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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: January 27, 2017

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Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 208798 and 208799

Applicant Name: Teva Respiratory, LLC

Date of Submission: March 28, 2016

PDUFA Goal Date: January 28, 2017

Proprietary Name: ArmonAir RespiClick, and AirDuo RespiClick

Established Name: Fluticasone propionate (for ArmonAir RespiClick), and
Fluticasone propionate and salmeterol (for AirDuo RespiClick)

Dosage form: Inhalation powder

Strength: Fluticasone propionate 55 mcg, 113 mcg, and 232 mcg (for
ArmonAir RespiClick), and fluticasone propionate and salmeterol
55 mcg/14 mcg, 113mcg/14 mcg, and 232 mcg/14 mcg (for
AirDuo RespiClick)

Proposed Indications: Asthma

Action: Approval

1. Introduction

Teva submitted two 505(b)(2) new drug applications for use of ArmonAir RespiClick (fluticasone propionate 55 mcg, 113 mcg, and 232 mcg, per inhalation) and AirDuo RespiClick (fluticasone propionate 55 mcg, 113 mcg, and 232 mcg, in combination with salmeterol 14 mcg, per inhalation) for the treatment of asthma in patients 12 years of age and older. The proposed dose is one inhalation twice daily. GlaxoSmithKline's (GSK's) Flovent Diskus and Advair Diskus are reference products for ArmonAir RespiClick and AirDuo RespiClick, respectively. The two applications are based on clinical efficacy and safety studies. This summary review will provide an overview of the two applications, with a focus on the clinical efficacy and safety studies.

In the NDA submissions, Teva has used some legacy approximation numbers as the nominal dose (50 mcg, 100 mcg, and 200 mcg for fluticasone propionate, and 12.5 mcg for salmeterol), which has been carried forward in some FDA reviews. In this document and also in the product labels, these legacy nominal dose numbers will not be used; rather the metered dose numbers will be used, which is the strength of the labeled dose.

2. Background

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 a combination product. 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).

Teva's proposed products ArmonAir RespiClick contains fluticasone propionate and AirDuo RespiClick contains fluticasone propionate and salmeterol, which are the same active moieties present in GSK's Flovent Diskus (fluticasone propionate) and Advair Diskus (fluticasone propionate and salmeterol), respectively. Flovent Diskus is marketed in three strengths (50 mcg, 100 mcg, and 250 mcg of fluticasone propionate) with the proposed dose of 100 mcg to 1000 mcg twice daily for patients 12 years of age and older. Advair Diskus is marketed in three strengths (100/50 mcg, 250/50 mcg, and 500/50 mcg of fluticasone propionate/salmeterol) with the proposed doses of 100/50 mcg, 250/50 mcg, and 500/50 mcg twice daily for patients 12 years of age and older. Teva's proposed fluticasone monoproduct, ArmonAir RespiClick, mirrors the three dose strengths of GSK's product Flovent diskus; however, the recommended daily dose is lower for ArmonAir RespiClick at 110 mcg to 464 mcg. For Teva's ICS/LABA product, AirDuo RespiClick, there are also three dosage strengths, similar to GSK's Advair Diskus; however, for AirDuo RespiClick, the metered doses for both active moieties is lower at the low, mid, and high dose strengths when compared to Advair Diskus. This is due to a lower salmeterol dose (approximately one-fourth of that in Advair Diskus), and the fact that salmeterol is combined with the lowest dose of fluticasone (55 mcg) in Teva's product, whereas the medium dose of fluticasone in GSK's product was carried forward into the Advair Diskus. Therefore, in AirDuo RespiClick, the metered dose of fluticasone propionate is approximately one-half of that of fluticasone propionate in Advair Diskus for the corresponding low, mid, and high dosage strengths.

Historical safety issues with the ICS component fluticasone propionate and the LABA component salmeterol are briefly discussed below, followed by a discussion of regulatory interaction between the Agency and Teva related to these applications.

Fluticasone propionate:

Corticosteroids administered systemically at large doses have a 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. Besides identifying the appropriate dose, identifying the appropriate dosing frequency of ICS is important because the same metered dose given once daily can have substantially less efficacy compared to twice daily dosing, as was seen with fluticasone propionate and ciclesonide in patients with asthma.^{1, 2} Therefore, it is important to select appropriate dose and dosing frequency with any ICS.

