1. Introduction

Teva submitted two 505(b)(2) New Drug Applications (NDAs) 208798 and 208799 on March 27, and March 28, 2016, respectively, for ArmonAir RespiClick and AirDuo RespiClick for the treatment of asthma in patients 12 years of age and older. ArmonAir RespiClick is comprised of fluticasone propionate (Fp), an inhaled corticosteroid (ICS), and is provided in 3 dose strengths (55, 113, and 232 mcg), delivered by a proprietary multi-dose dry powder inhaler (MDPI), the RespiClick device; the reference listed drug is Flovent Diskus (NDA 20833, approved
AirDuo RespiClick is a combination product comprised of fluticasone propionate (Fp), an ICS, and salmeterol xinafoate (Sx), a long-acting beta-agonist (LABA). AirDuo RespiClick is also provided in 3 dose strengths, corresponding to the 3 dose strengths of Fp provided in ArmonAir RespiClick, combined with salmeterol 14 mcg, delivered in the same MDPI. The reference listed drug for AirDuo RespiClick is Advair Diskus (NDA 21077, approved August 24, 2000). The proposed dosing regimen for both products is one inhalation twice daily (BID).

Throughout this document, the products will be referred to as Fp and FpS for ArmonAir and AirDuo RespiClick, respectively. The dose strengths of Fp will be referred to in terms of the metered doses of 55, 113, and 232 mcg, respectively. Similarly, Sx will also be referred to as the metered dose of 14 mcg throughout this review. In the NDA submissions, the Applicant has used legacy approximation numbers to refer to the dose strengths of Fp and Sx (50 mcg, 100 mcg, and 200 mcg for Fp and 12.5 mcg for salmeterol). In this review and the product labels, the metered doses will be used.

To support the efficacy and safety of Fp and FpS administered twice daily for asthma, Teva conducted a full development program which consisted of 6 key studies: two 12-week Fp dose-ranging studies, a single-dose salmeterol dose-ranging study, two 12-week efficacy and safety studies which included the usual factorial design to support the efficacy and safety of both the Fp monocomponent and the FpS combination product, and a supportive 26-week long-term safety study. Although the products are under two different NDAs (208798 and 208799), due to the overlapping nature of their development programs, the data supporting the efficacy and safety of both Fp and FpS can be found across all six studies; therefore, the data for these two applications will be covered by this single memorandum.

This memo provides an overview of the application, summarizing the data which demonstrate the safety and efficacy of all three strengths of both Fp and FpS. This memo also summarizes the recommendations for each of the individual review disciplines.

2. Background

Asthma is a chronic inflammatory respiratory disease characterized by periods of acute symptoms of wheezing and shortness of breath. There are several drug classes available to treatment patients with persistent asthma, and these include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agonists (LABA), leukotriene modifying drugs, methylxanthines, inhaled anticholinergics, anti-IL-5 monoclonal antibodies, and an anti-IgE antibody.

Inhaled corticosteroids play a principal therapeutic role in the management of patients with persistent asthma. Patients with persistent asthma whose disease remains uncontrolled in spite of treatment with controller therapy such as inhaled corticosteroids are candidates for treatment with ICS/LABA fixed-dose combination products. Combination ICS plus LABA products to treat patients with more severe asthma include Advair metered-dose inhaler (MDI) and dry-powder inhaler (DPI) (fluticasone/ salmeterol), Dulera MDI (mometasone furoate/ formoterol...
fumarate), Symbicort MDI (budesonide/ formoterol fumarate), and Breo Ellipta (fluticasone furoate/vilanterol) dry powder inhaler.

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 at three strengths (50 mcg, 100 mcg, and 250 mcg of fluticasone propionate) with the labeled doses ranging from 100 mcg to 1000 mcg twice daily for patients 12 years of age and older. Advair Diskus is marketed at three strengths (100/50 mcg, 250/50 mcg, and 500/50 mcg of fluticasone propionate/salmeterol) with labeled 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 monoprod, 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 lowest dose strength of 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 dose strengths.

