beclomethasone dipropionate BAI 320 mcg/day (160 mcg twice daily) plus placebo MDI, twice daily
- beclomethasone dipropionate BAI 640 mcg/day (320 mcg twice daily) plus placebo MDI, twice daily
- beclomethasone dipropionate MDI 320 mcg/day (160 mcg twice daily) plus placebo BAI, twice daily
- beclomethasone dipropionate MDI 640 mcg/day (320 mcg twice daily) plus placebo BAI, twice daily
- matching placebo BAI (twice daily) plus placebo MDI (twice daily)

The treatment duration was 12-weeks.

The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate (320 or 640 mcg/day) administered via BAI or MDI compared with placebo treatment in patients 12 years of age and older with persistent asthma as assessed by the standardized baseline-adjusted trough morning (predose and prerescue bronchodilator) FEV_1 $AUEC_{(0\text{-}12wk)}$. (Sponsor's variable definition is attached in Appendix). Safety was assessed by monitoring adverse events, physical examination findings, oropharyngeal examination findings, clinical laboratory evaluations, and vital sign assessments.

Detailed primary and secondary endpoints are listed in Table 3.

Table 3: Primary and Secondary Endpoints of Study 301

	Study 301
Primary Endpoint	Standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)}$
Key Secondary Endpoints	Change from baseline in weekly average of daily trough morning Peak Expiratory Flow (PEF) over the 12-week treatment period
	Change from baseline in weekly average of daily evening PEF over the 12-week treatment period
	Change from baseline in weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12
	Change from baseline in the total daily asthma symptom score (the average of the daytime and nighttime scores) over weeks 1 to 12
	Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma

3.2.1.2 Study BDB-AS-304

Study BDB-AS-304 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of beclomethasone dipropionate treatment

administered via BAI at dosages of 80 and 160 mcg/day in patients 12 years of age and older with persistent asthma.

The study consisted of a 14- to 21-day run-in period, during which time patients continued their current ICS or protocol-allowed NCS therapy and took 1 inhalation twice a day of a single-blinded placebo BAI device. Patients on combination ICS and NCS discontinued the NCS at a prescreening visit and continued the ICS during the run-in period. Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned to 1 of 3 treatment groups:

- beclomethasone dipropionate BAI 80 mcg/day (40 mcg twice daily)
- beclomethasone dipropionate BAI 160 mcg/day (80 mcg twice daily)
- matching BAI placebo, twice daily

The treatment period lasted for 12 weeks.

The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate (80 or 160 mcg/day) administered via BAI compared with placebo treatment in patients 12 years of age and older with persistent asthma as assessed by the standardized baseline-adjusted trough morning (predose and prerescue bronchodilator) FEV_1 $AUEC_{(0\text{-}12wk)}$. Safety was assessed by monitoring adverse events, physical examination findings, oropharyngeal examination findings, and vital sign assessments.

Detailed primary and secondary endpoints are listed in Table 4.

Table 4: Primary and Secondary Endpoints of Study 304

	Study 304
Primary Endpoint	Standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)}$
Key Secondary Endpoints	Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period
	Change from baseline in weekly average of daily evening PEF over the 12-week treatment period
	Change from baseline in weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12
	Change from baseline in the total daily asthma symptom score over weeks 1 to 12
	Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma

3.2.1.3 Study BDB-AS-30039

Study BDB-AS-30039 was a 6-week, randomized, double-blind, placebo-controlled,

parallel-group study to evaluate the efficacy and safety of beclomethasone dipropionate treatment administered via BAI (320 or 640 mcg/day) or MDI (320 mcg/day) compared with placebo administered via BAI or MDI in patients 12 years of age and older with persistent asthma.

During the study patients were first randomly allocated to a device type (BAI or MDI) in a 2:1 ratio at the SV, which was maintained throughout the study.

The study consisted a 14- to 30-day run-in period, during which time patients discontinued their current asthma therapy and instead took 4 inhalations twice a day of a single-blinded placebo BAI or MDI device. Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned as follows via the IRT system:

1. Patients who were randomly assigned at SV to the BAI device were randomly assigned to 1 of 3 treatment groups at the RV:
   - beclomethasone dipropionate BAI 320 mcg/day (40 mcg/inhalation, 4 inhalations twice daily)
   - beclomethasone dipropionate BAI 640 mcg/day (80 mcg/inhalation, 4 inhalations twice daily)
   - matching BAI placebo (4 inhalations twice daily)
2. Patients who were randomly assigned at SV to the MDI device were randomly assigned to 1 of 2 treatment groups at the RV:
   - beclomethasone dipropionate MDI 320 mcg/day (40 mcg/inhalation, 4 inhalations twice daily)
   - matching MDI placebo (4 inhalations twice daily)

The treatment period lasted for 6 weeks.

The primary objective of the study was to evaluate the efficacy of beclomethasone dipropionate administered via BAI at a dose strength of 40 or 80 mcg per oral inhalation (320 or 640 mcg/day, respectively) compared with placebo treatment in patients 12 years of age and older with persistent asthma as assessed by the standardized baseline-adjusted trough morning (predose and prerescue bronchodilator) FEV_1 $AUEC_{(0\text{-}6wk)}$. Safety was assessed by monitoring adverse events, physical examination findings, oropharyngeal examination findings, and vital sign assessments.

Detailed primary and secondary endpoints are listed in Table 5.

Table 5: Primary and Secondary Endpoints of Study 30039

	Study 30039
Primary Endpoint	Standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}6wk)}$
Key Secondary Endpoints	Change from baseline in weekly average of daily trough morning PEF over the 6-week treatment period
	Change from baseline in weekly average daily trough morning FEV_1 by handheld spirometer

	over the 6-week treatment period
	Change from baseline in weekly average of total daily (24-hour) rescue medication use (number of inhalations) over 6-week treatment period
	Change from baseline in the weekly average of the total daily asthma symptom score over the 6-week treatment period
	Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma

3.2.1.4 Study BDB-AS-302

Study BDB-AS-302was a 12-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to evaluate the efficacy and safety of beclomethasone dipropionate treatment administered via BAI or MDI at dosages of 80 and 160 mcg/day in pediatric patients 4 through 11 years of age with persistent asthma.

The study consisted of a 14- to 21-day run-in period, during which time patients continued their current ICS or protocol-allowed NCS therapy and took 1 inhalation twice a day of a single-blinded placebo BAI device and 1 inhalation twice a day of a single-blinded placebo MDI device.

Patients who were being treated with ICS in combination with NCS medication discontinued the NCS therapy at a prescreening visit. Patients who were being treated with combination ICS and LABA therapy discontinued this therapy at a prescreening visit and were placed on study supplied fluticasone propionate MDI at a total dose of 176 mcg/day or equivalent and stayed on this therapy during the run-in period.

Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned to 1 of 5 treatment groups:

- beclomethasone dipropionate BAI 80 mcg/day (40 mcg twice daily) plus placebo MDI, twice daily
- beclomethasone dipropionate BAI 160 mcg/day (80 mcg twice daily) plus placebo MDI, twice daily
- beclomethasone dipropionate MDI 80 mcg/day (40 mcg twice daily) plus placebo BAI, twice daily
- beclomethasone dipropionate MDI 160 mcg/day (80 mcg twice daily) plus placebo BAI, twice daily
- matching placebo BAI (twice daily) plus placebo MDI (twice daily)

The treatment period lasted for 12 weeks.

Detailed primary and secondary endpoints are listed in Table 6.

Table 6: Primary and Secondary Endpoints of Study 302

	Study 302
Primary Endpoint	Standardized baseline-adjusted trough morning percent predicted FEV_1 $AUEC_{(0\text{-}12wk)}$
Key Secondary Endpoints	Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period
	Change from baseline in weekly average of daily evening PEF over the 12-week treatment period
	Change from baseline in weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over 12-week treatment period
	Change from baseline in the weekly average of the total daily asthma symptom score over the 12-week treatment period
	Change from baseline in trough morning FEV_1 over the 12-week treatment period
	Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma

3.2.2 Statistical Methodologies

3.2.2.1 Study 301

The efficacy analyses are conducted on the full analysis set (FAS). The FAS includes all patients in the intent-to-treat (ITT) population who receive at least 1 dose of study drug and have at least 1 post-baseline trough morning (pre-dose and pre-rescue bronchodilator) assessment of FEV_1.

The primary efficacy variable is the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV_1 $AUEC_{(0\text{-}12wk)}$. It is analyzed using an ANCOVA model with effects due to baseline trough morning FEV_1, sex, age, and treatment. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI and MDI dose versus placebo are constructed.

The estimated treatment difference between each active treatment group and the placebo group are reported with a two-sided 95% confidence interval and a p-value.

A fixed-sequence multiple testing procedure is used to interpret the results from the primary analysis while controlling the family-wise error rate at 5%.

Table 7 lists the multiple testing procedure for primary efficacy measure.

Table 7: Applicant's Testing Procedure for the Primary Efficacy Measure for Study 301

Comparisons from the ANCOVA model	Sequence
Beclomethasone dipropionate BAI 640 mcg/day vs placebo	1
Beclomethasone dipropionate BAI 320 mcg/day vs placebo	2
Beclomethasone dipropionate MDI 640 mcg/day vs placebo	3
Beclomethasone dipropionate MDI 320 mcg/day vs placebo	4

Secondary efficacy analyses use FAS population. The analysis of change from baseline value over the 12-week treatment period is performed using a MMRM with effects due to baseline, sex, age, treatment, time, and time-by-treatment interaction.

The analysis of time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period is performed using the Kaplan-Meier method. The log-rank test is used to compare the survival curves between active treatments and placebo.

Testing of secondary efficacy measures for each treatment proceeds in the sequential manner.

Figure 1 lists the multiple testing procedures for secondary efficacy measures.

Figure 1: Applicant's Testing Procedure to Adjust for Multiplicity for Study 301

Endpoint	Hypothesis Testing			
	BAI 640 vs. Placebo	**BAI 320 vs. Placebo**	**MDI 640 vs. Placebo**	**MDI 320 vs. Placebo**
Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓ →	↓ →	↓
Change from baseline in weekly average of daily evening PEF over the 12-week treatment period	↓ →	↓ →	↓ →	↓
Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol over weeks 1-12	↓ →	↓ →	↓ →	↓
Change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1-12	↓ →	↓ →	↓ →	↓
Time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period	→	→	→	□

Source: Applicant's SAP.

3.2.2.2 Study 304

The efficacy analyses are conducted on the FAS population. The FAS includes all patients in the intent-to-treat (ITT) population who receive at least 1 dose of study drug and have at least 1 post-baseline trough morning (pre-dose and pre-rescue bronchodilator) assessment of FEV_1.

The primary efficacy variable is the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV_1 $AUEC_{(0\text{-}12wk)}$. It is analyzed using an ANCOVA model with effects due to baseline trough morning FEV_1, sex, age, treatment, and current protocol allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of SV and during the run-in period and treatment. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI dose versus placebo are constructed.

The estimated treatment difference between each active treatment group and the placebo group are reported with a two-sided 95% confidence interval and a p-value.

A fixed-sequence multiple testing procedure is used for the primary analysis while controlling the family-wise error rate at 5%.

Table 8 lists the multiple testing procedure for the primary efficacy measure.

Table 8: Applicant's Testing Procedure for the Primary Efficacy Measure for Study 304

Comparisons from the ANCOVA model	Sequence
Beclomethasone dipropionate BAI 160 mcg/day vs placebo	1
Beclomethasone dipropionate BAI 80 mcg/day vs placebo	2

The secondary analyses use FAS population. The analysis of change from baseline value over the 12-week treatment period is conducted using a MMRM with effects due to baseline, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of SV and during the run-in period, treatment, time, and time-by-treatment interaction.

The analysis of time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period is performed using the Kaplan-Meier method. The log-rank test is used to compare the survival curves between active treatments and placebo.

Testing of secondary efficacy measures for each treatment proceeds in the sequential manner.

Figure 2 lists the multiple testing procedure for secondary efficacy measures.

Figure 2: Applicant's Testing Procedure to Adjust for Multiplicity for Study 304

Endpoint	Hypothesis Testing	
	BAI 160 mcg/day vs. Placebo	BAI 80 mcg/day vs. Placebo
Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓
Change from baseline in weekly average of daily evening PEF over the 12-week treatment period	↓ →	↓
Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol over weeks 1-12	↓ →	↓
Change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1-12	↓ →	↓
Time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period	↓ →	□

Source: Applicant's SAP

3.2.2.3 Study 30039

The efficacy analyses are conducted on the modified intent-to-treat (mITT) population. The mITT analysis set includes all patients in the ITT analysis set and included the available data for those patients until they discontinued study drug treatment.

There was a problem of dosage mixed up, causing a reversal dose of 320 mcg/day and 640 mcg/day, the analyses were conducted on the data where the dosage actually received.

The primary efficacy variable is the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV_1 $AUEC_{(0\text{-}6wk)}$. It is analyzed using an ANCOVA model with effects due to baseline trough morning FEV_1, sex, age, current protocol allowed asthma therapy (ICS or NCS; If a patient is on combination ICS and NCS therapy, they are stratified as an ICS patient) at the time of SV and during the run-in period, and treatment period.

The estimated treatment difference between each active treatment group and the placebo group is reported with a two-sided 95% confidence interval and the p-value. A fixed-sequence multiple testing procedure is used for the primary analysis while controlling the family-wise error rate at 5%.

Table 9 lists the multiple testing procedure for the primary efficacy measure.

Table 9: Applicant's Testing Procedure for the Primary Efficacy Measure for Study 30039

Comparisons from the ANCOVA model	Sequence
Beclomethasone dipropionate BAI 640 mcg/day vs placebo	1
Beclomethasone dipropionate BAI 320 mcg/day vs placebo	2

The secondary analyses use mITT population. The analysis of change from baseline value over the 6-week treatment period is performed using a MMRM with effects due to baseline, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of SV and during the run-in period, treatment, time, and time-by-treatment interaction.

The analysis of time to withdrawal due to meeting stopping criteria for worsening asthma during the 6-week treatment period is performed using the Kaplan-Meier method. The log-rank test is used to compare the survival curves between active treatments and placebo.

Testing of secondary efficacy measures for each treatment proceeds in the sequential manner.

Figure 3 lists the multiple testing procedure for secondary efficacy measures.

Figure 3: Applicant's Testing Procedure to Adjust for Multiplicity for Study 30039

Endpoint	Hypothesis Testing	
	BAI 640 mcg/day vs. Placebo	BAI 320 mcg/day vs. Placebo
Change from baseline in weekly average of daily trough morning PEF by handheld spirometer over the 6-week treatment period	↓ →	↓
Change from baseline in weekly average of daily trough morning FEV_1 by handheld spirometer over the 6-week treatment period	↓ →	↓
Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol over weeks 1-6	↓ →	↓
Change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1-6	↓ →	↓
Time to withdrawal due to meeting stopping criteria for worsening asthma during the 6-week treatment period	↓ →	□

Source: Applicant's SAP

3.2.2.4 Study 302

The efficacy analyses are conducted on the FAS population. The full analysis set includes all patients in the ITT population who received at least 1 dose of study drug and had at least 1 postbaseline trough morning (pre-dose and pre-rescue bronchodilator) assessment of percent predicted FEV_1.

The primary efficacy variable is the standardized baseline-adjusted trough morning percent predicted FEV_1 $AUEC_{(0\text{-}12wk)}$. It is analyzed using an ANCOVA model with effects due to baseline trough morning FEV_1, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of SV and during the run-in period, and treatment. Contrasts for pairwise comparisons of each beclomethasone dipropionate BAI and MDI dose versus placebo are constructed.