Salmeterol:

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.^{3, 4, 5, 6} Inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.⁷ This has been discussed at FDA Advisory Committee meetings,⁸ which has led to publications expressing concerns on safety,^{9, 10, 11} and the establishment of a safe use strategy outlined by the FDA.¹² To further assess the safety of LABAs in asthma, FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus ICSs as compared with ICSs alone.¹³ Some of these studies have been

¹ Purucker ME, Rosebraugh CJ, Zhou F, Meyer RJ. Inhaled fluticasone propionate by diskus in the treatment of asthma: A comparison of the efficacy of the same nominal dose given either once or twice a day. *Chest* 2003; 124:1584-93.

² Chowdhury BA. Ciclesonide inhalation aerosol for persistent asthma. *J Allergy Clin Immunol* 2006; 117:1194-6. And, Alvesco (ciclesonide) Inhalation Aerosol, Package Insert, Product Label, Section 14.

³ Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. *J Allergy* 1948; 19:129-140.

⁴ Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproterenol in spontaneous and induced asthma. *N Eng J Med* 1949; 240:45-51.

⁵ Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. *Thorax* 1991; 46:105-111.

⁶ Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. *N Eng J Med* 1992; 326:501-506.

⁷ US Product Labels of salmeterol and formoterol containing products.

⁸ Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.

⁹ Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. *New Eng J Med* 2005; 353:2637-2639.

¹⁰ Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. *New Eng J Med* 2009; 360:1952-1955.

¹¹ Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *New Eng J Med* 2009; 360:1671-1672.

¹² Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *New Eng J Med* 2010; 362:1169-1171.

¹³ Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *New Eng J Med* 2011; 364:2473-2475.

completed and published in the literature,^{14, 15}

(b) (4)

The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a (b) (4) higher dose caused more severe asthma exacerbation compared to the approved lower dose.¹⁶ The selection of an appropriate and safe dose is an important consideration for development of all LABAs, including salmeterol at a lower metered dose.

Relevant regulatory interactions between the Agency and Teva:

The Division and Teva had typical milestone meetings during the development of ArmonAir and AirDuo. In these meetings the scope of the program, duration of various studies, selection of dose and dosing interval were discussed and agreed upon.

3. Chemistry, Manufacturing, and Controls

ArmonAir RespiClick is provided in three different dosage strengths of 55 mcg, 113 mcg, and 232 mcg of fluticasone propionate (metered dose). Under standardized in vitro conditions, ArmonAir RespiClick delivers 51 mcg, 103 mcg, and 210 mcg of fluticasone propionate (emitted dose). AirDuo RespiClick is also provided in three different dosage strengths containing 55 mcg, 113 mcg, and 232 mcg of fluticasone propionate and 14 mcg of salmeterol base (metered dose). Under standardized in vitro conditions, AirDuo RespiClick delivers 49 mcg, 100 mcg, and 202 mcg of fluticasone propionate and 12.75 mcg of salmeterol base (emitted dose). The emitted dose for fluticasone propionate for the two products are not identical, but are close and are within 5 percent.

For the dose-ranging studies, the calculated metered doses (fluticasone propionate: 16 mcg, 28 mcg, 59 mcg, 118 mcg, 225 mcg and 434 mcg; salmeterol: 6.8 mcg, 13.2 mcg, 26.8 mcg, and 57.4 mcg) are slightly different from the actual measured metered dose for the pivotal and long-term safety studies (using the to-be-marketed product) as the formulation blend composition and dose cup size were different.

RespiClick, the delivery device for the products, is a multiple dose dry powder inhaler that Teva uses in an inhaled albuterol product (NDA 20-636 ProAir RespiClick approved in 2015). ArmonAir and AirDuo contain the active moieties of fluticasone propionate alone or fluticasone propionate in combination with salmeterol with lactose. The dry powder formulation is contained in the reservoir of RespiClick device and the device meters each dose prior to delivery. The delivery of a dose is based on a pneumatic system in the RespiClick device that is activated by the patient inhaling through the

¹⁴ Stempel DA, Rappiou IH, Kenneth MK, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *New Eng J Med* 2016; 374: 1822-1830.