Relevant Regulatory History for Fp and FpS

The development of Fp and FpS was subject to the usual milestone meetings under IND 108,838 and IND 72,240, respectively. Several important discussion points during pre-IND and End-of-Phase 2 meetings are highlighted here. During pre-IND interactions (December 2005, December 2009, and July 2010), it was determined that the

During an End-of-Phase 2 meeting in January 2014, the Division provided advice regarding the inclusion of a mid-dose treatment arm to Study 301, to demonstrate the incremental benefit of the higher dose over the lower doses in one study. The Division also recommended that the clinical development program include a 6-month safety study. When the protocols were submitted for Studies 301 and 30017, the Division also recommended the primary endpoint be changed from a continuous endpoint (change from baseline in FEV1 over the 12-week treatment period) to a landmark endpoint (change from baseline in FEV1 at Week 12).

3. CMC/Device

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.

The 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 mouthpiece of the device.
The device has a built in dose 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 washed
with water or immersed in water.

Teva has submitted the necessary data to support the quality and manufacture of the two
products, and granted 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/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is
Approval. There are no outstanding nonclinical issues at this time.

The Sponsor refers to the reference listed drugs, Flovent Diskus (marketed under NDA 20-833),
and Advair Diskus (marketed under NDA 21-077) which utilize the same active pharmaceutical
ingredients, fluticasone propionate, and fluticasone propionate/salmeterol, respectively.
Complete nonclinical programs were conducted for both the individual monoproducts as well as
the combination product. No new nonclinical pharmacology or toxicology studies were
conducted or required to directly support the safety of Fp and FpS in ArmonAir and AirDuo
RespiClick, respectively. Based upon the Agency’s previous findings of safety and efficacy for
the reference listed drugs, Flovent Diskus and Advair Diskus, and there is sufficient information from the nonclinical perspective to recommend the approval of NDA 208798 and NDA 208799.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from a Clinical Pharmacology perspective is Approval. There are no outstanding clinical pharmacology issues at this time.

To support these NDA submissions, the Applicant provided information from 6 clinical pharmacology studies. Highlights of the clinical pharmacology review are summarized here. For further details, refer to the review of Dr. Lei He.

Teva has developed Fp MDPI and FpS MDPI, to deliver lower doses of Fp in the Fp MDPI, Fp and salmeterol xinafoate (Sx) in the FpS MDPI than their corresponding reference products, Flovent Diskus and Advair Diskus, while achieving similar or lower systemic exposure and similar efficacy. The following key points were noted in the clinical pharmacology review:

1) Following the administration of the proposed products, Fp and FpS, the systemic exposures of Fp and Sx were similar or lower compared to their corresponding reference products in asthma patients
2) Although the accumulation of Fp and Sx is expected to occur following twice-daily administration of Fp and FpS given the half-lives of Fp (t\(_{1/2}\) ~11 hours) and Sx (t\(_{1/2}\) ~12 hours), the systemic exposures of Fp and Sx are still expected to be lower or similar to their reference products. Therefore, we are able to rely on some relevant labeling information from the approved reference listed drugs for Fp and Sx, including pharmacokinetics (PK), drug interaction, PK in special populations, systemic safety, etc.
3) Dose-ranging has been adequately explored for both Fp and Sx in the dose-ranging studies (details in Section 6).

6. Clinical Microbiology

Non-applicable.

7. Clinical/Statistical-Efficacy

Overview of the clinical program

The clinical program to support Fp and FpS for the treatment of asthma in patients 12 years of age and older consisted of 6 key studies: two 12-week Fp dose-ranging studies (FpS 201 and FpS 202), a single dose Sx dose-ranging study (FSS 201), two 12-week efficacy and safety studies which included the usual factorial design for a dual combination ICS/LABA product, and a supportive 26-week open-label safety study. The dose-selection studies for Fp and Sx are
summarized in Table 1; the other relevant efficacy and safety studies are summarized in Table 2. This memorandum summarizes the main results from these studies.