The estimated treatment difference between each active treatment group and the placebo group are reported with a two-sided 95% confidence interval and the p-value.

A fixed-sequence multiple testing procedure is used to interpret the results from the primary analysis while controlling the family-wise error rate at 5%.

Table 10 presents the multiple testing procedure for primary efficacy measure.

Table 10: Applicant's Testing Procedure for the Primary Efficacy Measure for Study 302

Comparisons from the ANCOVA model	Sequence
Beclomethasone dipropionate BAI 160 mcg/day vs placebo	1
Beclomethasone dipropionate BAI 80 mcg/day vs placebo	2
Beclomethasone dipropionate MDI 160 mcg/day vs placebo	3
Beclomethasone dipropionate MDI 80 mcg/day vs placebo	4

Secondary efficacy analyses use FAS population. The analysis of change from baseline value over the 12-week treatment period is performed using a MMRM with effects due to baseline, sex, age, current protocol-allowed asthma therapy (ICS or non-corticosteroid therapy) at the time of SV and during the run-in period, treatment, time, and time-by-treatment interaction.

The analysis of time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period is performed using the Kaplan-Meier method. The log-rank test is used to compare the survival curves between active treatments and placebo.

Testing of secondary efficacy measures for each treatment is proceed in the sequential manner.

Figure 4 describes the multiple testing procedure for secondary efficacy measures.

Figure 4: Applicant's Testing Procedure to Adjust for Multiplicity for Study 302

Endpoint	Hypothesis Testing	
	BAI 160 mcg/day vs. Placebo	BAI 80 mcg/day vs. Placebo
Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓ →	↓
Change from baseline in weekly average of daily evening PEF over the 12-week treatment period	↓ →	↓
Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol over weeks 1-12	↓ →	↓
Change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1-12	↓ →	↓
Change from baseline in trough morning FEV_1 over the 12-week treatment period	↓ →	↓
Time to withdrawal due to meeting stopping criteria for worsening asthma during the 12-week treatment period	↓ →	□

Source: Applicant's SAP

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

In this application, among the four phase 3 studies, the main reason for treatment discontinuation was lack of efficacy. Among all the treatment arms, placebo arm had the largest treatment discontinuation rate. The patient dispositions for these studies are summarized in Table 11 to Table 14.

3.2.3.1.1 Study 301

Table 11: Patient Disposition of Study 301

	BAI 320 N (%)	BAI 640 N (%)	MDI 320 N (%)	MDI 640 N (%)	Placebo N (%)	Total N (%)
Total	106 (100)	106 (100)	107 (100)	107 (100)	106 (100)	532 (100)
Randomized Set	106 (100)	106 (100)	107 (100)	107 (100)	106 (100)	532 (100)
Safety Set	106 (100)	106 (100)	107 (100)	107 (100)	106 (100)	532 (100)
Full Analysis Set	104 (98)	106 (100)	106 (99)	107 (100)	106 (100)	529 (99)
Complete Treatment	100 (94)	99 (93)	96 (90)	104 (97)	84 (79)	483 (91)
Reason for discontinuing treatment						
Adverse event	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (0)
Lack of efficacy	3 (3)	2 (2)	5 (5)	1 (1)	14 (13)	25 (5)
Lost to follow-up	0 (0)	0 (0)	1 (1)	0 (0)	3 (3)	4 (1)
Non-compliance	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	3 (1)
Protocol violation	0 (0)	1 (1)	3 (3)	1 (1)	2 (2)	7 (1)
Withdrawal by subject	3 (3)	1 (1)	1 (1)	1 (1)	2 (2)	8 (2)

3.2.3.1.2 Study 304

Table 12: Patient Disposition of Study 304

	BAI 80 N (%)	BAI 160 N (%)	Placebo N (%)	Total N (%)
Total	90 (100)	92 (100)	91 (100)	273 (100)
Randomized Set	90 (100)	92 (100)	91 (100)	273 (100)
Safety Set	90 (100)	92 (100)	91 (100)	273 (100)
Full Analysis Set	88 (98)	92 (100)	90 (99)	270 (99)
Complete Treatment	83 (92)	88 (96)	79 (87)	250 (92)
Reason for discontinuing treatment				
Adverse event	0 (0)	0 (0)	1 (1)	1 (0)
Lack of efficacy	2 (2)	0 (0)	4 (4)	6 (2)
Lost to follow-up	2 (2)	1 (1)	1 (1)	4 (1)
Non-compliance	1 (1)	0 (0)	0 (0)	1 (0)
Protocol violation	1(1)	0 (0)	2 (2)	3 (1)
Withdrawal by subject	1(1)	3 (3)	4 (4)	8 (3)

3.2.3.1.3 Study 30039

Table 13: Patient Disposition of Study 30039

	BAI 320 N (%)	BAI 640 N (%)	MDI 640 N (%)	Placebo N (%)	Total N (%)
Total	105 (100)	108 (100)	105 (100)	107 (100)	425 (100)
Randomized Set	105 (100)	108 (100)	105 (100)	107 (100)	425 (100)
Safety Set	105 (100)	108 (100)	105 (100)	107 (100)	425 (100)
Full Analysis Set	105 (100)	108 (100)	105 (100)	107 (100)	425 (100)
Complete Treatment	104 (99)	101 (94)	103 (98)	95 (89)	403 (95)
Reason for discontinuing treatment					
Adverse event	1 (1)	2 (2)	0 (0)	0 (0)	3 (1)
Lack of efficacy	0 (0)	1 (1)	1 (1)	8 (8)	10 (2)
Lost to follow-up	0 (0)	1 (1)	0 (0)	1 (1)	2 (0)
Non-compliance	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)
Other	0 (0)	1 (1)	0 (0)	0 (0)	1 (0)
Withdrawal by subject	0 (0)	2 (2)	1 (1)	2 (2)	5 (1)

3.2.3.1.4 Study 302

Table 14: Patient Disposition of Study 302

	BAI 160 N (%)	BAI 80 N (%)	MDI 160 N (%)	MDI 80 N (%)	Placebo N (%)	Total N (%)
Total	125 (100)	126 (100)	125 (100)	125 (100)	127 (100)	628 (100)
Randomized Set	125 (100)	126 (100)	125 (100)	125 (100)	127 (100)	628 (100)
Safety Set	125 (100)	126 (100)	125 (100)	125 (100)	127 (100)	628 (100)
Full Analysis Set	125 (100)	126 (100)	125 (100)	125 (100)	127 (100)	628 (100)
Complete Treatment	113 (90)	116 (92)	112 (90)	112 (90)	109 (86)	562 (89)
Reason for discontinuing treatment						
Adverse event	1 (1)	1 (1)	2 (2)	0 (0)	1 (1)	5 (1)
Lack of efficacy	4 (3)	3 (2)	5 (4)	6 (5)	6 (5)	24 (4)
Lost to follow-up	3 (2)	1 (1)	4 (3)	1 (1)	4 (3)	13 (2)
Non-compliance	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)
Protocol violation	2(2)	1(1)	0 (0)	3 (2)	0 (0)	8 (1)
Withdrawal by subject	2 (2)	3 (2)	2 (2)	3 (2)	4 (3)	14 (2)

3.2.3.2 Patient Demographic and Baseline Characteristics

Demographics and baseline characteristics data for the ITT population are summarized in Table 15 to Table 18. As expected, due to the random treatment assignment, the treatment arms are fairly balanced with respect to each factors considered.

3.2.3.2.1 Study 301

Table 15: Demographic and Baseline Characteristics by Treatment Group (ITT Population) of Study 301

	Placebo	BAI 320	BAI 640	MDI 320	MDI 640	Total
Total, n (%)	106 (100)	106 (100)	106 (100)	107 (100)	107 (100)	532 (100)
Sex, n (%)						
Male	38 (36)	37 (35)	39 (37)	42 (39)	41 (38)	197 (37)
Female	68 (64)	69 (65)	67 (63)	65 (61)	66 (62)	335 (63)
Age Group, n (%)						
12 - 17 years	4 (4)	5 (5)	7 (7)	4 (4)	6 (6)	26 (5)
18 - 64 years	94 (89)	86 (81)	92 (87)	93 (87)	92 (86)	457 (86)
>= 65 years	8 (8)	15 (14)	7 (7)	10 (9)	9 (9)	49 (9)
Race, n (%)						
White	73 (69)	85 (80)	87 (82)	89 (83)	81 (76)	415 (78)
Black	27 (26)	18 (17)	14 (13)	16 (15)	24 (22)	99 (19)
Other	6 (6)	3 (3)	5 (5)	2 (2)	2 (2)	18 (3)
Ethnicity, n (%)						
Not Hispanic or Latino	97 (92)	95 (90)	100 (94)	100 (94)	101 (94)	493 (93)
Hispanic or Latino	9 (9)	11 (10)	6 (6)	7 (7)	6 (6)	39 (7)
Age in years, mean (SD)	44 (15)	48 (16)	46 (15)	47 (15)	46 (15)	46 (15)
Weight in kg, mean (SD)	85 (25)	86 (22)	86 (22)	82 (20)	86 (20)	85 (22)
Height in cm, mean (SD)	168 (9)	169 (9)	168 (9)	167 (9)	169 (11)	168 (10)
BMI in kg/m^2, mean (SD)	30 (9)	30 (7)	30 (7)	29 (6)	30 (6)	30 (7)

Table 16: Demographic and Baseline Characteristics by Treatment Group (ITT Population) of Study 304

	Placebo	BAI 160	BAI 80	Total
Total, n (%)	91 (100)	90 (100)	92 (100)	273 (100)
Sex, n (%)				
Male	45 (50)	36 (40)	36 (39)	117 (43)
Female	46 (50)	54 (60)	56 (61)	156 (57)
Age Group, n (%)				
12 -17 years	10 (10)	8 (9)	13 (14)	30 (11)
18 -64 years	80 (88)	79 (88)	75 (82)	234 (86)
>= 65 years	2 (2)	3 (3)	4 (4)	9 (3)

Race, n (%)				
White	73 (80)	64 (71)	72 (78)	209 (77)
Black	13 (14)	17 (19)	15 (15)	44 (16)
Asian	3 (3)	2 (2)	1 (1)	6 (2)
Native Hawaiian or other PI*	1 (1)	0 (0)	0 (0)	1 (0)
Other	1 (1)	7 (8)	5 (5)	13 (5)
Ethnicity, n (%)				
Not Hispanic or Latino	81 (89)	79 (88)	83 (90)	243 (89)
Hispanic or Latino	10 (11)	11 (12)	9 (10)	30 (11)
Age in years, mean (SD)	37 (15)	39 (15)	37 (16)	38 (15)
Weight in kg, mean (SD)	82 (24)	85 (22)	80 (21)	83 (22)
Height in cm, mean (SD)	169 (9)	171 (10)	169 (9)	170 (10)
BMI in kg/m^2, mean (SD)	28 (7)	29 (8)	28 (7)	29 (7)

*PI = Pacific Islander

3.2.3.2.2 Study 30039

Table 17: Demographic and Baseline Characteristics by Treatment Group (ITT Population) of Study 30039

	Placebo	BAI 320	BAI 640	MDI 320	Total
Total, n (%)	107 (100)	108 (100)	105 (100)	105 (100)	425 (100)
Sex, n (%)					
Male	41 (38)	40 (37)	38 (36)	46 (44)	165 (39)
Female	66 (62)	68 (63)	67 (64)	59 (56)	260 (61)
Age Group, n (%)					
12 - 17 years	8 (8)	2 (2)	4 (4)	7 (7)	21 (5)
18 - 64 years	98 (92)	101 (94)	94 (90)	85 (81)	378 (89)
>= 65 years	1 (1)	5 (5)	7 (7)	13 (12)	26 (6)
Race, n (%)					
White	87 (81)	92 (85)	83 (79)	84 (80)	346 (81)
Black	15 (14)	12 (11)	19 (18)	17 (16)	63 (15)
Asian	3 (3)	1 (1)	0 (0)	1 (1)	5 (1)
American Indian or AN*	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)
Other	1 (1)	3 (3)	3 (3)	3 (3)	10 (2)
Ethnicity, n (%)					
Not Hispanic or Latino	89 (83)	90 (83)	93 (89)	88 (84)	360 (85)
Hispanic or Latino	18 (17)	18 (17)	12 (11)	17 (16)	65 (15)
Age in years, mean (SD)	39 (13)	42 (14)	43 (14)	43 (16)	42 (15)
Weight in kg, mean (SD)	84 (25)	90 (25)	86 (26)	89 (24)	87 (25)
Height in cm, mean (SD)	167 (10)	169 (9)	168 (9)	169 (9)	168 (9)
BMI in kg/m^2, mean (SD)	30 (8)	31 (8)	30 (8)	31 (8)	31 (8)

*AN = Alaskan Native

3.2.3.2.3 Study 302

Table 18: Demographic and Baseline Characteristics by Treatment Group (ITT Population) of Study 302

	Placebo	BAI 160	BAI 80	MDI 160	MDI 80	Total
Total, n (%)	127 (100)	126 (100)	125 (100)	125 (100)	125 (100)	628 (100)
Sex, n (%)						
Male	86 (68)	74 (59)	79 (63)	76 (61)	75 (60)	390 (62)
Female	41 (32)	52 (41)	46 (37)	49 (39)	50 (40)	238 (38)
Race, n (%)						
White	71 (56)	69 (55)	69 (55)	76 (61)	63 (50)	348 (55)
Black	42 (33)	34 (27)	33 (26)	37 (30)	49 (39)	95 (31)
Other	14 (11)	23 (18)	23 (18)	12 (10)	13 (10)	85 (14)
Ethnicity, n (%)						
Not Hispanic or Latino	100 (79)	89 (71)	92 (74)	100 (80)	103 (82)	484 (77)
Hispanic or Latino	27 (21)	37 (29)	33 (26)	25 (20)	22 (18)	144 (23)
Age in years, mean (SD)	8 (2)	9 (2)	8 (2)	8 (2)	8 (2)	8 (2)
Weight in kg, mean (SD)	34 (12)	35 (12)	35 (13)	34 (12)	35 (12)	35 (12)
Height in cm, mean (SD)	134 (13)	136 (14)	136 (13)	136 (12)	135 (13)	135 (13)
BMI in kg/m^2, mean (SD)	19 (4)	18 (4)	19 (4)	18 (4)	19 (4)	19 (4)

3.2.4 Results and Conclusions

Primary and secondary endpoints and analysis methods were introduced in section 3.2.2.

For study 301, the trial failed on the primary endpoint. According to the predefined testing procedure, it automatically failed on all the secondary endpoints.

Similarly, pediatric study 302 failed on the primary endpoint and all the secondary endpoints.

For study 304, both the QVAR REDIHALER 80 mcg and 160 mcg doses produced statistically significant improvements in trough $FEV_1AUEC_{(0\text{-}12wk)}$ and endpoint of change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period. For the secondary endpoints of change from baseline in weekly average of daily evening PEF over the 12-week treatment period, change from baseline in weekly average of total daily use of rescue medication over the treatment period, change from baseline in the total daily asthma symptom score over the treatment period, and time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma there were no statistically significant benefits of QVAR REDIHALER over the placebo.

For Study 30039, both the QVAR REDIHALER 320 mcg and 640 mcg doses produced statistically significant improvements in trough $FEV_1AUEC_{(0\text{-}6\ wk)}$. Both doses of QVAR REDIHALER produced statistically significant improvements in all secondary endpoints: 1) Change from baseline in weekly average of daily trough morning PEF over the 6-week treatment period. 2) Change from baseline in weekly average daily trough morning FEV_1 by handheld

spirometer over the 6-week treatment period. 3) Change from baseline in weekly average of total daily rescue medication use over the 6-week treatment period. 4) Change from baseline in the weekly average of the total daily asthma symptom score over the 6-week treatment period. 5) Time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma.