¹⁵ Stempel DA, Szefer SJ, Pederson S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma; *New Eng J Med* 2016; 375: 840-849.

¹⁶ Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. *Chest* 2003; 124:70-74.

mouthpiece of the device. The device has a built in counter. The RespiClick device outwardly generally resembles a typical press-and-breathe metered dose inhaler. But, given the formulation and mechanism, RespiClick does not require priming, and should not be used with spacer or volume holding chamber. The mouthpiece needs to be kept clean and dry, and the product should not be immersed or washed with water.

Teva has submitted all data to support the quality and manufacture of the two products, and granted an expiry periods range from 12 to 17 months for the different strengths of the ArmonAir and from 19 to 22 months for the different strengths of AirDuo products. All manufacturing and testing facilities associated with these two drug product have acceptable establishment evaluation status.

4. Nonclinical Pharmacology and Toxicology

No new nonclinical studies were conducted or required to support these applications. Teva refers to Flovent Diskus and Advair Diskus that has the same active ingredients fluticasone propionate and salmeterol.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology program to support these applications was limited because a full program was conducted by GSK for fluticasone propionate and salmeterol individually and in combination. One of the aims of Teva's clinical pharmacology program was to assess systemic exposure from its product compared to the corresponding GSK products. The results showed that the systemic exposure from Teva's products was generally lower or similar compared to GSK's corresponding products. For ArmonAir RespiClick, following a single inhalation of 200 mcg, the exposure (C_{max} and AUC) of fluticasone propionate was about 20-30% lower compared to Flovent Diskus (250 mcg×2 inhalation). For AirDuo RespiClick, following a single inhalation of 200/12.5 mcg, the systemic exposure (C_{max} and AUC) of fluticasone propionate was similar to Advair Diskus (500/50 mcg×1 inhalation), while the exposure (C_{max} and AUC) of salmeterol was about 20-50% lower compared to Advair Diskus (500/50 mcg×1 inhalation).

6. Clinical Microbiology

Teva proposed an acceptable testing regimen involving the bulk drug product and the final dosage form.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Teva's clinical program provides data to support the metered dose of fluticasone propionate and salmeterol, efficacy and safety data for fluticasone propionate alone (to support ArmonAir RespiClick), and efficacy and safety data for the combination product fluticasone propionate and salmeterol (to support AirDuo RespiClick). The dosing frequency of fluticasone propionate and salmeterol was not investigated as these have been previously investigated. Some characteristics of the relevant clinical studies that

form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant dose-ranging studies and pivotal studies in patients with asthma

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
Fluticasone propionate dose-ranging studies					
Fp201 [2012- 2013]	- 12 to 81 yr - Asthma - Parallel arm, DB - 12 weeks	Fp 16 mcg BID Fp 28 mcg BID Fp 59 mcg BID Fp 118 mcg BID Flovent 100 mcg BID Placebo	103 104 104 103 104 104	FEV ₁ trough, change from baseline over 12 weeks	US, Europe, Israel (70% US)
Fp202 [2012- 2013]	- 12 to 83 yr - Asthma - Parallel arm, DB - 12 weeks	Fp 59 mcg BID Fp 118 mcg BID Fp 225 mcg BID Fp 434 mcg BID Flovent 250 mcg BID Placebo	107 107 106 107 107 106	FEV ₁ trough, change from baseline over 12 weeks	US, Canada, Europe, Israel, New Zealand (56% US)
Salmeterol dose-ranging study					
FSS201 [2013]	- 13 to 86 yr - Asthma - Crossover, open label - Single dose	FpS 1118/0 mcg FpS 1118/6.25 mcg FpS 1118/12.5 mcg FpS 1118/25 mcg FpS 118/50 mcg Advair 100/50 mcg	67 68 69 67 68 66	FEV ₁ AUC 0-12 hr	US
Fluticasone propionate plus salmeterol pivotal bronchodilator (or lung function) studies					
301 [2014- 2015]	- 12 to 86 yr - Asthma - Parallel arm, DB - 12 weeks	FpS 55/14 mcg BID FpS 113/14 mcg BID Fp 55 mcg BID Fp 113 mcg BID Placebo	129 129 129 130 130	FEV ₁ trough, change from baseline at week 12 Δ FEV ₁ AUC 0-12 hr at week 12	US, Canada, Europe, South Africa (56% US)
30017 [2014- 2015]	- 12 to 84 yr - Asthma - Parallel arm, DB - 12 weeks	FpS 113/14 mcg BID FpS 232/14 mcg BID Fp 113 mcg BID Fp 232 mcg BID Placebo	145 146 146 146 145	FEV ₁ trough, change from baseline at week 12 Δ FEV ₁ AUC 0-12 hr at week 12	US, Canada, Europe, South Africa (59% US)
Fluticasone propionate plus salmeterol supportive long-term safety study					
305 [2014- 2015]	- 12 to 79 yr - Asthma - Parallel arm, OL - 26 weeks	FpS 113/14 mcg BID FpS 232/14 mcg BID Fp 113 mcg BID Fp 232 mcg BID Flovent 110 mcg BID Flovent 220 mcg BID Advair 250/50 mcg BID Advair 500/50 mcg BID	120 133 127 126 42 41 41 44	Safety (primary) Δ FEV ₁ trough, over 26 weeks (secondary)	US
* Study ID shown (top to bottom) as Teva's study number, and year [year study started-completed] † DB=double blind; OL=open label ‡ Fp=fluticasone propionate in RespiClick device; FpS=fluticasone propionate plus salmeterol in RespiClick device; Note that the dose-ranging studies reflect a calculated metered dose, which differ from the pivotal and long-term safety studies (using the to-be-marketed product) as the formulation blend composition and dose cup size were different. § Intent to treat ¶ Primary efficacy variables are shown.					