| Table 1. Fluticasone propionate (Fp) and Salmeterol (Sx) Dose Selection Studies |
|---|---|---|---|---|
| **ID Year** | **Study Characteristics †** | **Treatment groups ‡** (mcg) | **N §** | **Primary efficacy variables** | **Regions and Countries (% US sites)** |
| **FpS dose selection** |  |  |  |  |  |
| **FpS 201 [2012-2013]** | - 12 to 81 years - Asthma - Parallel arm, DB, AC - 12 weeks | Fp 16 mcg BID Fp 28 mcg BID Fp 59 mcg BID Fp 118 mcg BID Flovent Diskus 100 BID Placebo | 103 104 104 104 104 | CFB Trough FEV1 over 12 weeks | US, Ukraine, Hungary, Israel, Bulgaria, Poland, Croatia, Spain, Serbia (70% US) |
| **FpS 202 [2012-2013]** | - 12 to 83 years - Asthma - Parallel arm, DB, AC - 12 weeks | Fp 59 mcg BID Fp 118 mcg BID Fp 225 mcg BID Fp 434 mcg BID Flovent Diskus 250 BID Placebo | 107 107 106 107 106 | CFB Trough FEV1 over 12 weeks | US, Canada, Ukraine, Hungary, Germany, Israel, Romania, Bulgaria, Poland, Spain, Greece, N. Zealand, Croatia, Serbia (56% US) |
| **Salmeterol dose selection** |  |  |  |  |  |
| **FSS 201 [Jan-Jun 2013]** | - 13 to 86 years - Asthma - Cross over, DB, AC - Single Dose | FpS 118/0 mcg FpS 118/6.8 mcg FpS 118/13.2 mcg FpS 118/26.8 mcg FpS 118/57.4 mcg Advair Diskus 100/50 | 67 68 69 67 68 66 | Baseline adjusted FEV1 (AUC 0-12h) | US |

* Study ID shown (top to bottom) as Teva’s study number, and [year study started-completed]
† DB=double blind; AC: active controlled
‡ Fp: fluticasone propionate in Respiclick device; FpS: fluticasone/salmeterol in Respiclick device; Flovent Diskus (fluticasone propionate inhalation powder); Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) - 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 (ITT)
CFB: change from baseline
Table 2. Fp and FpS MDPI Clinical Development Program

<table>
<thead>
<tr>
<th>ID Year*</th>
<th>Study Characteristics †</th>
<th>Treatment groups ‡ (mcg)</th>
<th>N §</th>
<th>Efficacy Variables</th>
<th>Regions and Countries (% US Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal bronchodilator (or lung function) efficacy and safety studies</strong></td>
<td></td>
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</tr>
<tr>
<td>301 [2014-2015]</td>
<td>- 12 to 86 years - Asthma - Parallel arm, DB - 12 weeks</td>
<td>FpS 55/14 mcg BID FpS 113/14 mcg BID Fp 55 mcg BID Fp 113 mcg BID Placebo</td>
<td>129</td>
<td>CFB Trough FEV1 at Week 12 FEV1 AUC (0-12h)</td>
<td>US, Canada, Poland, Russia, S.Africa, Ukraine, Hungary (57% US)</td>
</tr>
<tr>
<td>30017 [2014-2015]</td>
<td>- 12 to 84 years - Asthma - Parallel arm, DB - 12 weeks</td>
<td>FpS 113/14 mcg BID FpS 232/14 mcg BID Fp 113 mcg BID Fp 232 mcg BID Placebo</td>
<td>146</td>
<td>CFB Trough FEV1 at Week 12 FEV1 AUC (0-12h)</td>
<td>US, Canada, Czech Rep, Poland, Russia, S.Africa, Ukraine, Hungary (57% US)</td>
</tr>
<tr>
<td><strong>Supportive long-term safety study</strong></td>
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</tr>
<tr>
<td>305 [2014-2015]</td>
<td>- 12 to 79 years - Asthma - Parallel arm, OL - 26 weeks</td>
<td>FpS 113/14 mcg BID FpS 232/14 mcg BID Fp 113 mcg BID Fp 232 mcg BID Flovent HFA 110 mcg BID Flovent HFA 220 mcg BID Advair Diskus 250/50 BID Advair Diskus 500/50 BID</td>
<td>133</td>
<td>CFB Trough FEV1 over 26 weeks†</td>
<td>US</td>
</tr>
</tbody>
</table>

* Study ID shown (top to bottom) as Teva’s study number, and [year study started-completed] † DB = double blind, OL=open label ‡ Fp: fluticasone propionate in Respiclick device; FpS: fluticasone/salmeterol in Respiclick device; Flovent Diskus (fluticasone propionate inhalation powder); Flovent HFA (fluticasone propionate inhalation aerosol); Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) § Intent to treat (ITT) CFB: change from baseline † Study 305 was primarily designed to evaluate safety.