Table 19 to Table 43 summarizes the primary endpoint results and all secondary results for all four studies.

3.2.4.1 Study 301 Primary and Secondary Endpoints Results

Table 19: Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV_1 Area Under the Effect Curve From Week 0 to Week 12 (FAS)

P 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.056	0.090	0.101	0.041	0.096
Difference of LS mean from PBO: (95% CI)		0.034 (-0.027, 0.095)	0.045 (-0.015, 0.106)	-0.015 (-0.075, 0.046)	0.040 (-0.020, 0.100)
p-value		0.2720	0.1415	0.6356	0.1932

Table 20: Analysis of Change from Baseline in Weekly Average of Daily Trough Morning PEF (L/min) Over the 12-week Treatment Period (FAS)

S1 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.056	0.090	0.101	0.041	0.096
Difference of LS mean from PBO: (95% CI)		10.616 (3.489, 17.744)	8.419 (1.309, 15.530)	6.004 (-1.121, 13.129)	12.512 (5.435, 19.589)
p-value		0.0036	0.0204	0.0984	0.0006

Table 21: Analysis of Change from Baseline in Weekly Average of Daily Evening PEF (L/min) Over the 12-Week Treatment Period (FAS)

S2 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	-4.708	4.439	4.462	-0.620	5.594
Difference of LS mean from PBO: (95% CI)		9.147 (1.866, 16.429)	9.170 (1.914, 16.425)	4.088 (-3.191, 11.367)	10.301 (3.073, 17.530)
p-value		0.0139	0.0133	0.2704	0.0053

Table 22: Analysis of Change from Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 (FAS)

S3 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	0.478	-0.226	-0.213	-0.173	-0.323
Difference of LS mean from PBO: (95% CI)		-0.703 (-1.044, -0.363)	-0.691 (-1.029, -0.352)	-0.651 (-0.994, -0.309)	-0.801 (-1.138, -0.464)
p-value		<0.0001	<0.0001	0.0002	<0.0001

Table 23: Analysis of Change from Baseline in Weekly Average of Total Daily Asthma Symptom Score Over Weeks 1-12 (FAS)

S4 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
LS mean	-0.058	-0.207	-0.159	-0.247	-0.274
Difference of LS mean from PBO: (95% CI)		-0.149 (-0.265, -0.033)	-0.102 (-0.217, 0.014)	-0.189 (-0.306, -0.072)	-0.216 (-0.332, -0.101)
p-value		0.0119	0.0854	0.0016	0.0003

Table 24: Analysis of Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S5 301	Placebo	320 BAI	640 BAI	320 MDI	640 MDI
FAS Population	N = 106	N = 104	N = 106	N = 106	N = 107
Number of patients withdrawn due to meeting stopping criteria	15 (15)	3 (3)	3 (3)	5 (5)	1 (1)
Number of patients censored	91 (86)	101 (97)	103 (97)	101 (95)	106 (99)
Log-rank test p-value (compared to placebo)		0.0030	0.0030	0.0195	0.0002

3.2.4.2 Study 304 Primary and Secondary Endpoints Results

Table 25: Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV1 Area Under the Effect Curve From Time Zero to 12 Weeks (FAS)

P 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
LS mean	0.048	0.171	0.164
Difference of LS mean from PBO: (95% CI)		0.124 (0.054, 0.193)	0.116 (0.048, 0.185)

p-value		0.0005	0.0010

Table 26: Analysis of Change From Baseline in Weekly Average of Daily Trough Morning PEF (L/min) Over the 12-week Treatment Period (FAS)

S1 304	**Placebo**	**80 BAI**	**160 BAI**
FAS population	N = 90	N = 88	N = 92
LS mean	-0.795	12.849	7.116
Difference of LS mean from PBO: (95% CI)		13.645 (5.843, 21.446)	7.911 (0.202, 15.621)
p-value		0.0007	0.0443

Table 27: Analysis of Change From Baseline in Weekly Average of Daily Evening PEF (L/min) Over the 12-Week Treatment Period (FAS)

S2 304	**Placebo**	**80 BAI**	**160 BAI**
FAS population	N = 90	N = 88	N = 92
LS mean	-0.797	10.105	4.608
Difference of LS mean from PBO: (95% CI)		10.902 (2.500, 19.303)	5.405 (-2.905, 13.715)
p-value		0.0112	0.2014

Table 28: Analysis of Change From Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol Over Weeks 1-12 (FAS)

S3 304	**Placebo**	**80 BAI**	**160 BAI**
FAS population	N = 90	N = 88	N = 92
LS mean	-0.010	-0.368	-0.398
Difference of LS mean from PBO: (95% CI)		-0.358 (-0.678, -0.038)	-0.388 (-0.708, -0.068)
p-value		0.0285	0.0175

Table 29: Analysis of Change From Baseline in Weekly Average of Total Daily Asthma Symptom Scores Over Weeks 1-12 (FAS)

S4 304	**Placebo**	**80 BAI**	**160 BAI**
FAS population	N = 90	N = 88	N = 92
LS mean	-0.166	-0.293	-0.304
Difference of LS mean from PBO: (95% CI)		-0.127 (-0.255, 0.001)	-0.137 (-0.263, -0.011)
p-value		0.0509	0.0335

Table 30: Analysis of Time to Withdrawal from the Study Treatment Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S5 304	Placebo	80 BAI	160 BAI
FAS population	N = 90	N = 88	N = 92
Number of patients withdrawn due to meeting stopping criteria	5 (6)	2 (2)	0
Number of patients censored	85 (94)	86 (98)	92 (100)
Log-rank test p-value compared to placebo		0.2384	0.0208

3.2.4.3 Study 30039 Primary and Secondary Endpoints Results

Table 31: Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV1 Area Under the Effect Curve from Time Zero to 6 Weeks by Actual Treatment Received (mITT)

P 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.062	0.205	0.212	0.210
Difference of LS mean from PBO: (95% CI)		0.144 (0.0807, 0.2066)	0.150 (0.0868, 0.2132)	0.148 (0.0847, 0.2114)
p-value		< 0.0001	< 0.0001	< 0.0001

Table 32: Analysis of Change from Baseline in Weekly Average of Daily Trough Morning PEF Rate (L/min) by Handheld Spirometer over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S1 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	-10.0	20.1	11.9	10.9
Difference of LS mean from PBO: (95% CI)		30.1 (18.33, 41.90)	21.9 (10.11, 33.71)	21.0 (9.14, 32.83)
p-value		<0.0001	0.0003	0.0006

Table 33: Analysis of Change from Baseline in Weekly Average of Daily Trough Morning FEV1 (L) by Handheld Spirometer over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S2 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	-0.008	0.162	0.135	0.125
Difference of LS mean from PBO: (95% CI)		0.17 (0.0985, 0.241)	0.143 (0.0717, 0.214)	0.133 (0.0613, 0.204)
p-value		<0.0001	<0.0001	0.0003

Table 34: Analysis of Change from Baseline in Weekly Average of Total Daily (24-hour) Rescue Medication Use (Number of Inhalations) over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S3 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.37	-0.73	-0.66	-0.66
Difference of LS mean from PBO: (95% CI)		-1.10 (-1.482, -0.717)	-1.02 (-1.408, -0.640)	-1.03 (-1.415, -0.643)
p-value		<0.0001	<0.0001	<0.0001

Table 35: Analysis of Change from Baseline in Weekly Average of Total Daily Asthma Symptom Scores over the 6-Week Treatment Period by Actual Treatment Received (mITT)

S4 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
LS mean	0.06	-0.18	-0.26	-0.24
Difference of LS mean from PBO: (95% CI)		-0.25 (-0.365, -0.128)	-0.32 (-0.440, -0.203)	-0.30 (-0.423, -0.185)
p-value		<0.0001	<0.0001	<0.0001

Table 36: Analysis of Time to Patient Study Drug Treatment Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma during the 6-Week Treatment Period by Actual Treatment Received (mITT)

S5 30039	Placebo	320 BAI	640 BAI	320 MDI
mITT population	N = 107	N = 108	N = 105	N = 105
Number of patients withdrawn from study drug treatment due to meeting stopping criteria	10 (9)	1 (1)	0 (0)	1 (1)

Number of patients censored	97 (91)	107 (99)	105 (100)	104 (99)
Log-rank test p-value (compared to placebo)		0.0058	0.0014	0.0062

3.2.4.4 Study 302 Primary and Secondary Endpoints Results

Table 37: Primary Analysis of Standardized Baseline-Adjusted Trough Morning Percent Predicted FEV1 Area Under the Effect Curve from Time Zero to 12 Weeks (FAS)

P 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 113	N = 111	N = 116	N = 114	N = 114
LS mean	2.62	5.43	3.25	3.54	3.71
Difference of LS mean from PBO: (95% CI)		2.81 (0.796, 4.821)	0.63 (–1.354, 2.614)	0.92 (–1.077, 2.924)	1.09 (–0.902, 3.088)
p-value		0.0063	0.5332	0.3649	0.2823

Table 38: Analysis of Change from Baseline in Weekly Average of Daily Trough Morning PEF (L/min) over the 12-Week Treatment Period (FAS)

S1 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	4.3	15.6	12.8	11.9	10.8
Difference of LS mean from PBO: (95% CI)		11.3 (5.58, 17.06)	8.5 (2.71, 14.24)	7.6 (1.79, 13.35)	6.5 (0.71, 12.23)
p-value		0.0001	0.0041	0.0103	0.0278

Table 39: Analysis of Change from Baseline in Weekly Average of Daily Evening Peak Expiratory Flow (L/min) over the 12-Week Treatment Period (FAS)

S2 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	1.4	13.1	11.4	11.3	10.1
Difference of LS mean from PBO: (95% CI)		11.7 (5.96, 17.45)	10.0 (4.20, 15.76)	9.9 (4.11, 15.68)	8.7 (2.95, 14.49)
p-value		<0.0001	0.0007	0.0008	0.0031

Table 40: Analysis of Change from Baseline in Weekly Average of Total Daily Use of Albuterol/Salbutamol Inhalation Aerosol over Weeks 1-12 (FAS)

S3 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	-0.36	-0.72	-0.5	-0.41	-0.54
Difference of LS mean from PBO: (95% CI)		-0.36 (–0.548, -0.174)	-0.14 (–0.331, 0.044)	-0.05 (–0.240, 0.136)	-0.18 (–0.369, 0.007)
p-value		0.0002	0.132	0.5866	0.0587

Table 41: Analysis of Change from Baseline in Weekly Average of Total Daily Asthma Symptom Scores over Weeks 1-12 (FAS)

S4 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	-0.27	-0.44	-0.36	-0.31	-0.36
Difference of LS mean from PBO: (95% CI)		-0.16 (–0.261, -0.065)	-0.09 (–0.185, 0.013)	-0.04 (–0.138, 0.060)	-0.08 (–0.180, 0.017)
p-value		0.0011	0.0869	0.4388	0.1041

Table 42: Analysis of Change from Baseline in Trough Morning FEV1 (L) over the 12-Week Treatment Period (FAS)

S5 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
LS mean	0.067	0.132	0.092	0.091	0.091
Difference of LS mean from PBO: (95% CI)		0.065 (0.0174, 0.1123)	0.025 (–0.0218, 0.0721)	0.024 (–0.0228, 0.0715)	0.025 (–0.0226, 0.0719)
p-value		0.0075	0.2928	0.3112	0.3060

Table 43: Analysis of Time to Withdrawal Due to Meeting Stopping Criteria for Worsening Asthma (FAS)

S6 302	Placebo	80 BAI	160 BAI	80 MDI	160 MDI
FAS population	N = 124	N = 124	N = 122	N = 121	N = 123
Number (%) of patients withdrawn due to meeting stopping criteria	6 (5)	3 (2)	4 (3)	6 (5)	5 (4)
Number (%) of patients censored	118 (95)	121 (98)	118 (97)	115 (95)	118 (96)
Log-rank test p-value compared to placebo		0.2870	0.5257	0.9982	0.7633

3.3 Evaluation of Safety

See review of safety evaluation in the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this review, subgroup analyses were conducted on primary endpoints for both study 304 and 30039.

For the primary endpoint, subgroup analyses were performed for the following factors: sex (F, M), age (12-17, 18-64, >=65), and race (White, Black, and Other).

4.1 Sex, Race, Age, and Geographic Region

Subgroup analyses were performed on sex, race and age. Since most of the clinical trials were conducted in the USA, there were no subgroup analyses on geographic region.

The subgroups analyses results are consistent to the primary analysis results, except some of the results have large confidence intervals due to small sample size.

Figure 5: Subgroup Analysis of Primary Endpoint of 80 mcg Arm Compare to Placebo in Study 304 on Sex, Age and Race

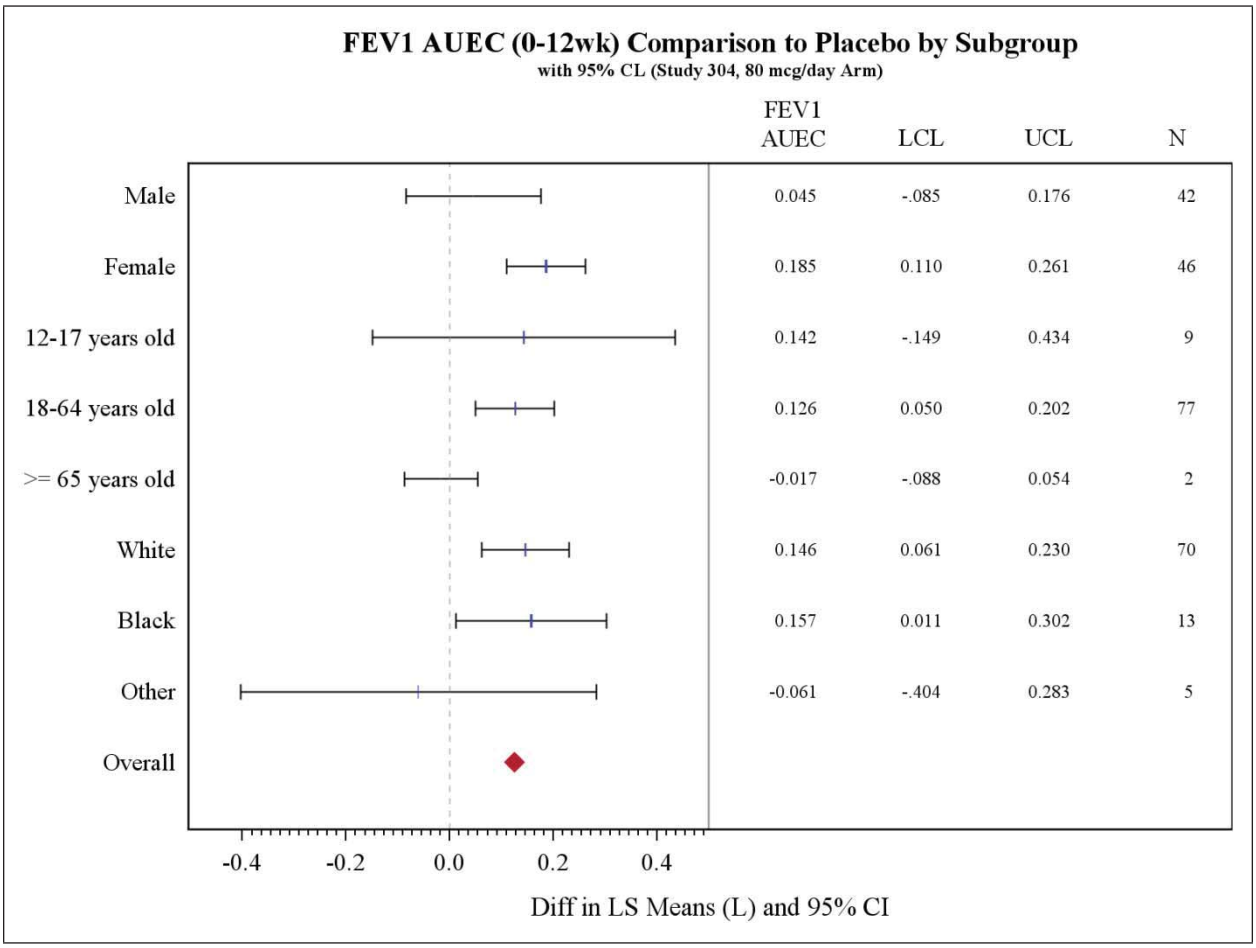


Figure 6: Subgroup Analysis of Primary Endpoint of 160 mcg Arm Compare to Placebo in Study 304 on Sex, Age and Race

