DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
CDER/ODE 2/DPARP

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From: Keith Hull MD, PhD
Medical Officer

Through: Sally Seymour MD
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Product: fluticasone furoate inhalation powder (ARNUITY ELLIPTA)

Subject: Supplemental NDA
Treatment of children ages 5 to 11 years old with asthma

Sponsor: GlaxoSmithKline (GSK)

Application: NDA 205635/Seq. No. 0041

EXECUTIVE SUMMARY

Fluticasone furoate (FF) inhalation powder is an inhaled corticosteroid (ICS) administered by the ELLIPTA dry powder inhaler (DPI). The current submission provides data to support approval for the extension of the ARNUITY ELLIPTA indication to include once daily (OD) maintenance treatment in children ages 5 to 11 years of age who are diagnosed with asthma.

The primary data for this review is derived from Study HZA106855, a well-controlled study assessing the efficacy of FF in 596 children ages 5 to 11 years with uncontrolled asthma. Clinically and statistically significant improvements were observed over Weeks 1 through 12 compared with placebo in AM PEF for all three doses of FF investigated (FF 25 OD, FF 50 OD and FF 100 OD).

Studies HZA107112 and HZA107118 assessed the pharmacodynamic effects of FF on short-term lower leg growth and HPA axis suppression, respectively. Review of the studies did not demonstrate clinically significate changes in either assessment in FF-treated subject compared to placebo-treated subjects.

Two clinical pharmacology studies, HZA102942 and HZA112777, were also included in this submission; however, this review only included the data as it related to the safety assessment of FF. Efficacy results are discussed in the Clinical Pharmacology review by Manuela Grimstein, PhD.

Review of the safety database, which consisted of 817 subjects, demonstrated that the incidence of adverse events (AE) was low across all five studies with no apparent

dose-response effect. There were no deaths and only a total of two serious adverse events (SAE) in FF-treated subjects both of whom made a full recovery. The types and frequencies of common AEs were similar to that reported in the current ARNUITY ELLIPTA USPI and no new safety signals were identified. Review of the 120-day safety update was consistent with the data presented in the initial submission and no new safety signals were identified.

Based on review of the data, I recommend approval of the current NDA expanding the indication to include once daily maintenance treatment with FF 50 mcg QD in children ages 5 to 11 years of age who are diagnosed with asthma.

BACKGROUND

Asthma affects the airway passages of the lungs, and is characterized by airway inflammation and bronchial hyper-responsiveness. During acute asthmatic episodes, the airway passages become narrower and more obstructed, resulting in coughing, wheezing, tightness of the chest, shortness of breath, and increased mucus production. It is believed that these asthma symptoms may be associated with chronic changes in airway structure and function, increasing the morbidity and mortality of those affected.

In the US, asthma affects more than 22 million persons and is one of the most common chronic diseases of childhood, affecting more than 6 million children. Asthma contributed to over 1.3 million visits to hospital outpatient departments with asthma listed as the primary diagnosis and to 1.8 million emergency department visits in 2010, leading to over 439,000 patients requiring hospitalization with an average length of hospital stay of four days.

Short-acting ß2-adrenergic agonists, such as albuterol, are a mainstay of asthma management and are the recommended drugs for relief of acute asthmatic symptoms and prophylaxis for exercise-induced bronchoconstriction. They are not intended to modify the disease process and are taken as needed for relief of symptoms. The use of ß2-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. For this reason, early consideration should be given to adding anti-inflammatory agents, such as corticosteroids, to the therapeutic regimen.

As a class, the ICS are considered the most effective anti-inflammatory treatments for all severities of asthma, and allow for the control of asthma symptoms, improvement in lung function and decreased airway hyper-responsiveness. Guidelines for diagnosis and treatment of asthma in children over the age of 5 years are generally similar to those used and recommended for adults with a tailored stepwise approach to achieving asthma control. Most ICS formulations currently available for use in pediatric patients (e.g., fluticasone propionate) are administered twice daily (BD). The development of an OD ICS has the potential to improve patient adherence to therapy, and consequently, improved disease management.

Doses of ARNUITY ELLIPTA 100 mcg and 200 mcg were approved in the US on August 20, 2014 of for the treatment of asthma patients aged 12 years and older. The combination product BREO ELLIPTA, consisting of FF and vilanterol (VI), was approved in the US on April 20, 2015 for the treatment of asthma in patients ages 18 years and

older. Fluticasone furoate is also licensed for two other indications; BREO ELLIPTA for the treatment of chronic obstructive pulmonary disease (COPD), and as VERAMYST/FLONASE as an aqueous suspension for intranasal administration for the treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ages 2 years and older.

CLINICAL PROGRAM

The current submission contains five studies to support the extension of the current FF indication for the treatment of asthma to patients 5 years and older. Study HZA114971 is currently ongoing and not included in the present review. These studies are outlined in Table 1 and summarized as follows:

- Study HZA106855
  - Parallel group, dose-ranging efficacy and safety study. Results from this study will be used as the primary source of data to support the current supplemental NDA indication.
- Study HZA107112
  - Two-way crossover study of short-term lower leg growth
- Study HZA107118
  - Parallel group study assessing the effect of FF on the hypothalamic-pituitary-adrenocortical (HPA) axis
- HZA102942 and HZA112777
  - Two-way crossover, safety, tolerability, PD and PK clinical pharmacology studies. These two studies were previously submitted as part of the original adult and adolescent NDAs and have been discussed in previous reviews.