Dose selection

The dose selection of both fluticasone propionate and salmeterol are described below. The reader should 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. In the NDA submission, the Sponsor referred to the dose strengths in the dose-ranging studies using legacy approximation numbers (50 mcg, 100 mcg, and 200 mcg for fluticasone propionate, and 12.5 mcg for salmeterol). In some FDA reviews, the legacy approximation numbers were also used to describe the dose strengths, both in the dose-ranging and confirmatory studies. While there were small differences in the dose strengths, the Applicant conducted adequate dose exploration for the fluticasone and salmeterol components in the drug product. The studies and their results are described below.

Fluticasone propionate (Fp)

The dose selection studies evaluated six doses of Fp ranging from 16 to 118 mcg (expressed as metered doses) one inhalation twice daily delivered via the RespiClick device. Both Fp dose selection studies were placebo-controlled, randomized, double-blind, parallel group studies.
which included Flovent Diskus at different dose strengths as an active comparator. These studies were conducted in patients 12 years and older with persistent asthma with varying severity commensurate to the doses of Fp used. Study FpS 201 enrolled patients who were symptomatic on non-steroidal therapy and Study FpS 202 enrolled patients who were symptomatic on high dose ICS, or ICS/LABA therapy. Study treatment arms and primary efficacy variables are shown in Table 1.

In both Studies FpS 201 and FpS 202, the primary endpoint was the change from baseline in trough FEV₁ over the 12-week treatment period. While it is preferable that the primary endpoint of trough FEV₁ be measured as a landmark endpoint, the Applicant had pre-specified that the evaluation be conducted “over” 12 weeks. Given that the trends in response are similar, this memo summarizes the pre-specified primary analysis for the dose-ranging studies, and this analysis is also included in the clinical studies section of the package insert. The primary analysis was performed using a mixed model repeated measures (MMRM) method with covariates of baseline trough FEV₁, gender, age, visit, treatment, and visit-by-treatment interaction based on the Full Analysis Set (FAS). The FAS included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 post-baseline trough FEV₁ assessment and was deemed the primary efficacy analysis set by the Applicant. Sensitivity analysis of the ITT population was supportive of the primary analysis.

Study FpS 201 randomized 622 patients with similar demographics and baseline disease characteristics across the treatment groups. The study population was 58% female and 85% Caucasian, with a mean age of 40 years. Mean %-predicted FEV₁ was 66% predicted at screening. Study FpS 202 randomized 640 patients who also had similar demographics and baseline disease characteristics across study groups. The study populations was 59% female and 88% Caucasian, with a mean age of 49 years. Mean %-predicted FEV₁ was 64% at screening.

The results of Studies FpS 201 and FpS 202 are summarized in Figure 1 and Table 3 below.

Figure 1. Studies FpS 201 and FpS 202: Change from Baseline Trough FEV₁ (L) over the 12-Week Treatment Period (FAS)
Table 3: Studies FpS 201 and FpS 202: Change from Baseline in Trough FEV$_1$ (mL) over 12 Weeks (FAS Population)

<table>
<thead>
<tr>
<th>Treatment *</th>
<th>N</th>
<th>Change (mL)</th>
<th>Diff from Placebo (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study FpS 201</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fp 16 mcg</td>
<td>102</td>
<td>170</td>
<td>52 (-0.032, 0.136)</td>
<td>0.222</td>
</tr>
<tr>
<td>Fp 28 mcg</td>
<td>101</td>
<td>229</td>
<td>111 (0.028, 0.194)</td>
<td>0.009</td>
</tr>
<tr>
<td>Fp 59 mcg</td>
<td>102</td>
<td>243</td>
<td>126 (0.044, 0.208)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fp 118 mcg</td>
<td>102</td>
<td>267</td>
<td>149 (0.066, 0.233)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flovent 100 mcg</td>
<td>102</td>
<td>232</td>
<td>114 (0.033, 0.195)</td>
<td>0.006</td>
</tr>
<tr>
<td>Placebo</td>
<td>102</td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study FpS 202</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fp 59 mcg</td>
<td>107</td>
<td>59</td>
<td>6 (-0.07, 0.083)</td>
<td>0.869</td>
</tr>
<tr>
<td>Fp 118 mcg</td>
<td>106</td>
<td>101</td>
<td>48 (-0.029, 0.124)</td>
<td>0.222</td>
</tr>
<tr>
<td>Fp 225 mcg</td>
<td>102</td>
<td>109</td>
<td>56 (-0.022, 0.133)</td>
<td>0.159</td>
</tr>
<tr>
<td>Fp 434 mcg</td>
<td>107</td>
<td>125</td>
<td>72 (-0.004, 0.149)</td>
<td>0.064</td>
</tr>
<tr>
<td>Flovent 250 mcg</td>
<td>103</td>
<td>106</td>
<td>53 (-0.025, 0.130)</td>
<td>0.182</td>
</tr>
<tr>
<td>Placebo</td>
<td>105</td>
<td>53</td>
<td></td>
<td></td>
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</table>