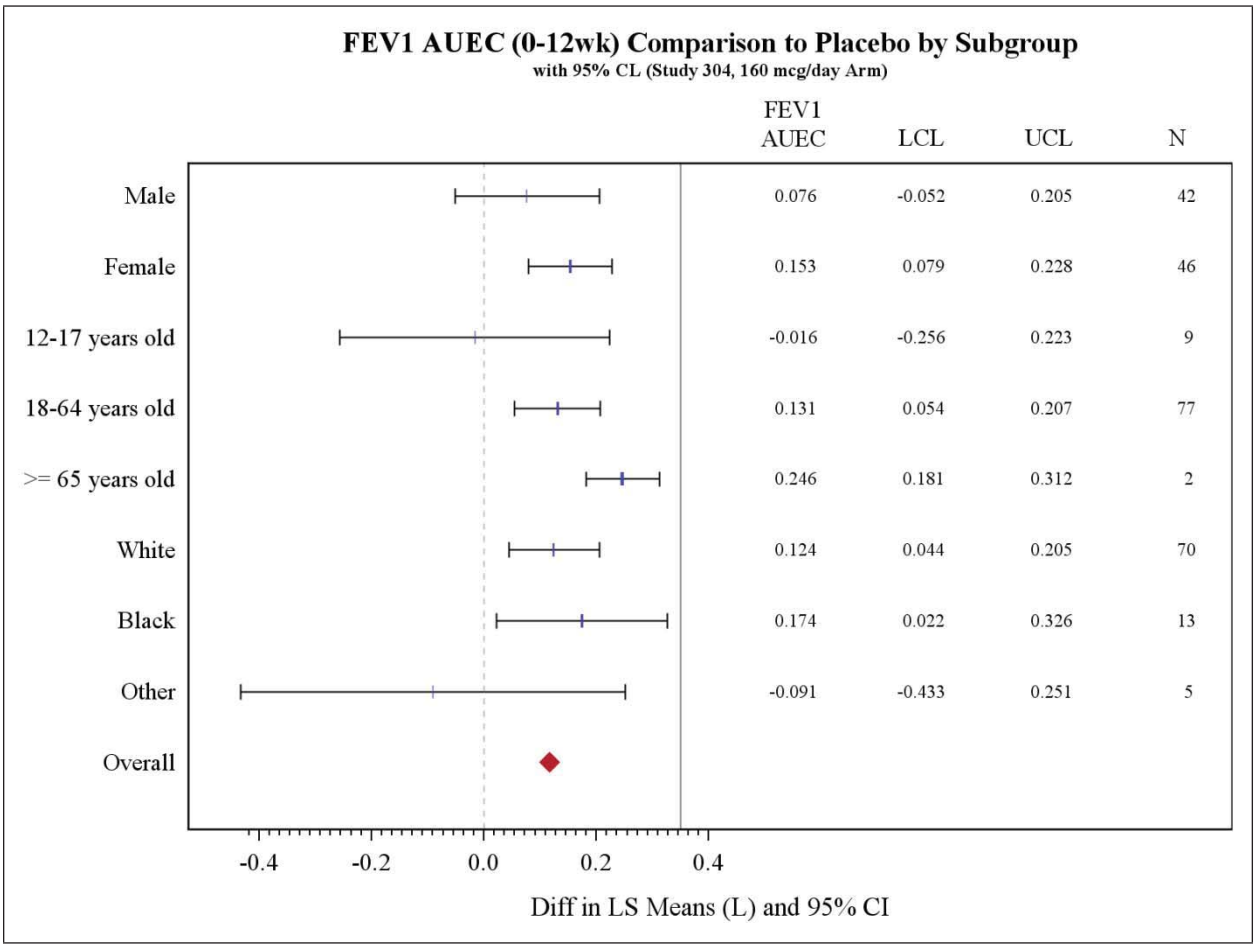


Figure 7: Subgroup Analysis of Primary Endpoint of 320 mcg Arm Compare to Placebo in Study 30039 on Sex, Age and Race

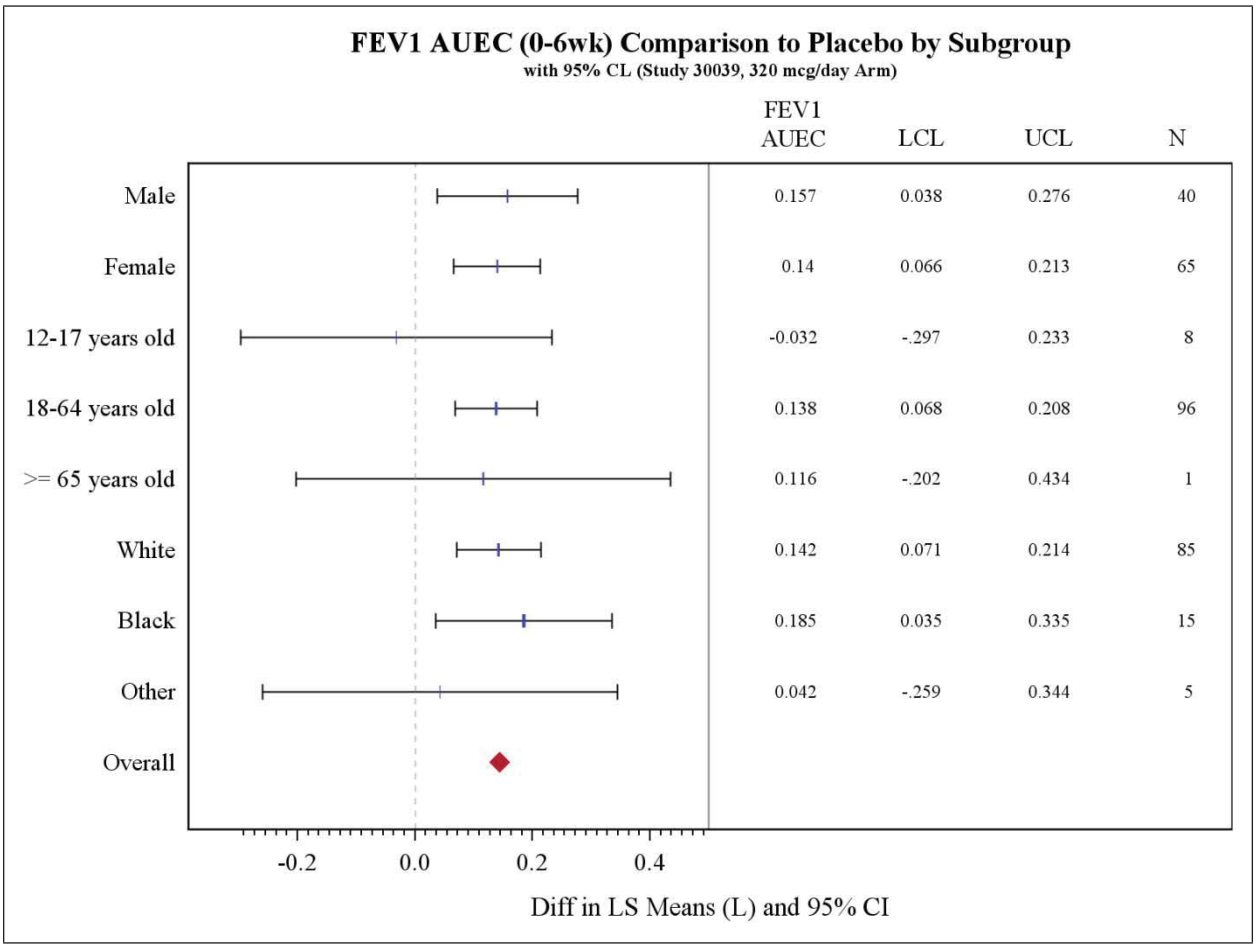
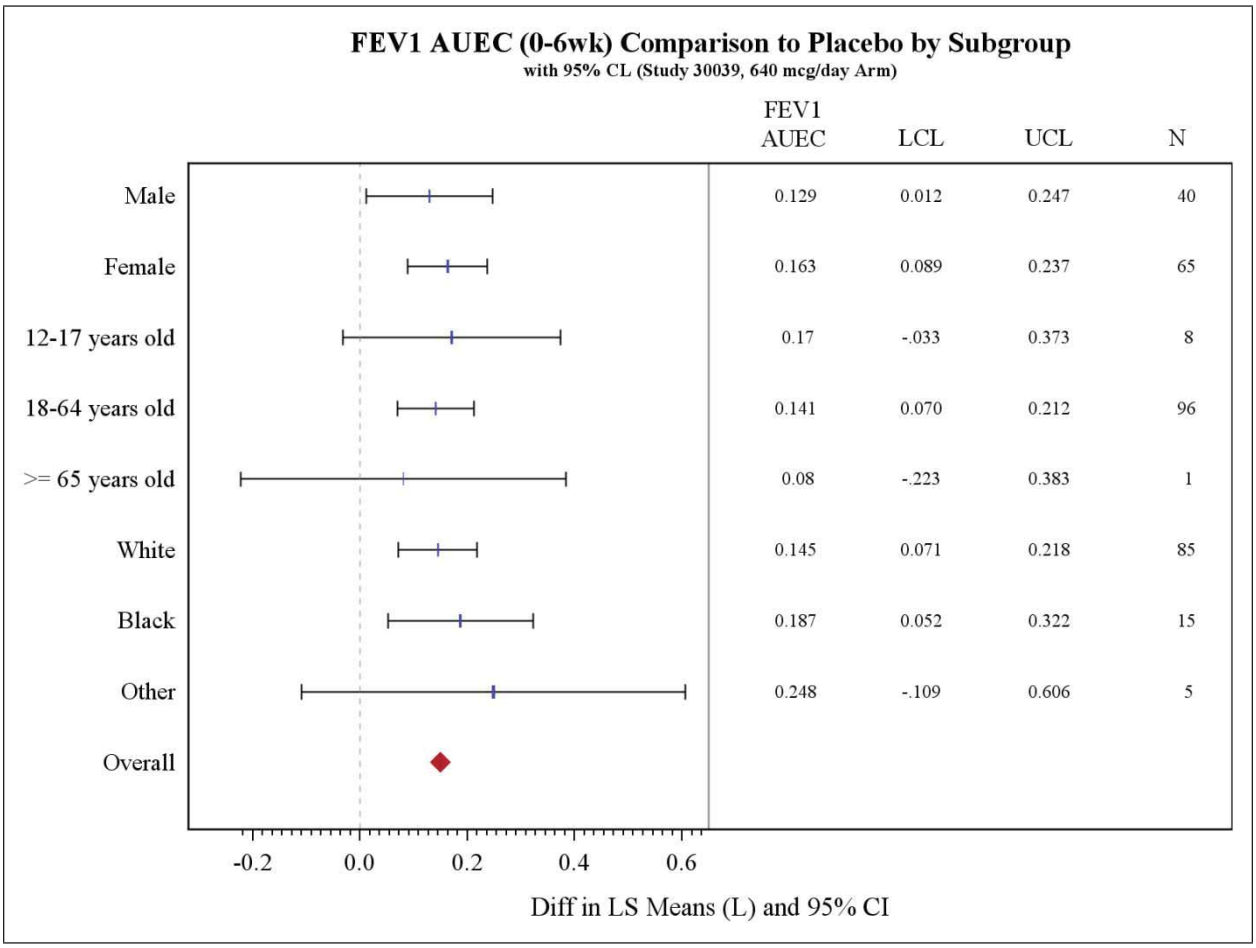


Figure 8: Subgroup Analysis of Primary Endpoint of 640 mcg Arm Compare to Placebo in Study 30039 on Sex, Age and Race



4.2 Baseline LABA Use

For study 30039, the clinical team asked sponsor to clean up the data about patient's baseline ICS/LABA use information (yes or no). Based on this newly available variable, we have conducted additional analyses to assess the baseline ICS/LABA use to the treatment effect. We conducted analyses on the ITT population on the primary endpoint standardized baseline-adjusted trough morning FEV1 area under the effect curve from time zero to 6 weeks. Due to reversal dose of 320 mcg/day and 640 mcg/day, the analyses were conducted on the data where the dosage actually received.

Following are the two analyses approaches:

1. We stratified the data into two sets, the first set includes all the subjects who did not use ICS/LABA at baseline, the second set patients used ICS/LABA at baseline. Then we used the same original ANOVA model to conduct analyses on these two sets.

2. We added baseline ICS/LABA use (yes, no) in the ANCOVA model as a covariate, in addition to baseline trough morning FEV1, sex, age, current protocol allowed asthma therapy to conduct the analyses use all data without stratification. We also include the interaction term of baseline ICS/LABA use and treatment group.

Figure 9 illustrates the analyses results using Approach 1.

Figure 10 illustrates the analyses results using Approach 2.

Figure 9 showed that patients used ICS/LABA at baseline has larger confidence interval than those who did not use ICS/LABA at baseline, but the mean values are very close to each other. Baseline ICS/LABA use or not does not cause significant differences in treatment effects.

Figure 10 showed that adding or not adding baseline ICS/LABA in the analyses model the results are very similar. Baseline ICS/LABA use is not a significant factor.

Conclusions from two approaches are consistent.