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
Fluticasone propionate dose-ranging studies					
// Europe included Bulgaria, Croatia, Czech Republic, Germany, Greece, Hungary, Poland, Romania, Russia, Serbia, Spain, Ukraine					

b. Design and conduct of the studies

Fluticasone propionate and salmeterol dose ranging studies in asthma:

These studies were conducted in patients with persistent asthma with varying severity. Study treatment arms and primary efficacy variable are shown in Table 1.

ArmonAir RespiClick (fluticasone propionate) and AirDuo RespiClick (fluticasone propionate plus salmeterol) studies in asthma:

The bronchodilator (or lung function) studies were similar in design with differences in study treatment arms, and of disease severity. Patients eligible for the studies were required to have a diagnosis of asthma per standard and accepted definition with predefined FEV₁ bounds, and bronchodilator reversibility of at least 12% and 200 mL of FEV₁. Eligible patients entered a run-in period, and at the end of the run-in period patients were randomized to different treatment arms as shown in Table 1. Study treatment arms and primary efficacy variables are shown in Table 1.

The open label long-term study was designed to primarily provide 6-month safety data of the products. Efficacy was measured as a secondary endpoint.

c. Efficacy findings and conclusions

The clinical program is adequate to support efficacy of ArmonAir RespiClick (fluticasone propionate) 55 mcg, 113 mcg, and 232 mcg, and AirDuo RespiClick (fluticasone propionate and salmeterol) 55/14 mcg, 113/14 mcg, and 232/14 mcg for twice-daily treatment of patients 12 years of age and older with asthma.

Fluticasone propionate dose ranging in asthma:

In the dose ranging studies, trough FEV₁ responses showed efficacy across a range of doses (Figure 1). In study 201, all doses with the exception of the lowest dose were statistically significantly different from placebo, with a dose response, and treatment effect size ranging from 52 to 148 mL. In study 202, there was some evidence of dose response, but no treatment group demonstrated a statistically significant difference compared to placebo. This was likely due to a large number of study patients discontinuing the study due to meeting the study specified stopping criteria of FEV₁ decrease of less than 80% predicted (31% of placebo, 12-18% of active treatment).

Results in Figure 1 are shown as over 12 weeks, which was the primary analysis specified in the protocol. Results on landmark analysis (our preferred analysis), such as at 12 weeks, showed similar results. These data, along with results of Study 30017 (discussed below) that included higher doses of fluticasone propionate, support the fluticasone propionate doses of 55 mcg, 113 mcg, and 232 mcg.