*All treatments administered BID
*All Fp treatment arms administered via the RespiClick MDPI
*Flovent: administered via the Diskus
Fp: fluticasone propionate; Diff: LS Mean Difference; CI: confidence interval
Source: Primary statistical review, Studies FpS 201 and 202 CSR, Table 13.

In Study FpS 201, all doses, with the exception of the lowest (Fp 16 mcg) were significantly different than placebo with a treatment effect size ranging from 52 mL to 148 mL (Fp 16 mcg to Fp 118 mcg). When the landmark analysis (not shown here) was evaluated, the treatment effect size covered a similar range (44 mL to 150 mL). Study FpS 202 included Fp 59, 118, 225, and 434 mcg, compared to Flovent Diskus 250 mcg, all delivered BID. While there was some evidence of dose response, no treatment group demonstrated a statistically significant benefit over placebo. This is likely due to nearly half of the subjects in the placebo group discontinuing due to meeting the stopping criteria of FEV$_1$ decrease to <80% predicted. Landmark analysis (not shown here) of the endpoint showed similar results, with the exception that Fp 225 demonstrated a statistically significant benefit over placebo (99 mL; 95% CI [1, 196]. Given the results of Studies 30017 which examined the Fp 232 mcg BID dose (discussed below), and the totality of the data, the results support the Fp 55, 113, and 232 mcg doses chosen.

**Salmeterol dose selection**

The efficacy and safety of four doses of salmeterol xinafoate were evaluated in Study FSS 201, a double-blind, single dose, 6-period crossover study comparing Fp MDPI and open label Advair Diskus 100/50 mcg dry powder inhaler as an active comparator in patients with persistent asthma. The salmeterol doses studied in the MDPI were 6.8 mcg, 13.2 mcg, 26.8 mcg and 57.4 mcg in combination with fluticasone propionate 118 mcg delivered by MDPI. Plasma for pharmacokinetic characterization was obtained at each dosing period. The subject demographics were similar to the other dose selection studies. The primary efficacy variable was the standardized (ANCOVA with fixed effects of sequence, period, and treatment) baseline-adjusted FEV$_1$ AUC 0-12 hours.
The results of Study FSS 201 are presented in Table 4, Figure 2, and Figure 3 below.

**Figure 2. Study FSS 201: Mean Baseline Adjusted FEV₁ (mL) over 12 hours by Treatment Group (FAS)**

The baseline adjusted FEV₁ AUC 0-12 hours demonstrated a dose-related increase across FpS treatment groups, with a treatment effect size (when compared to Fp 118 mcg alone) ranging from 152 mL to 251 mL. The salmeterol dose of 13.2 mcg was most comparable in clinical efficacy to the 50 mcg of salmeterol contained in the approved active comparator, Advair (193 mL vs. 197 mL, respectively). Establishment of similar efficacy with a lower dose of salmeterol is of note in this clinical development program.

**Confirmatory Studies: Studies 301 and 30017**

Studies 301 and 30017 were lung function studies, and were similar in design, conducted in patients with persistent asthma with varying severity commensurate to the dose of study drug. They were randomized, double-blind, placebo-controlled, parallel group studies of 12 weeks’ duration. Study 301 enrolled patients 12 years of age and older who had persistent asthma and...
were symptomatic despite low-dose or mid-dose ICS therapy. The study included Fp and FpS pairs at low and mid-doses of Fp: Fp 55 mcg versus FpS 55/14 mcg, Fp 113 versus FpS 113/14 mcg BID and a placebo control. Study 30017 included Fp and FpS at medium and high doses of Fp: Fp 113 mcg versus FpS 113/14 mcg, Fp 232 mcg versus FpS 232/14 mcg and a placebo control, all given BID.