Figure 9: Comparison of Differences of FEV_1 $AUEC_{(0\text{-}6wk)}$ From Placebo in Each Dosage Arm W/ or W/O Stratification on Baseline ICS/LABA Use

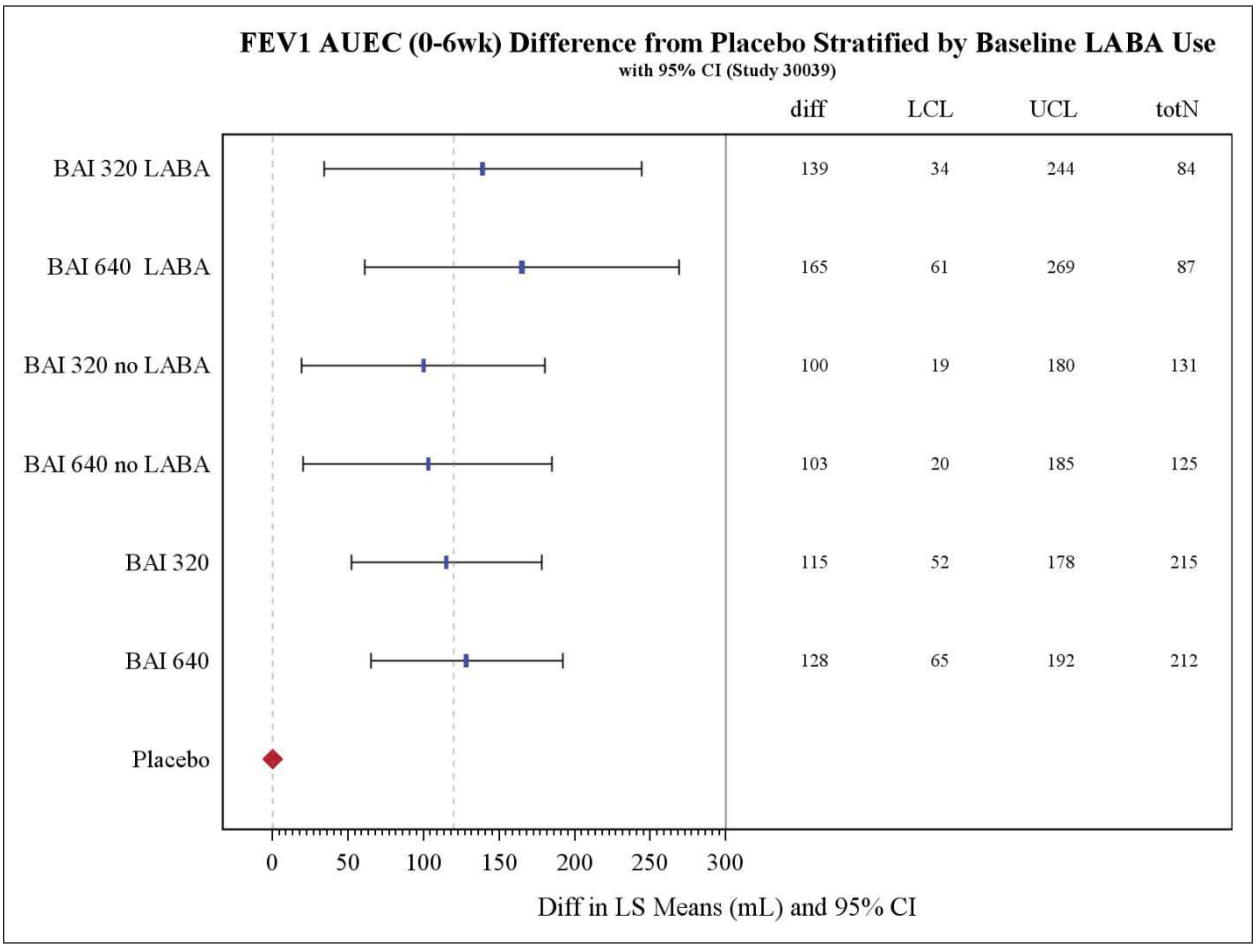
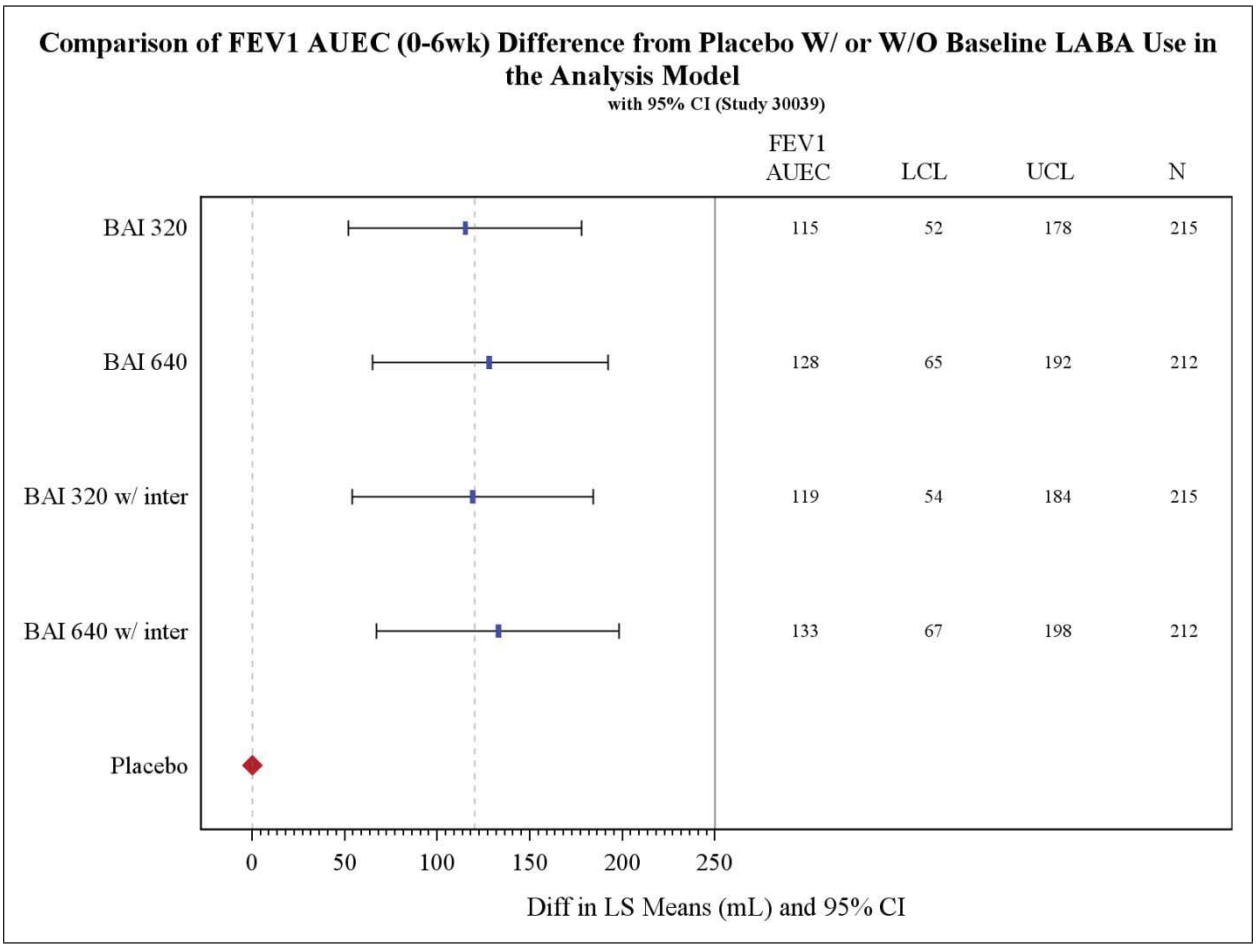


Figure 10: Comparison of Differences of FEV_1 $AUEC_{(0\text{-}6wk)}$ from Placebo Using Different Model



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

5.1.1 Missing Data and Sensitivity Analysis

For study 304 and study 30039, for analyses based on the primary efficacy variable, missing data caused by early drop out from the study was handled by penalizing the positive standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)or\ (0\text{-}6wk)}$ using a baseline observation carried forward (BOCF) method. This method assigned these patients a standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)\ or\ (0\text{-}6wk)}$ of zero. No penalty was applied to early withdrawal patients with a negative standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12wk)or\ (0\text{-}6wk)}$, and the standardized baseline-adjusted trough morning $FEV_1AUEC_{(0\text{-}12wk)\ or\ (0\text{-}6wk)}$ was derived using available data. The missing rate is small in the treatment arms with relatively higher rate in the placebo arms (Table 44). Since the analyses already used a conservative approach penalizing the missing data, we did not conduct additional sensitivity analyses.

Table 44: Missing Data in Study 304 and Study 30039

	Placebo	80 mcg	160 mcg	320 mcg	640 mcg
Study 304, n (%)	12 (13)	7 (8)	4 (4)		
Study 30039, n (%)	12 (11)			1 (1)	7 (6)

5.1.2 Subgroup Analysis

Studies 304 and 30039 were not pre-planned for subgroup analyses in terms of sample sizes. Some of the subgroups have small sample sizes and result in wide confidence interval. The direction of subgroup efficacy results are consistent with the overall results despite some of them have wide confidence intervals.

5.2 Collective Evidence

As summarized in Table 45, effectiveness of four different doses was examined: QVAR REDIHALER 80 mcg/day, QVAR REDIHALER 160 mcg/day, QVAR REDIHALER 320 mcg/day, and QVAR REDIHALER 640 mcg/day. The review focused on four phase 3 studies: study 301, study 304, study 30039, and pediatric study 302.

Study 301 and study 302 failed on the primary endpoint.

Statistically significant efficacy of QVAR REDIHALER over placebo was achieved in standardized baseline-adjusted trough morning FEV_1 $AUEC_{(0\text{-}12\ wk)\ or\ (0\text{-}6wk)}$, and change from baseline in weekly average of daily trough morning PEF over the treatment period for all four doses.

Table 45: Summary of the Key Efficacy Test Results in Study 304 and Study 30039

	Study 304		**Study 30039**	
Endpoints	**80 mcg vs. Placebo**	**160 mcg vs. Placebo**	**320 mcg vs. Placebo**	**640 mcg vs. Placebo**
FEV_1 $AUEC_{(0\text{-}12wk)\ or\ (0\text{-}6wk)}$	✓	✓	✓	✓
Morning PEF	✓	✓	✓	✓
Morning FEV_1	n/a	n/a	✓	✓
Evening PEF	×	×	n/a	n/a
Rescue Med	×	×	✓	✓
Asthma Symptom Score	×	×	✓	✓
Time to Withdrawal	×	×	✓	✓

5.3 Conclusions and Recommendations

Teva has proposed QVAR REDIHALER 80 mcg, 160 mcg, 320 mcg, and 640 mcg per day for treating patients 4 years or older with asthma.

Effectiveness and safety of four different dosages of QVAR REDIHALER were examined with this submission: QVAR REDIHALER 80 mcg/day, QVAR REDIHALER 160 mcg/day, QVAR REDIHALER 320 mcg/day, and QVAR REDIHALER 640 mcg/day. The review focused on four phase 3 studies to investigate the efficacy of QVAR REDIHALER in terms of standardized baseline-adjusted trough morning FEV_1 AUEC over the treatment period.

The contribution of QVAR REDIHALER over placebo for all major endpoints was directly examined. There is one study to support the efficacy of each proposed dose of QVAR REDIHALER over placebo in terms of standardized baseline-adjusted trough morning FEV_1 AUEC over the treatment period, and change from baseline in weekly average of daily trough morning PEF over the treatment period.

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors age, sex, race, and baseline LABA use. Almost all the subgroups have consistent results as the overall data results except some of the subgroups have wider confidence interval due to small sample sizes in these subgroups.

This submission supports effectiveness of QVAR REDIHALER 80 mcg, QVAR REDIHALER 160 mcg, QVAR REDIHALER 320 mcg, and QVAR REDIHALER 640 mcg for the treatment of patients with asthma who are 12 years or older in terms of standardized baseline-adjusted trough morning FEV1 AUEC over the treatment period, and change from baseline in weekly average of daily trough morning PEF over the treatment period. However, there is no statistically significant benefit of change from baseline in weekly average of daily evening PEF over the treatment period, change from baseline in weekly average of total daily use of rescue medication, change from baseline in the total daily asthma symptom score over the treatment period, and time to withdrawal from the study treatment due to meeting stopping criteria for worsening asthma.

Due to lack of efficacy in the pediatric study, the recommended regulatory action for this application is Approval in those age 12 years and older.

Appendix

Variable Definition:

The primary efficacy variable is the standardized baseline-adjusted trough morning (pre-dose and pre-rescue bronchodilator) FEV_1 $AUEC_{(0\text{-}12wk)}$.

The baseline trough morning FEV_1 is defined as the measurement obtained before the first dose of double-blind study treatment at RV.

Baseline-adjusted FEV_1 $AUEC_{(0\text{-}12wk)}$ will be calculated using the trapezoidal rule as follows:

$$Baseline\text{-}adjusted\ FEV_1\ AUEC_{(0\text{-}12wk)} = \sum_{i=1}^{I} \frac{f_i + f_{i-1}}{2}(t_i - t_{i-1})$$

where I is the number of non-missing time points (I<=4 for this study), and f_i is the change from baseline in through morning FEV_1 at time t_i (2, 4, 8, and 12 weeks). For AUEC calculations, t_0 will be the start time of dose administration (t_0=0), and f_0 will be 0. The intermediate missing FEV_1 measurement will be ignored in this calculation. For patients with missing baseline FEV_1, their AUEC values will be missing.

Let Y denote the standardized baseline-adjusted FEV_1 $AUEC_{(0\text{-}12wk)}$, then

$$Y = \frac{Baseline\text{-}adjusted\ FEV_1\ AUEC_{(0\text{-}12wk)}}{12}$$

To handle possible early drop out, the calculation of Y can be modified as follows

$$Y = \frac{Baseline\text{-}adjusted\ FEV_1\ AUEC_{(0\text{-}t)}}{t} \qquad [1]$$

Where

- t =12 weeks for patients who complete the FEV_1 assessment at Week 12
- t <12 weeks (2, 4, or 8 weeks) for patients who drop out early from the study

The primary analysis variable that accounts for early drop out, S, will be defined as follows:

$$S = \begin{cases} Y, & \text{if } Y \le 0 \\ Y^*P, & \text{if } Y > 0 \end{cases} \qquad [2]$$

where Y is given by equation [1], P=1, if a patient completes the study per protocol or if a patient's final FEV_1 is measured at Week 12, and P=0, otherwise. Note that S≤0 for patients without FEV_1 at Week 12 due to early drop out from the study.

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/s/

MINGYU XI
06/23/2017

YONGMAN KIM
06/23/2017
I concur.

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	207-921	**SDN**	1
Applicant	Teva Pharmaceuticals	**Submission Date**	October 1, 2016
Generic Name	Beclomethasone dipropionate	**Brand Name**	QVAR REDIHALER
Drug Class	Corticosteroid		
Indications	Treatment of asthma		
Dosage Regimen	40 – 320 µg twice daily for age ≥ 12 years 40 – 80 µg twice daily for age 4 – 11 years		
Dosage Form	Aerosol, Metered Inhalation (breath-actuated)	**Route of Administration**	Inhalation
OCP Division	2	**OND Division**	DPARP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	S.W. Johnny Lau	Bhawana Saluja
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/16/2016	**74-Day Letter Date**	12/16/2016
Review Due Date	6/29/2017	**PDUFA Goal Date**	8/3/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

The sponsor conducted 4 Phase 3 clinical studies (BDB-AS-301, BDB-AS-302, BDB-AS-304, and BDB-AS-30039).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Study BDB-AS-101
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☑ Other (e.g. dose proportionality)			Study BDB-AS-101 (160 µg vs. 320 µg)
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	See Filing Memo at the end of this review.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	Referenced the approved beclomethasone dipropionate inhalation aerosol (QVAR) data.
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Study BDB-AS-101
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Study BDB-AS-101
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Validation report LCMSD 333.1 and bioanalytical report DP-2014-049
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	The 4 Phase 3 studies (301, 302, 303, and 304) supported dosing.
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	Study BDB-AS-101

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Exempt from PREA because beclomethasone dipropionate BAI is neither a new active ingredient, indication, dosage form, dosing regimen, or route of administration per EOP2 meeting
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Formulation

The beclomethasone dipropionate breath actuated inhaler drug product tested in Study BDB-AS-101 is comparable to the to-be-marketed beclomethasone dipropionate breath actuated inhaler drug product. The sponsor addressed the changes to the breath actuated inhaler drug product tested in Study BDB-AS-101 in prior communications with the Food and Drug Administration. Thus, these changes will be review issues.

The batch size of the beclomethasone dipropionate breath actuated inhaler drug product used in Study BDB-AS-101 was (b) (4), which is the same as the to-be-marketed batch size.