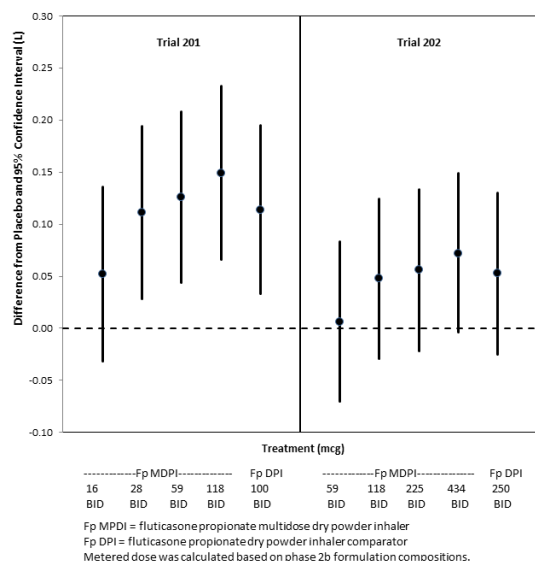


Figure 1. Change from baseline trough FEV₁ (L) over the 12-week treatment period

Salmeterol dose ranging in asthma:

In the dose ranging study, different doses of salmeterol showed a dose related increase in FEV₁ response with all doses statistically significantly different from placebo (Figure 2). The salmeterol dose of 14 mcg for the Teva's product was most comparable to the GSK's Advair Diskus 50 mcg dose (193 mL vs 197 mL, respectively). Results of this study support the salmeterol dose of 14 mcg for the Teva's product.

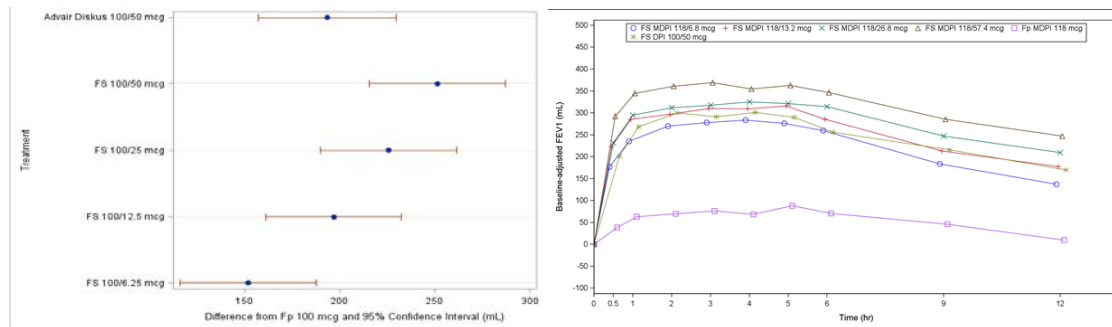


Figure 2. Mean change in FEV₁ AUC 0-12 hr (left panel) and over 12 hours (right panel) after dosing.

ArmonAir RespiClick (fluticasone propionate) and AirDuo RespiClick (fluticasone propionate and salmeterol) in asthma:

Fluticasone propionate as a single ingredient product and in combination with salmeterol has been studied extensively by GSK and others in the past. Both (fluticasone propionate, fluticasone propionate in combination with salmeterol) are approved marketed products for asthma. Teva's development program was designed to support the marketing of these same ingredients, but at lower metered doses. The dose ranging studies discussed above support the doses for Teva's products as noted above. The essence of the pivotal studies for ArmonAir (fluticasone propionate) was to confirm and demonstrate sustained efficacy with incremental benefit with higher doses over a longer treatment period. The essence of the pivotal studies for AirDuo (fluticasone propionate and salmeterol) was to demonstrate added benefit of salmeterol over fluticasone propionate and vice versa (contribution of the components; direct comparison of fluticasone propionate over salmeterol is not available due to the study design as discussed below). The efficacy parameter of interest studied in the pivotal studies is bronchodilation (lung function) benefit.

ArmonAir RespiClick (fluticasone propionate) in asthma:

The efficacy measure of interest for fluticasone propionate in asthma is trough FEV₁ compared to placebo. Results of this finding are shown in Table 2. All doses of fluticasone propionate showed statistically significant difference in trough FEV₁ over placebo at the landmark analysis time point of week 12. There were numerical trends in higher FEV₁ response with higher dose compared to lower dose in both the studies. Secondary measures of efficacy, such as trough FEV₁ at earlier time points, peak expiratory flow measures, rescue albuterol use, patient withdrawal for worsening asthma, AQLQ, etc., were generally supportive of efficacy.