Key criteria for inclusion at screening included: FEV1 40%-85% percent predicted, reversibility of at least 15% and a 200 mL increase from baseline FEV1 post-bronchodilator, treatment with low- or mid-dose ICS or ICS/LABA for at least 1 month prior to providing informed consent. For Study 30017, the qualifying doses ranges of ICS were given only a lower bound to allow for enrollment of patients with mid- to high-dose of ICS, as contrast to the ranges given in Study 301 of a fixed range of low- to mid-dose ICS.

Both studies included pre-screening, run-in, double-blind treatment, and follow-up periods. For patients treated with ICS/LABA prior to enrollment, the LABA was discontinued at the pre-screening visit and the ICS had to stable for ≥ 1 month before the informed consent was signed. There were also medication-specific washout periods for patients who were taking protocol prohibited medications. During the run-in period, baseline measurements of asthma control were obtained, baseline safety evaluations were completed, and patient compliance was evaluated. Patients who satisfied the selection criteria were randomized in equal ratios into one of the treatment arms for the 12-week treatment period.

The co-primary endpoints for Studies 301 and 30017 are as follows:

- change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 at Week 12
- standardized baseline-adjusted area under the effect curve for FEV1 from time 0 to 12 hours postdose (FEV1 AUC 0-12h) at week 12 (analyzed for the subset of approximately 312 patients who performed postdose serial spirometry)

**Efficacy Results**

In both studies, baseline demographic characteristics were well-balanced across treatment groups in both trials. In both studies, approximately 60% of subjects were female, 80% Caucasian, with a mean age of 41 to 44 years. Baseline FEV1 was 2.1-2.2L. The two studies differed in baseline asthma therapy, with Study 301 enrolling patients on low to medium dose ICS or ICS/LABA, whereas Study 30017 included more patients on medium and high dose ICS or ICS/LABA, consistent with the inclusion of patients with more severe asthma in Study 30017. The results of the primary efficacy analysis for trough FEV1 and FEV1 AUC 0-12 hours are shown in below.
Table 5: Change from Baseline in Trough FEV₁ (mL) at Week 12 (FAS Population)

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

*All treatments administered mcg BID
Fp and FpS treatment arms administered via the RespiClick device
Fp: fluticasone propionate; FpS: fluticasone propionate/salmeterol; Diff: LS Mean Difference; CI: confidence interval

Figure 4. LS Mean Change from Baseline in Trough FEV₁ at Each Visit by Treatment Group Study 301 (left panel) and Study 30017 (right panel).

A summary of the trough FEV₁ analysis results at Week 12 is provided in Table 5. This co-primary efficacy endpoint was primarily used to evaluate the efficacy of both the single and combination drug products versus placebo. Statistically significant differences were observed in favor of all Fp and FpS treatment groups when compared to placebo.
A summary of the FEV\textsubscript{1} AUC 0-12 hours analysis results at Week 12 is provided in Table 6. This co-primary efficacy endpoint was used to demonstrate the added benefit of Sx in the FpS combination product. It was also used to evaluate the efficacy of the combination compared to placebo. Statistically significant differences were first observed in favor of the combination drugs relative to the single ingredient counterparts: FpS 232/13 vs. Fp 232, FpS 113/114 vs. Fp 113, and FpS 55/14 vs. Fp 55. Following the pre-planned fixed-sequence multiple testing procedure, statistically significant differences were observed in favor of the combination drugs relative to placebo. Similar results were noted in Study 30017.
Figure 5. Mean Change from Baseline in FEV\(_1\) (L) at Day 1 (left panel) and Week 12 (right panel) by Time Point and Treatment Group – Study 301 – (FAS, Serial Spirometry Subset)

“FP and FS Tradename” refers to the ArmonAir and AirDuo RespiClick, respectively.
N’s in figure (and package insert) represent completers within the serial spirometry subset.