The sponsor confirms that the reference product used in Study BDB-AS-101 was the U.S. QVAR® (beclomethasone dipropionate HFA) Inhalation Aerosol (NDA 020911) approved and marketed at that time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
12/01/2016

BHAWANA SALUJA
12/02/2016

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 207921
Related IND #:	IND 114865
Product Name:	QVAR REDIHALER 80, 160, 320, or 640 mcg/day
Indication:	Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older
Applicant:	Teva Branded Pharmaceutical Products R&D Inc.
Dates:	Stamp Date: 10/4/2016
Review Priority:	Standard
Biometrics Division:	Office of Biostatistics, DB II
Statistical Reviewer:	Mingyu Xi Ph.D.
Concurring Reviewers:	Gregory Levin, Ph.D. (statistical team leader)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Kathleen Donohue, M.D., Banu Karimi-Shah, M.D.
Project Manager:	Laura Musse

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
BDB-AS-304 (12/26/2013 – 12/24/2014)	MC, R, DB, PG, PC trial, 12 years of age or older (12 wks)	**A**: TV-44643 40 mcg BID N_A = 88 **B**: TV-44643 80 mcg BID N_B = 92 Placebo (P): N_P = 90	**Primary**: Standardized baseline adjusted trough morning FEV1 $AUEC_{(0\text{-}12wk)}$, **Key Secondary**: 1. Change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period 2. Change from baseline in weekly average of daily evening PEF over the 12-week treatment period. 3. Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 4. Change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and nighttime scores) over weeks 1 to 12. 5. Time to withdrawal due to worsening asthma during the 12-week treatment period.	**Primary**: A vs P: 0.124 (0.054, 0.193) P = 0.0005 B vs P: 0.116 (0.048, 0.185) P = 0.0010 **Key Secondary**: 1. A vs P: 13.645 (5.843, 21.446) P = 0.0007 B vs P: 7.911 (0.202, 15.621) P = 0.0443 2. A vs P: 10.902 (2.500, 19.303) P = 0.0112 B vs P: 5.405 (-2.905, 13.715) P = 0.2014 3. A vs P: -0.358 (-0.678, -0.038) P = 0.0285 B vs P: -0.388 (-0.708, -0.068) P = 0.0175 4. A vs P: -0.127 (-0.255, 0.001) P = 0.0509 B vs P: -0.137 (-0.263, -0.011) P = 0.0335 5[a]. A vs P: P = 0.2384

				B vs P: P = 0.0208
BDB-AS-30039 (9/16/2015 – 3/2/2016)	MC, R, DB, PG, PC trial, 12 years of age or older (6 wks)	**A**: BAI 160 mcg BID N_A = 108 **B**: BAI 320 mcg BID N_B = 105 **C**: MDI 320 mcg BID N_B = 105 Placebo (P): N_P = 107	**Primary**: Standardized baseline adjusted trough morning FEV1 $AUEC_{(0\text{-}6wk)}$, **Key Secondary**: 1. Change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period 2. Change from baseline in weekly average daily trough morning FEV1 by handheld spirometer over the 6-week treatment period 3. Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 6 4. Change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and nighttime scores) over weeks 1 to 6. 5. Time to withdrawal due to worsening asthma during the 6-week treatment period.	**Primary**: A vs P: 144 (80.7, 206.6) P < 0.0001 B vs P: 150 (86.8, 213.2) P < 0.0001 C vs P: 148 (84.7, 211.4) P < 0.0001 **Key Secondary**: 1. A vs P: 30.1 (18.33, 41.90) P < 0.0001 B vs P: 21.9 (10.11, 33.71) P = 0.0003 C vs P: 21.0 (9.14, 32.83) P = 0.0006 2. A vs P: 170 (98.5, 240.5) P < 0.0001 B vs P: 143 (71.7, 214.1) P < 0.0001 C vs P: 133 (61.3, 204.3) P = 0.0003 3. A vs P: -1.1 (-1.482, -0.717) P < 0.0001 B vs P: -1.02 (-1.408, -0.640) P < 0.0001 C vs P: -1.03 (-1.415, -0.643) P < 0.0001 4. A vs P: -0.25 (-0.365, -0.128) P < 0.0001 B vs P: -0.32 (-0.440, -0.203) P < 0.0001 C vs P: -0.30 (-0.423, -0.185) P < 0.0001 5[a]. A vs P: P = 0.0058 B vs P: P = 0.0014 C vs P: P = 0.0062
BDB-AS-301 (1/2/2014 – 11/20/2014)	MC, R, DB, DD**, PG, PC trial, 12 years of age or older (12 wks)	**A**: BAI 160 mcg BID N_A = 104 **B**: BAI 320 mcg BID N_B = 106 **C**: MDI 160 mcg BID N_c = 106 **D**: MDI 320 mcg BID N_D = 107 Placebo (P): N_P = 106	**Primary**: Standardized baseline adjusted trough morning FEV1 $AUEC_{(0\text{-}12wk)}$, **Key Secondary**: 1. Change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period 2. Change from baseline in weekly average of daily evening PEF over the 12-week treatment period. 3. Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 4. Change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and nighttime scores) over weeks 1 to 12. 5. Time to withdrawal due to worsening asthma during the 12-week treatment period.	**Primary**: A vs P: 0.034 (-0.027, 0.095) P = 0.2720 B vs P: 0.045 (-0.015, 0.106) P = 0.1415 C vs P: -0.015 (-0.075, 0.046) P = 0.6356 D vs P: 0.040 (-0.020, 0.100) P = 0.1932 **Key Secondary**: 1. A vs P: 10.616 (3.489, 17.744) P = 0.0036 B vs P: 8.419 (1.309, 15.530) P = 0.0204 C vs P: 6.004 (-1.121, 13.129) P = 0.0984 D vs P: 12.512 (5.435, 19.589) P = 0.0006 2. A vs P: 9.147 (1.866, 16.429) P = 0.0139 B vs P: 9.170 (1.914, 16.425) P = 0.0133 C vs P: 4.088 (-3.191, 11.367) P = 0.2704 D vs P: 10.301 (3.073, 17.530) P = 0.0053 3. A vs P: -0.703 (-1.044, -0.363) P < 0.0001

				B vs P: -0.691 (-1.029, -0.352) P < 0.0001 C vs P: -0.651 (-0.994, -0.309) P = 0.0002 D vs P: -0.801 (-1.138, -0.464) P < 0.0001 4. A vs P: -0.149 (-0.265, -0.033) P = 0.0119 B vs P: -0.102 (-0.217, 0.014) P = 0.0854 C vs P: -0.189 (-0.306, -0.072) P = 0.0016 D vs P: -0.216 (-0.332, -0.101) P = 0.0003 5[a]. A vs P: P = 0.0030 B vs P: P = 0.0030 C vs P: P = 0.0195 D vs P: P = 0.0002
BDB-AS-302	MC, R, DB, PG, PC trial, 4 to 11 years of age (12 wks)	**A**: BAI 40 mcg BID N_A = 111 **B**: BAI 80 mcg BID N_B = 116 **C**: MDI 40 mcg BID N_c = 113 **D**: MDI 80 mcg BID N_D = 114 Placebo (P): N_P = 112	**Primary**: Standardized baseline adjusted trough morning FEV1 $AUEC_{(0\text{-}12wk)}$, **Key Secondary**: 1. Change from baseline in weekly average of daily trough morning (pre-dose and pre-rescue bronchodilator) PEF over the 12-week treatment period 2. Change from baseline in weekly average of daily evening PEF over the 12-week treatment period. 3. Change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 4. Change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and nighttime scores) over weeks 1 to 12. 5. Change from baseline in trough morning FEV1 over the 12-week treatment period. 6. Time to withdrawal due to worsening asthma during the 12-week treatment period.	**Primary**: A vs P: 2.81 (0.796, 4.821) P = 0.0063 B vs P: 0.63 (-1.354, 2.614) P = 0.5332 C vs P: 0.92 (-1.077, 2.924) P = 0.3649 D vs P: 1.09 (-0.902, 3.088) P = 0.2823 **Key Secondary**: 1. A vs P: 11.3 (5.58, 17.06) P = 0.0001 B vs P: 8.5 (2.71, 14.24) P = 0.0041 C vs P: 7.6 (1.79, 13.35) P = 0.0103 D vs P: 6.5 (0.71, 12.23) P = 0.0278 2. A vs P: 11.7 (5.96, 17.45) P < 0.0001 B vs P: 10.0 (4.20, 15.76) P = 0.0007 C vs P: 9.9 (4.11, 15.68) P = 0.0008 D vs P: 8.7 (2.95, 14.49) P = 0.0031 3. A vs P: -0.36 (-0.548, -0.174) P = 0.0002 B vs P: -0.14 (-0.331, 0.044) P = 0.1320 C vs P: -0.05 (-0.240, 0.136) P = 0.5866 D vs P: -0.18 (-0.369, 0.007) P = 0.0587 4. A vs P: -0.16 (-0.261, -0.065) P = 0.0011 B vs P: -0.09 (-0.185, 0.013) P = 0.0869 C vs P: -0.04 (-0.138, 0.060) P = 0.4388 D vs P: -0.08 (-0.180, 0.017) P = 0.1041 5. A vs P: 0.065 (0.0174, 0.1123) P = 0.0075 B vs P: 0.025 (-0.0218, 0.0721)

P = 0.2928
C vs P: 0.024(-0.0228, 0.0715)
P = 0.3112
D vs P: 0.025 (-0.0226, 0.0719)
P = 0.3060

5[a]. A vs P: P = 0.2870
B vs P: P = 0.5257
C vs P: P = 0.9982
D vs P: P = 0.7633

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled
** DD: double dummy
[a] Log-rank test p-value

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**N/A**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**N/A**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**TBD: Whether IR for tipping point sensitivity analyses will be sent will be determined during the review**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA207921\0001\m5\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	adprim.xpt (study 304), adprim.xpt (study 30039), adprim.xpt (study 301), adprim.xpt (study 302)

Content Parameter	Response/Comments
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No initial concerns. Potential sites for inspection, if any, to be determined based on site-level summaries and discussion with the clinical team.
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

N/A

5.2. Information Requests/Review Issues

The following are potential review issues:

1. Adequacy of evidence of effectiveness for different doses in different age groups, nothing that:
    - There is evidence from only a single study supporting each of the four proposed doses in adults (study 304 and study 30039 each included two unique doses), with an additional study that did not show evidence of benefit for the two highest proposed doses (study 301)
    - A single study in pediatrics did not show convincing evidence of efficacy (Study 302; lack of statistical significance for the highest dose)

2. Adequacy of proposed labeling, including such issues as:
    - For study 304, the labeling claims a reduction in asthma symptoms but results for this secondary endpoint do not appear to be statistically significant
    - (b) (4)
    - Study 301 did not provide evidence of efficacy, and is not described in the label
    - The pediatric study 302 did not provide evidence of efficacy for the highest dose, but the proposed labeling still extends the indication to include patients as young as age 4

3. Impact of missing data: the missing data rate was about 8%, and it is unclear whether the applicant's sensitivity analysis sufficiently explore the space of plausible violations in the missing data assumptions of the primary analysis

We not have any information requests at this time, but may request additional missing data sensitivity analyses during the review.

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/s/

MINGYU XI
12/01/2016

GREGORY P LEVIN
12/01/2016

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)

Application #:	NDA 207921	**SD:**	1
Sponsor:	Teva	**eCTD:**	0001
Product:	Beclomethasone dipropionate, QVAR® Redihaler		
Reviewer:	Kathleen M. Donohue, MD, MSc	**Review Date:**	November 23, 2016

REVIEW SUMMARY: This is a medical officer filing memo for NDA 207921, Teva's 505(b)2 submission for beclomethasone dipropionate, QVAR® Redihaler, administered via a novel tidal breath inhaler. The reference product is BECLOVENT® Inhalation Aerosol (NDA 018153, GlaxoSmithKline), which is no longer marketed. The product is intended for the treatment of asthma. There are two formulations, one with 40 µg per inhalation and another with 80 µg. The intended dosing regimen is 40 to 320 µg twice daily for those age ≥ 12 years, and 40 to 80 µg for those age 4 to 11 years. See below for:

1. Internal notes from the filing meeting
2. The filing checklist
3. Slides from the filing meeting

Please convey the following comments to the sponsor in the 74 day letter:

1. The results of study 302 in pediatric patients age 4 to 11 are noted. The adequacy of the efficacy data to support an indication in pediatric patients will be a review issue.
2. Provide clarification that the Summary of Clinical Efficacy (with included hyperlinks) is intended to serve as the Integrated Summary of Efficacy (ISE). Alternatively submit the ISE or provide its location within the NDA.

OUTSTANDING ISSUES: Send comments below to Sponsor in 74 day letter

RECOMMENDED REGULATORY ACTION: Fileable

Medical Reviewer: Kathleen M. Donohue, MD, MSc

Medical Team Leader: Banu Karimi-Shah, MD

I. Filing Meeting Internal Notes

- Clinical Pharmacology - the active metabolite, 17-BMP, is bioequivalent to the reference product
- Given this, it was concluded that additional HPA axis studies or growth studies would not be needed as PMRs, as Teva could rely on the reference product for evidence of systemic safety.
- The statistics team raised concerns regarding the adequacy of the efficacy data to support the higher dose levels or a pediatric indication. In addition, there are concerns about the definition of the analysis population and the handling of missing data.
- There were several changes to the device over the course of the phase 3 studies, and more are planned prior to commercial release. CMC concluded that

these changes generally were minor, and were unlikely to be of sufficient clinical relevance to explain the contradictory efficacy findings from the clinical program.

- Human factors results are provided and DMEPA has been consulted
- CDRH has been consulted
- It was concluded that study site inspections are not needed
- Labeling review issues
    - a claim that study 30039 'improves exacerbations'
    - study 301 is not mentioned in the label
    - the need to include the pediatric study in the label (302)
    - (b) (4)

NDA/BLA Number: 207921 **Applicant: Teva** **Stamp Date: 10/1/2016**

Drug Name: beclomethasone **NDA/BLA Type: 505b2**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	✔			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	✔			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✔			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✔			
5.	Are all documents submitted in English or are English translations provided when necessary?	✔			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	✔			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✔			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	✔			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✔			Summary of clinical efficacy
10.	Has the applicant submitted a benefit-risk analysis for the product?	✔			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)2
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				BECLOVENT® Inhalation Aerosol (NDA 018153, GlaxoSmithKline) no longer marketed
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	✔			
14.	Describe the scientific bridge (e.g., BA/BE studies)				BE studies, phase 3 studies
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-	✔			PK data are acceptable as the canister is

	Content Parameter	Yes	No	NA	Comment
	ranging studies)? Study Number: 101 Treatment Arms: beclomethasone dipropionate 160 or 320 mcg via BAI or MDI				comparable to QVAR
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 - 304 Pivotal Study #2 - 30039	✔			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✔			Studies 304 and 30039 appear to meet the standard. The program also included two failed studies, studies 301 and 302
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✔			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			✔	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✔			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✔	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✔			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			✔	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✔	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	✔			MedDRA v 16.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✔			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✔			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✔			Human factors
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			✔	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✔			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm) ?			✔	Teva may rely on QVAR labeling
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✔	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			✔	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✔			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✔			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✔			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
37.	Are all datasets to support the critical safety analyses available and complete?	✔			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✔			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✔			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	✔			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	✔			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✔			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

n/a

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See summary above.