Table 2. Change from baseline in trough FEV₁ at week 12

Treatment *	N	Change (mL)	Diff from Placebo (95% CI)	P value	Diff from Fp (95% CI)	P value
Study 301						
Fp 55	128	172	119 (25, 212)	0.013	-	-
Fp 113	129	204	151 (57, 244)	0.002	-	-
FpS 55/14	128	319	266 (172, 360)	<0.001	147 (53, 242)	0.002
FpS 113/14	126	315	262 (168, 356)	<0.001	111 (17, 206)	0.02
Placebo	129	53	-	-	-	-
Study 30017						
Fp113	145	119	123 (38, 208)	0.005	-	-
Fp 232	146	179	183 (98, 268)	<0.001	-	-
FpS 113/14	141	271	274 (189, 360)	<0.001	152 (66, 237)	<0.001
FpS 232/14	145	272	276 (191, 361)	<0.001	93 (9, 178)	0.031
Placebo	143	0	-	-	-	-
* Fp=fluticasone propionate in RespiClick device; FpS=fluticasone propionate plus salmeterol in RespiClick device;						

AirDuo RespiClick (fluticasone propionate and salmeterol) in asthma:

Studies conducted to support combination products typically compare the combination to each component to show the contribution of each component, or, in other words, to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination that would justify the use of the combination product. Studies 301 and 30017 compared AirDuo RespiClick to fluticasone propionate, and also compared two doses of AirDuo RespiClick. For a combination product such as AirDuo RespiClick, the peak FEV₁ effect is expected to be primarily from salmeterol, and trough FEV₁ effect is expected to be primarily from fluticasone propionate.

The primary efficacy variable of FEV₁ AUC 0-12 hours is intended to show the benefit of AirDuo RespiClick over fluticasone propionate alone (show contribution of salmeterol in the combination). Results from the analysis of this efficacy variable are shown in Table 3. Results from the analysis showed a statistically significant difference between AirDuo RespiClick 55/14 mcg or 113/14 or 232/14 and fluticasone propionate at the corresponding 55 mcg or 113 mcg or 232 mcg doses, respectively (Table 3). The submitted data are adequate to show the benefit of AirDuo RespiClick over fluticasone propionate (contribution of salmeterol).

Table 3. Change from baseline in FEV₁ AUC 0-12 hour at week 12, serial spirometry subset

Treatment *	N	Change (mL)	Diff from Placebo (95% CI)	P value	Diff from Fp (95% CI)	P value
Study 301						
Fp 55	63	268	-	-	-	-
Fp 113	72	254	-	-	-	-
FpS 55/14	56	399	325 (203, 447)	<0.001	131 (11, 250)	0.032
FpS 113/14	61	408	335 (216, 453)	<0.001	154 (41, 267)	0.008
Placebo	60	74	-	-	-	-
Study 30017						
Fp113	64	260	-	-	-	-
Fp 232	61	267	-	-	-	-
FpS 113/14	58	442	322 (212, 432)	<0.001	182 (74, 291)	<0.001
FpS 232/14	68	446	326 (221, 431)	<0.001	179 (74, 285)	0.031
Placebo	61	121	-	-	-	-

* Fp=fluticasone propionate in RespiClick device; FpS=fluticasone propionate plus salmeterol in RespiClick device;

The primary efficacy variable of change in trough FEV₁ is intended to show the benefit of AirDuo RespiClick over salmeterol alone (show contribution of fluticasone propionate in the combination). Results from the analysis of this efficacy variable are shown in Table 2 above. The studies understandably do not have salmeterol only treatment arm because of the safety risk of serious asthma exacerbation with LABA monotherapy. Such direct comparison between AirDuo RespiClick and salmeterol would be ideal to evaluate the contribution of fluticasone propionate; however, clinically it is not necessary (to directly show contribution of fluticasone propionate) because efficacy of fluticasone propionate in the RespiClick device at various doses for patients with asthma is already demonstrated as discussed above; all drug formulations are in the same RespiClick device

and have the same lactose base formulation; in vitro and delivery characteristics do not suggest drug-drug interactions in the device, delivery path of the drug product, or in vivo in the body; and the two studies 301 and 30017 each have included two doses of AirDuo RespiClick from which the comparative efficacy between the two doses (differ in fluticasone propionate doses) can be gleaned. Based on this totality of evidence it can be concluded that the benefit of AirDuo RespiClick over salmeterol (contribution of fluticasone propionate) has been demonstrated.