Figure 6. Mean Change from Baseline in FEV\(_1\) (L) at Day 1 (left panel) and Week 12 (right panel) by Time Point and Treatment Group – Study 30017 – (FAS, Serial Spirometry Subset)

“FP and FS Tradename” refers to the ArmonAir and AirDuo RespiClick, respectively.
N’s in figure (and package insert) represent completers within the serial spirometry subset.
Secondary efficacy endpoints evaluated the efficacy of Fp MDPI and FpS MDPI on additional spirometry parameters, patient reported outcomes, time to event endpoints, and rescue medication use. They included: change from baseline measures of a) weekly average of the daily trough morning PEF over the 12-week treatment period, b) weekly average of the daily trough evening PEF over the 12-week treatment period, c) weekly average of the total daily asthma symptom score over Weeks 1 to 12, d) weekly average of total daily use of albuterol/salbutamol inhalation aerosol over Weeks 1 to 12, e) Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) score at Week 12 or at Endpoint, and time to event measures of f) time to patient withdrawal for worsening asthma during the 12-week treatment period, and g) time to 15% and 12% improvement from baseline in FEV$_1$ post-dose at the first treatment visit. In general, the secondary endpoints were supportive of the primary endpoint. Of note, the Applicant did not conduct a responder analysis of the AQLQ endpoint. For inclusion in the package insert, the Applicant will be asked to conduct this analysis, and this is pending at the time of this memorandum.

**Efficacy Conclusions**
The clinical program is adequate to support the efficacy of Fp and FpS at the three dose strengths of 55, 113, and 232 mcg, respectively, as well as each combined with 14 mcg of salmeterol in the combination products. The clinical studies demonstrated the efficacy of Fp and FpS with respect to FEV$_1$-based endpoint measurements (trough FEV$_1$ and FEV$_1$ AUC 0-12 hours). Notably, in this clinical development program, a lower dose of salmeterol than what is found in approved salmeterol-containing products was found to be effective. Additionally, the recommended daily doses of Fp are lower than that of the marketed approved fluticasone propionate.

**8. Safety**
The safety assessment of Fp and FpS is based on studies shown in Tables 1 and 2, as well as the large breadth of clinical and historical experience with these two active moieties, and ICS and LABA drug classes in general. No new safety signals were noted in this development program. A summary of the safety evaluation is provided here.

For these two applications, the safety evaluation included the pooled results of the four, 12-week studies. A 26-week open-label study provided supportive safety data and did not reveal any safety issues different from the 12-week studies. In the 12-week studies, a total of 2,625 subjects were treated twice daily with Fp 55, 113, 232 mcg or FpS 55/14, 113/14, 232/14 mcg, or placebo. Sixty percent (60%) of patients were female and 80% were Caucasian. A total of 674 patients were randomized into the 26-week open-label safety study.

Death was rare in the clinical program. There was one death in pertinent clinical studies, and was not deemed to be related to the study drug. Death occurred in a 44-year old black female after receiving FpS 113/14 mcg BID for 37 days and starting a new herbal supplement (moringa oleifera) on Day 22. Her liver enzymes continued to be elevated and she died on Day 72. While the case meets the criteria of drug-induced liver injury (Hy’s law), it is confounded by the use of
an herbal supplement. Given the large clinical experience with fluticasone/salmeterol, it is unlikely that this death is drug-related.

Serious adverse events (SAEs) were similarly rare in the clinical development program. The overall occurrence of serious adverse events (SAEs) was equally distributed across treatment groups (0% – 2%). The only SAE that occurred in more than one patient was asthma exacerbation. Asthma exacerbation was reported in 4 (1%) patients in the placebo arm and 1 (1%) patient in the FpS 200/12.5 mcg treatment arm. Dropouts and discontinuations were also low in the clinical studies. Events leading to dropouts and discontinuations were typical of events seen in asthma development programs.

Several cases (n=4) of liver enzyme elevation were noted in the clinical development program. However, there were no adverse events reported as a result of these laboratory abnormalities. In one patient, the elevations were noted to be ALT $\geq 5x$ ULN and AST $\geq 10x$ ULN, and a normal bilirubin. No follow up labs were reported and no further information was provided. Given the established safety experience with fluticasone propionate and salmeterol, it is unlikely that these findings are drug-related.

Common adverse events seen in the program were typical of asthma studies and studies using ICS and LABAs. Adverse reactions with a > 3% incidence and more common than placebo were nasopharyngitis, upper respiratory tract infection, oral candidiasis, back pain, headache, and cough.