Reviewing Medical Officer Date

Clinical Team Leader Date

NDA 207921

Teva

November 18, 2016

BECLOMETHASONE FOR ASTHMA

Overview

Product beclomethasone dipropionate BAI aerosol

Indications "Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. (b) (4) [redacted]

Doses 40 to 80 mcg per puff, up to 320 mcg twice daily

Regulatory history

- 505(b)2
- Beclomethasone dipropionate via MDI approved in US since 2000, Teva
- Listed drug - BECLOVENT® Inhalation Aerosol (NDA 018153, GlaxoSmithKline) no longer marketed

Reg history - efficacy

- Endpoint changed
  - Teva planned trough FEV1 over 12 weeks
  - FDA asked (8 Dec 2014) for landmark endpoint ie trough FEV1 at a given timepoint
  - Teva agreed, mITT

BAI


QVAR
RediHaler
40 mcg
QVAR
RediHaler
40 mcg
QVAR
RediHaler
40 mcg
120

Device history

(b) (4)

Clin Pharm

- Systemic exposure is higher than for the reference product

Clinical Trials

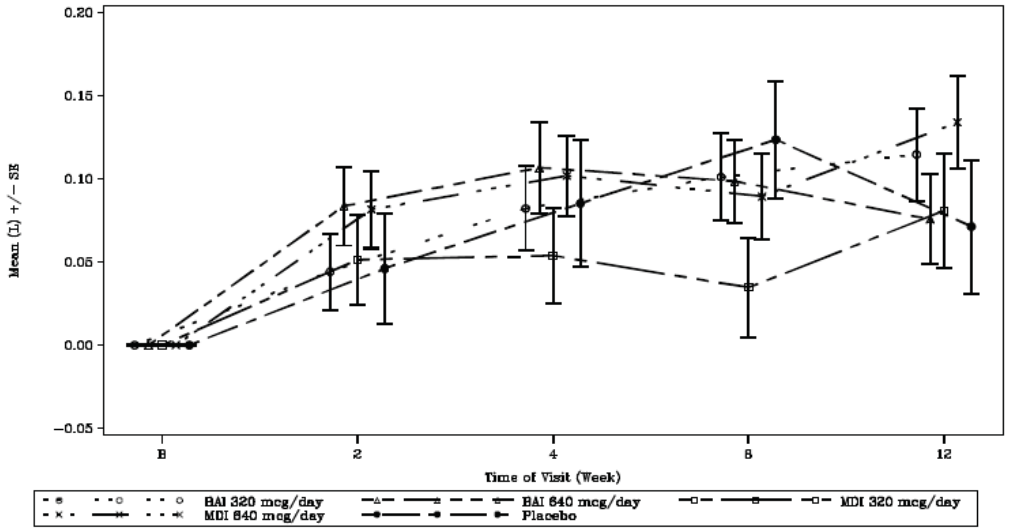
Trial	Population	N	Design	Dose (µg/day)	Wks	Endpoint
101	Healthy adults		P1 R OL XO SD	160,320 BAI, MDI		PK, safety
304	Asthma ≥ 12		P3 R DB PC PG	80, 160 BAI	12	Trough FEV_1
301	Asthma ≥ 12		P3 R DB DD PC PG	320, 640 BAI, MDI	12	NS
30039	Asthma ≥ 12		P3 R DB PC PG	BAI 320, 640 v. MDI 320	6	Trough FEV_1 *mITT
302	Asthma 4-11		P3 R DB DD PC PG	80, 160 BAI, MDI	12	Trough FEV_1

301

- P3 R DB DD PC PG 12 week study, n=529
- 135 centers Germany, Hungary, Poland, and US, Jan-Nov ‘14
- Beclomethasone 320 or 640 µg/day, BAI or MDI
- ≥ 12 years persistent asthma
  - FEV1 40 to 85%P
  - Stable dose ICS 440 mcg/day of fluticasone or equivalent or ICS/LABA for 4 weeks
  - 12% reversibility
- Did not meet primary endpoint; FEV1 values improved in the placebo group

301

Figure 3: Mean (+/-SE) Change from Baseline in Trough Morning FEV_1 (L) over 12-Week Treatment Period (Study BDB-AS-301 [FAS])



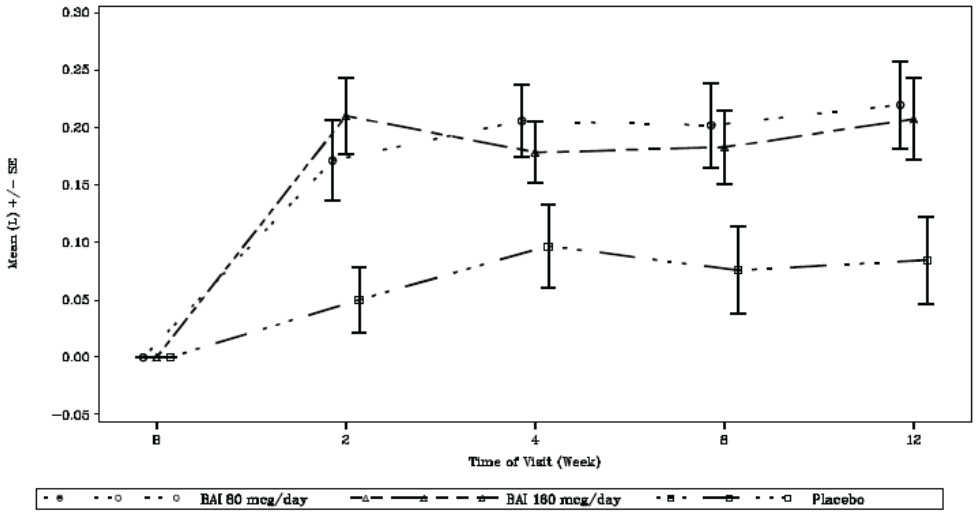
Source: Study BDB-AS-301 CSR Graph 15.1.4.
B=baseline; BAI=breath-actuated inhaler; FAS=full analysis set; FEV_1=forced expiratory volume in 1 second; MDI=metered-dose inhaler; SE=standard error.

304

- P3 R DB PC PG 12 week study, n=270
- Beclomethasone 80 or 160 µg/day, BAI
- 47 sites in the US, Dec 2013 to Dec 2014
- ≥ 12 years persistent asthma
  - ICS 220 mcg/day of fluticasone or equivalent or non ICS therapy
  - 15% reversibility

304

Figure 1: Mean (+/-SE) Change from Baseline in Trough Morning FEV_1 (L) over 12-Week Treatment Period (Study BDB-AS-304 [FAS])



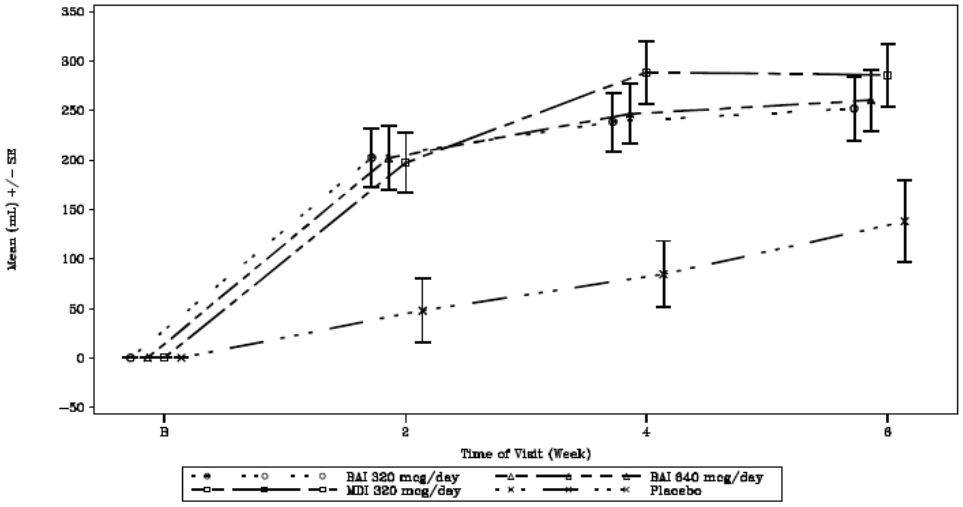
Source: Study BDB-AS-304 CSR Graph 15.1.4.
B=baseline; BAI=breath-actuated inhaler; FAS=full analysis set; FEV_1=forced expiratory volume in 1 second; SE=standard error.

30039

- P3 R DB DD PC PG 6 week, n=425
- Beclomethasone 320 or 640 µg/day BAI or 320 µg/day MDI
- Performed at 67 sites in the US, Sep ‘15-Mar ‘16
- ≥ 12 years persistent asthma
  - FEV1 50 to 100%P
  - 15% reversibility
  - Stable therapy (non ICS, ICS ± LABA)

30039

Figure 2: Mean (+/-SE) Change from Baseline in Trough Morning FEV_1 (mL) over 6-Week Treatment Period (Study BDB-AS-30039 [mITT Analysis Set])



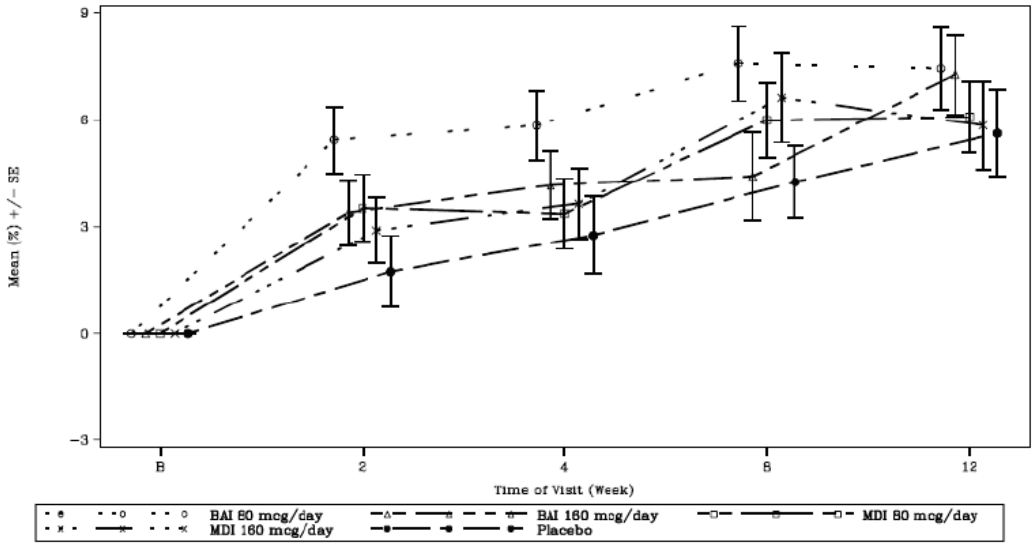
Source: Study BDB-AS-30039 CSR Graph 15.1.4a.
B=baseline; BAI=breath-actuated inhaler; FEV_1=forced expiratory volume in 1 second; MDI=metered-dose inhaler; mITT=modified intent-to-treat; SE=standard error.
Note: The placebo group for Study BDB-AS-30039 includes the placebo BAI and placebo MDI treatment groups.

302

- P3 R DB DD PC PG 12 week, n=628
- Beclomethasone 80 or 160 µg/day BAI or MDI
- 123 centers in Croatia, Mexico, Poland, Ukraine & US, Jan ‘14 to Feb ‘16
- Age 4 to 11 years with persistent asthma
- Did not meet primary endpoint

302

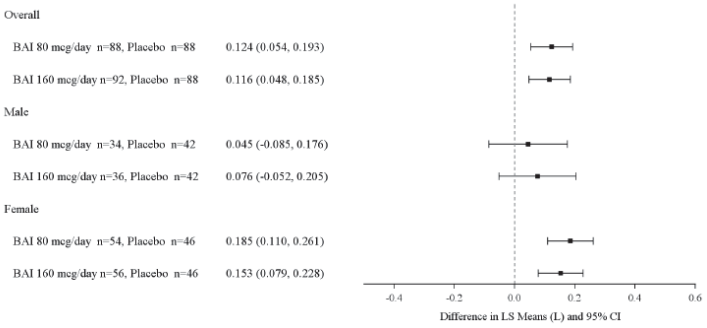
Figure 1: Mean (+/- SE) Change from Baseline in Trough Morning Percent Predicted FEV_1 over 12-Week Treatment Period (FAS)



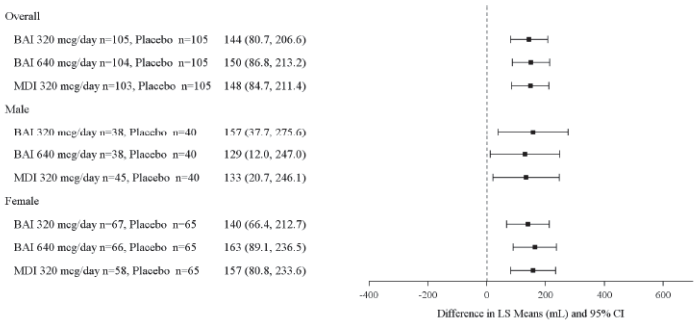
Source: Graph 15.1.4
B = baseline; BAI = breath-actuated inhaler; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; MDI = metered-dose inhaler.
Note: Peak-flow patients are not included in this analysis.

Subgroups: Sex

304



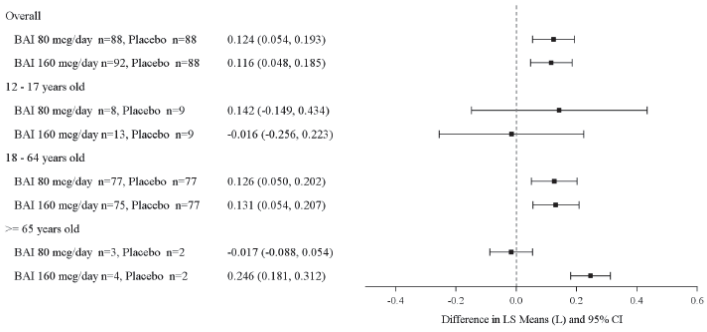
30039



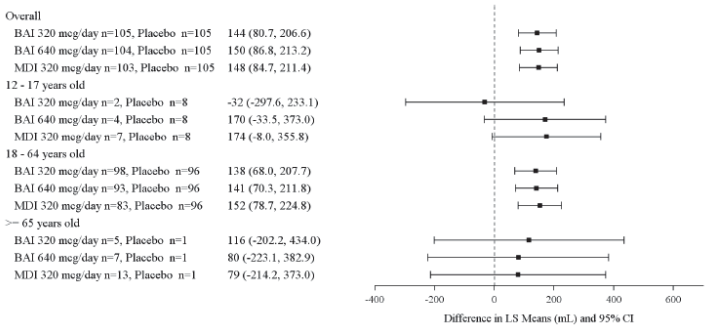
Forest Plots of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV1 AUEC(0-12wk, 304 or 0-6wk, 30039) by

Subgroups: Age

304



30039

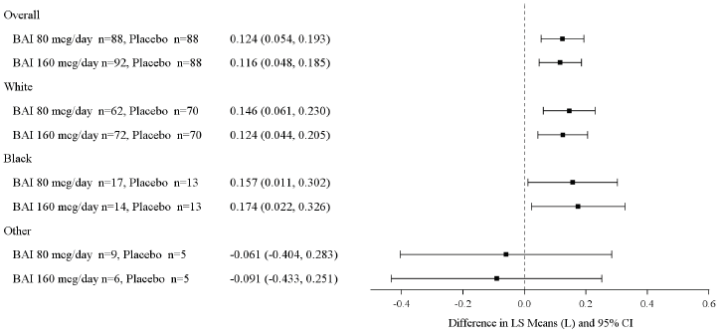


Forest Plots of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV1 AUEC(0-12wk, 304 or 0-6wk, 30039) by Age