Secondary measures of efficacy in studies 301 and 30017, such as FEV₁ measures at earlier time points, peak expiratory flow measures, rescue albuterol use, patient withdrawal for worsening asthma, AQLQ, etc., were generally supportive of efficacy.

Subgroup analysis of the data for gender, race, region, age, etc., supporting efficacy of ArmonAir RespiClick and AirDuo RespiClick did not show any concerning trends.

8. Safety

a. Safety database

The safety assessment of ArmonAir RespiClick and AirDuo RespiClick is based on studies shown in Tables 1, as well as the large clinical and historical experience with the two active moieties present in these two products.

b. Safety findings and conclusion

The submitted data support the safety of ArmonAir RespiClick and AirDuo RespiClick for the treatment of patients 12 years of age and older with asthma.

In the clinical studies submitted with this application no new safety signals were seen. There was one death in the program, which was deemed not related to the study drug. The death occurred in a 44 year old patient (on AirDuo 113/14 mcg treatment) who died of liver injury. The death was thought to be from an herbal supplement that the patient started taking while participating in the study. Serious adverse events¹⁷ 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 and ICS and LABA in combination.

¹⁷ 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.

c. REMS/RiskMAP

Teva submitted a risk management plan consisting of a pharmacovigilance plan with focus on events of interest. A REMS is not necessary as the labeling will be sufficient to communicate the safe use of the product.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy for ICS as a single ingredient product and ICS plus LABA as a combination product are well understood. There were no unique findings in the ArmonAir RespiClick and AirDuo RespiClick programs that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

Teva requested a deferral for studies in patients 4 to 11 years of age and a waiver for patients below 4 year of age with the reasoning that effective treatment for asthma for these ages are already available in the market and clinical studies in these patients are impractical. Patients between 12 and 17 years of age have been studied and the results are submitted with this application. Teva is conducting a PK study and a 12-week efficacy and safety study in patients 4 to 11 years of age. (b) (4)

Teva's proposal was discussed at the Pediatric Review Committee (PeRC) meeting on October 19, 2016, and PeRC found the proposal acceptable.

11. Other Relevant Regulatory Issues

a. OSI Audits

OSI conducted a sponsor level investigation and found no irregularities that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. None of the investigators had significant financial interest in Teva.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proprietary names ArmonAir RespiClick and AirDuo RespiClick were reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

The labels for ArmonAir RespiClick and AirDuo RespiClick were reviewed by various disciplines of this Division, as well as OPDP, DMPP, OSE, and DMEPA. Some changes to the labels proposed by Teva were done to make the labels conceptually consistent with some recently approved single ingredient ICS and combination ICS plus LABA products. The Division and Teva have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

The products will carry an asthma-related safety warning consistent with other products of the classes.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Teva has submitted adequate data to support approval of ArmonAir RespiClick (fluticasone propionate 55 mcg, 113 mcg, and 232 mcg, per inhalation) and AirDuo RespiClick (fluticasone propionate 55 mcg, 113 mcg, and 232 mcg, in combination with salmeterol 14 mcg, per inhalation) for treatment of asthma in patients 12 years of age and older at doses of one inhalation twice daily. The regulatory action for the two applications will be approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of ArmonAir RespiClick and AirDuo RespiClick at three strengths each as noted above for the treatment of asthma in patients 12 years of age and older. The risk with the use of ICS as a class and ICS plus LABA combination product as a class, and specifically for fluticasone propionate and salmeterol 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.

c. Post-marketing Risk Management Activities

Beyond the standard pharmacovigilance, no post-marketing risk management activities are required.

d. Post-marketing Study Commitments

No post-marketing commitment or required studies are necessary beyond the PREA requirement studies.

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BADRUL A CHOWDHURY
01/27/2017