Safety Conclusions
In general, the submitted safety data are consistent with the well-known safety profiles of ICS and ICS/LABA, and the submitted safety assessment is adequate. Evaluation of the deaths, serious adverse events, discontinuations due to adverse events, and common adverse events did not reveal any new safety signals.

9. Advisory Committee Meeting

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

10. Pediatrics

Efficacy and safety information for the adolescent population 12-17 years of age is presented throughout this review. For the population of 4-11 year olds, the sponsor submitted their pediatric study plan (PSP) in April 2014, and it was agreed upon in October 2014. The PSP includes a waiver for 0-3 years and a deferral for 4-11 years. Teva is conducting one PK study in 4-11 year olds (FSS-PK-10007) with an estimated completion date of June 2016. A 12-week, controlled, randomized clinical trial (Study FSS-AS-30003) is also planned in patients.
4 to 11 years of age, with an estimated completion date of May 2019. Other pediatric assessments (i.e. growth studies) are not planned, as the effect of Fp on growth is well-known, and the systemic exposure for fluticasone in the current products are lower than that of the reference listed drugs.

The Division’s plan was discussed with the Pediatric Review Committee (PeRC) on October 19, 2016, the PeRC was in agreement with the Division’s/Sponsor’s plan.

11. **Other Relevant Regulatory Issues**

- **Financial Disclosure:** Appropriate financial disclosure information was provided by the Applicant. None of the investigators reported any proprietary interests.
- **OSI audits information:** The Division requested a sponsor level investigation due to the allegations of an anonymous source that potential unblinding may have occurred at the investigator level. The inspection found the problem to be isolated to a single treatment arm (FpS 55/14 mcg), impacting only one study protocol (Study 301). If sponsor instructions for investigators to remove foil overwrap were followed, no unblinding of study subjects would have occurred. Investigator unblinding was also unlikely in this 5-arm study. Given the large number of clinical sites, the low potential of unblinding, and the objective nature of the efficacy results measured (lung function), it is unlikely that this issue affected the overall results of the clinical development program. The Office of Scientific Investigations determined that no action was indicated.
- **Office of Compliance:** The overall EES conclusion is Acceptable.

12. **Labeling**

A revised label was sent to the Applicant on November 23, 2016. Revisions were made to the ArmonAir RespiClick package insert in an attempt to harmonize with more recently approved ICS product labels. The Division recommended that the Applicant use the revisions to the ArmonAir package insert as a guide to similarly revising the AirDuo package insert. Major revisions suggested included removal of the...

The proposed label, carton and container labeling, and Patient IFU are being reviewed by the appropriate disciplines within the Division as well as OPDP, DMPP, OSE, and DMEPA at the time of this review. At the time of this memorandum, the Division awaits the substantially revised label, and final labeling language between the Applicant and the Division is still under discussion, with a labeling teleconference planned for January 9, 2017.
13. **Recommendations/Risk Benefit Assessment**

- **Recommended Regulatory Action**

  The recommended regulatory action is Approval for the three strengths of ArmonAir RespiClick (Fp; 55, 113, and 232 mcg) and AirDuo RespiClick (FpS; 55/14, 113/14, 232/14 mcg) twice daily for the treatment of asthma in patients 12 years of age and older.

- **Risk Benefit Assessment**

  The overall risk benefit assessment supports the approval of the three strengths of ArmonAir RespiClick (Fp; 55, 113, and 232 mcg) and AirDuo RespiClick (FpS; 55/14, 113/14, 232/14 mcg) twice daily for the treatment of asthma in patients 12 years of age and older. The risks with the use of ICS and ICS/LABA are well known, and no new safety signals were identified during this clinical development program. Notably, the doses of fluticasone and salmeterol are lower in the combination product than in the currently marketed fluticasone/salmeterol-containing products. In addition, the total recommended daily dose of fluticasone propionate is also lower in ArmonAir RespiClick than in currently marketed inhaled fluticasone propionate products. The efficacy findings were robust and consistent with the efficacy of ICS and ICS/LABA in asthma.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

  No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

- **Recommendation for other Postmarketing Requirements and Commitments**

  No additional post-marketing commitments or required studies are recommended beyond the PREA requirements which have been addressed by the Applicant in their pediatric study plan.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BANU A KARIMI SHAH
01/17/2017