Subgroups: Race

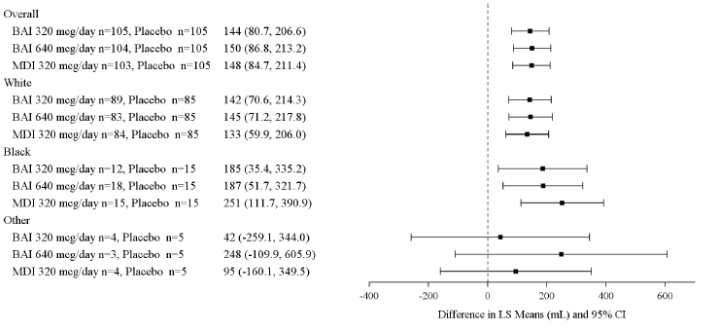
304

Figure 11: **Forest Plot of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV_1 $AUEC_{(0\text{-}12wk)}$ by Race Group (Study BDB-AS-304 [FAS])**



30039

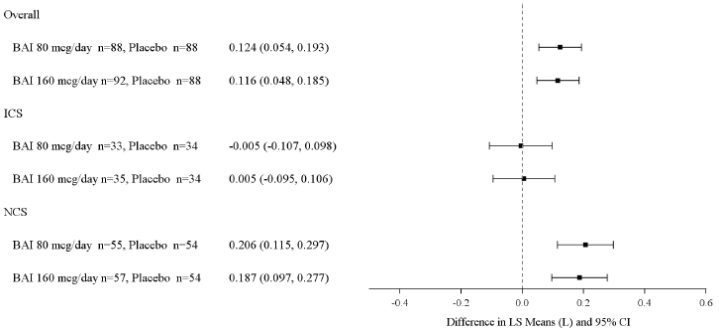
Figure 12: **Forest Plot of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV_1 $AUEC_{(0\text{-}6wk)}$ by Race Group (Study BDB-AS-30039 [mITT Analysis Set])**



Subgroups: Prior Treatment

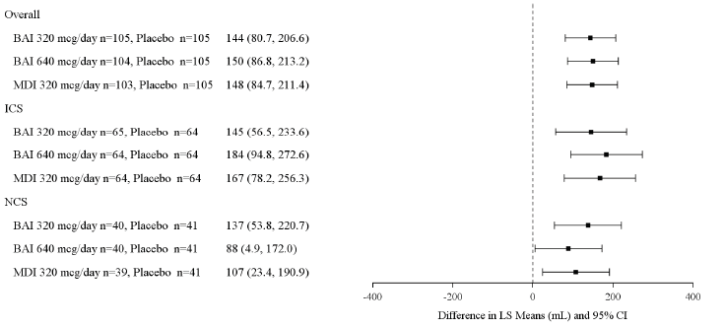
304

Figure 13: **Forest Plot of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV_1 $AUEC_{(0\text{-}12wk)}$ by Prior Asthma Therapy Group (Study BDB-AS-304 [FAS])**



30039

Figure 14: **Forest Plot of Model-Adjusted Treatment Differences and 95% CIs in Standardized Baseline-Adjusted Trough Morning FEV_1 $AUEC_{(0\text{-}6wk)}$ by Prior Asthma Therapy Group (Study BDB-AS-30039 [mITT Analysis Set])**



Safety

- No long term safety studies
- N=927 treated with BAI
- No deaths
- SAEs
  - BAI: ARF, asthma, diverticular perforation, vertigo, intentional overdose, suicidal behavior
  - MDI: pancreatitis, pharyngeal abscess
- DCs for AEs n=5 BAI, 1 placebo, none MDI

Adverse Events

incidence >3% and > placebo

Reference

- headache
- pharyngitis
- oral symptoms
- sinusitis

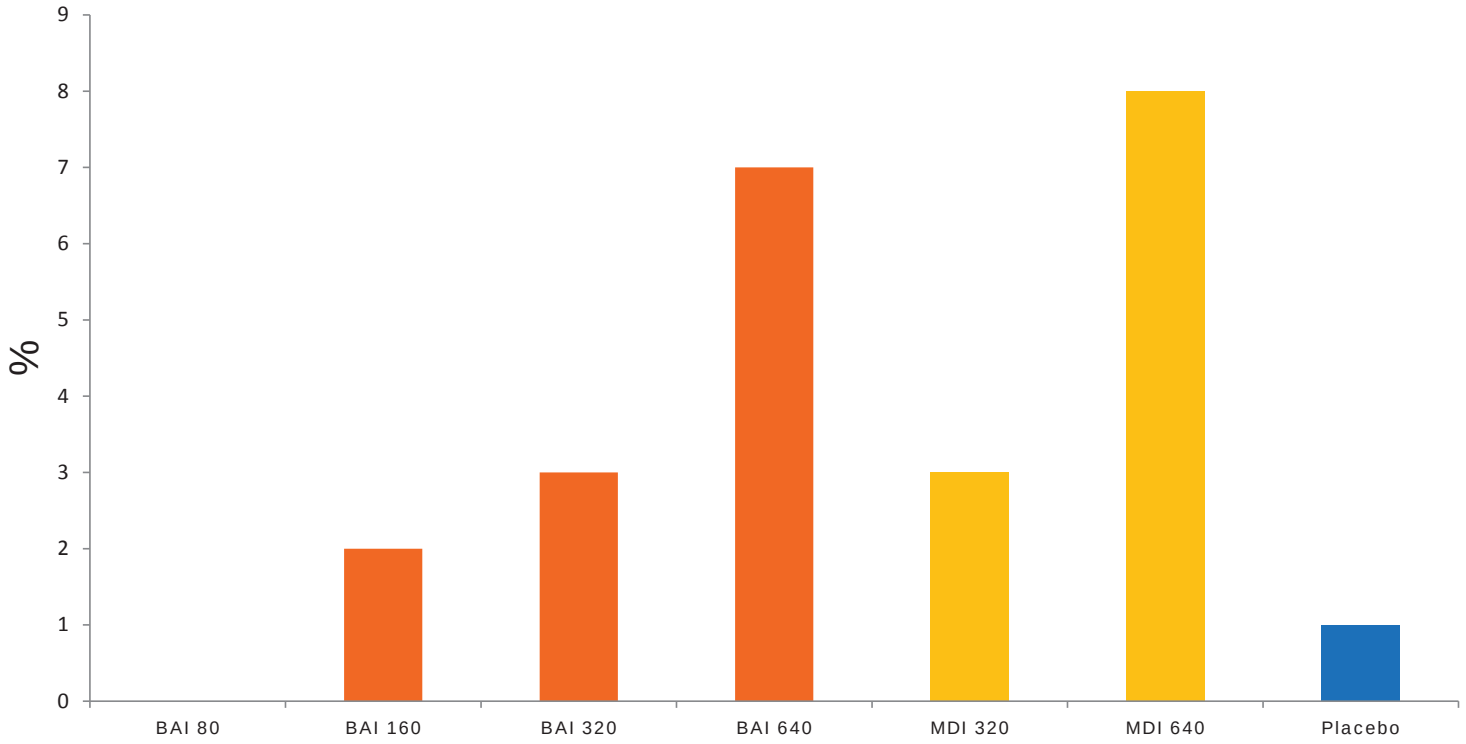
QVAR BAI

- oral candidiasis
- upper respiratory tract infection
- nasopharyngitis
- allergic rhinitis
- oropharyngeal pain
- sinusitis

Less common AEs

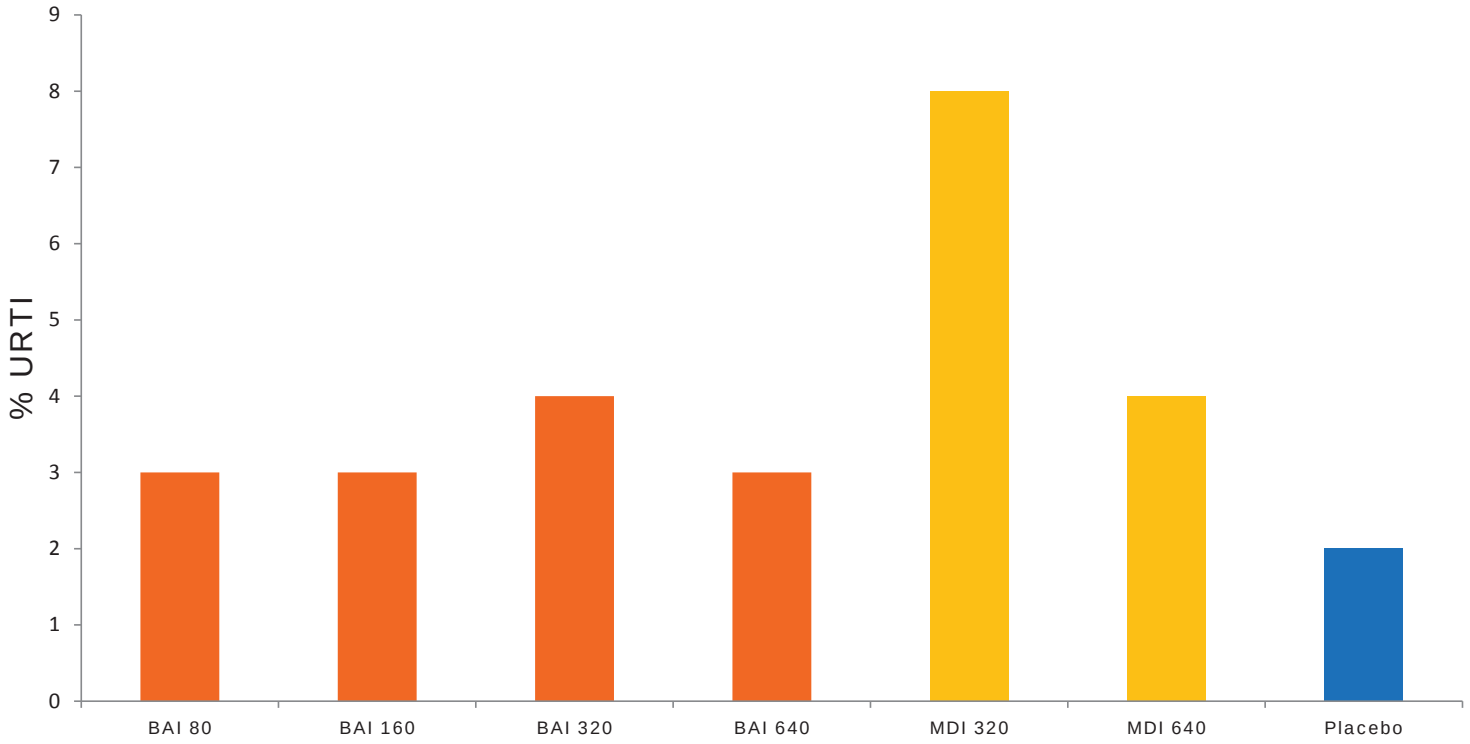
- Other adverse reactions that occurred with an incidence of 1% to 3% and at a greater incidence than placebo:
  - Back pain
  - Headache
  - Pain
  - Nausea
  - Cough

Oral candidiasis



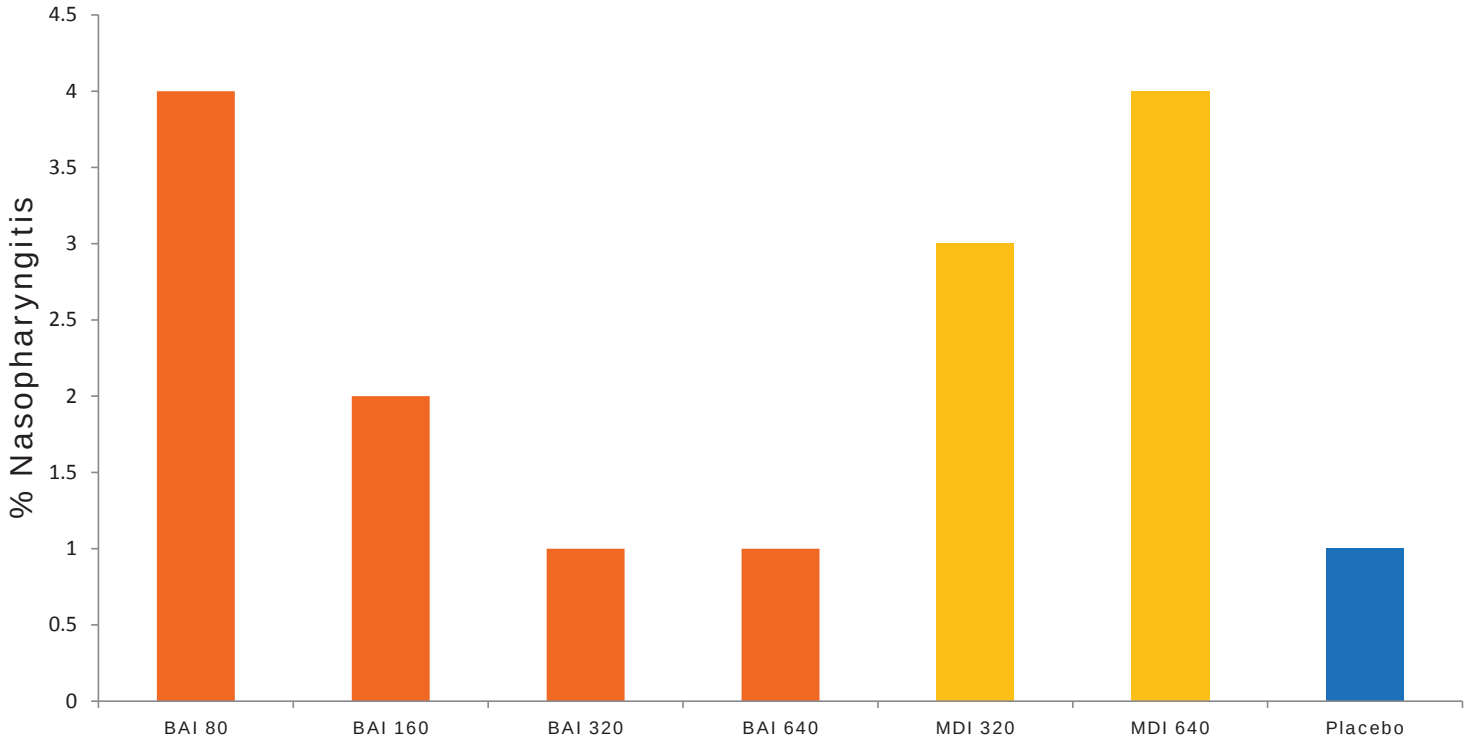
Reference ID: 4018301

URTI



Reference ID: 4018301

Nasopharyngitis



Reference ID: 4018301

Labeling

- PLLR format
- 2.2 “Improvement in lung function may also be seen as early as the first day after treatment initiation and maintained through the duration of therapy”
- 5.1 “After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.”

Proprietary Name

- Teva suggests ‘Redihaler’
- Concern re: whether that implies a fast acting rescue medication rather than a long term controller

Executive Summary

- Fileable
  - ISE, PLLR lit review
- Safety & efficacy as expected for an inhaled corticosteroid


FDA
U.S. FOOD & DRUG
ADMINISTRATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN M DONOHUE
11/23/2016

BANU A KARIMI SHAH
11/23/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207921 **Applicant: Teva** **Stamp Date: October 3, 2016**

Drug Name: TV-44643 **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. The sponsor relies on the nonclinical pharmacology/toxicology profiles of beclomethasone dipropionate as derived from previously approved product (i.e. QVAR Inhalation Aerosol, QNASL™ Nasal Aerosol, and BECLOVENT) and is supplemented by published literature.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Yes		The sponsor is using the text from RLD and other class label recommendations. The proposed sections are in accordance with 201.57 and PLLR
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	Yes		Toxicology review and risk assessment for extractables /leachables were submitted and will be reviewed.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAOCHUN CHEN
11/23/2016

CAROL M GALVIS
11/23/2016