Table 1. Overview of Study Designs

Study	Phase	Study Design	Run-in (weeks)	Treatment (weeks)	Follow-up (weeks)	Treatment Details (mcg)	No. Subjects Randomized[1]
Pivotal Study							
HZA106855	IIb/III	Multi-center, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled	4	12	1	FF 100 OD ELLIPTA and placebo BD DISKUS FF 50 OD ELLIPTA and placebo BD DISKUS FF 25 OD ELLIPTA and placebo BD DISKUS FP 100 BD DISKUS and placebo OD ELLIPTA Placebo OD ELLIPTA and placebo BD DISKUS	118 118 120 118 119
Supportive Studies							
HZA107112	III	Single-center, randomized, double-blind, two-way crossover, placebo-controlled	2	2 (per period)	1	FF 50 OD ELLIPTA Placebo OD ELLIPTA	58 60
HZA107118	IIIa	Multi-center, randomized, double-blind, parallel-group, placebo-controlled	2	6	1	FF 50 OD ELLIPTA Placebo OD ELLIPTA Background montelukast	56 55
Clinical Pharmacology Studies							
HZA102942	IIa	Multi-center, randomized, double-blind, two-way crossover, placebo-controlled	4	2 (per period)	2	FF 100 OD ELLIPTA Placebo OD ELLIPTA	25 26
HZA112777	IIa	Single-center, randomized, double-blind, repeat dose, two-way crossover	4	2 (per period)	2	FF/VI 100/25 OD ELLIPTA FF 100 OD ELLIPTA	25 25
Ongoing Study							
HZA114971	IV	Multi-center, randomized, double-blind, parallel-group, placebo-controlled	16	52	8	FF 50 OD ELLIPTA Placebo OD ELLIPTA Background montelukast	0 randomized (15 run-in), >225 per arm planned

*Source: Sponsor's Summary of Clinical Safety, Table 1, page 10

The efficacy portion of the current clinical review will mainly focus on Study HZA106855 while summarizing the data from Studies HZA10712 and 107118. The study design of the Clinical Pharmacology Studies HZA102942 and 112777 are discussed since the data is included in the safety database; however, the pharmacokinetic/pharmacodynamic data will not be discussed in this review. A detailed review can be found by the Clinical Pharmacology reviewer, Manuela Grimstein, PhD. Review of the safety data will also focus on Study HZA106855 with separate discussion of the supporting studies as appropriate.

EFFICACY ANALYSIS

Study HZA106855

Study HZA106855 was a multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study designed to assess the dose-response, efficacy and safety of three doses of FF inhalation powder administered once daily in the evening to children aged 5 to 11 years with persistent uncontrolled asthma over a 12-week treatment period.

Subjects meeting entry criteria at screening entered a 4-week run-in period during which time they continued their existing asthma medication. Baseline safety evaluations and measures of asthma status were completed during the run-in period. All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and treatment periods. A review of compliance with daily diary and run-in medication was performed during the run-in period and those subjects who met eligibility criteria and remained uncontrolled despite baseline therapy were randomized as baseline with stratification based on previous use of ICS. Subjects were randomized to one of five treatment groups:

- Group 1: FF 25 mcg OD
- Group 2: FF 50 mcg OD
- Group 3: FF100 mcg OD
- Group 4: Fluticasone propionate (FP) 100 mcg BD
- Group 5: Placebo

Subjects were assessed at visits on Weeks 2, 4, 8, and 12.

A total of 1540 subjects were screened for the study and 596 subjects were randomized with a 593 subjects included in the Intent-to-Treat (ITT) Population. As shown in Table 2, 421/593 (71%) of subjects completed the study with a higher proportion of placebo-treated patients (53/119; 45%) dropping out compared to FF-treated subjects. The primary reason for subject withdrawal in all groups was due to lack of efficacy. The rate of overall subject withdrawal, including higher proportion of placebo subject dropout, should not affect the ultimate interpretation of the data.

Table 2. Subject Disposition (ITT Population)

	Number (%) Subjects					
Status	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118	Total N=593
Completed	66 (55)	94 (80)	87 (73)	85 (72)	89 (75)	421 (71)
Withdrawn	53 (45)	24 (20)	33 (28)	33 (28)	29 (25)	172 (29)
Reason for withdrawal[1]						
Lack of efficacy	42 (35)	16 (14)	23 (19)	21 (18)	19 (16)	121 (20)
Investigator discretion	3 (3)	5 (4)	2 (2)	4 (3)	2 (2)	16 (3)
Withdrew consent	4 (3)	1 (<1)	3 (3)	4 (3)	3 (3)	15 (3)
Protocol deviation	1 (<1)	2 (2)	3 (3)	1 (<1)	3 (3)	10 (2)
Adverse event	1 (<1)	0	1 (<1)	2 (2)	1 (<1)	5 (<1)
Lost to follow-up	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	4 (<1)
Subject reached protocol defined stopping criteria	1 (<1)	0	0	0	0	1 (<1)

*Source: Sponsor's Clinical Overview, Table 3, page 19.

Eligible subjects for this study were male and female children ages 5 to 11 years and diagnosed with uncontrolled asthma despite receiving stable standard of care asthma therapy for a minimum of 4 weeks prior to screening. Subjects had to have a pre-bronchodilator peak expiratory volume (PEF) of ≥60% to ≤90% of their best post-bronchodilator value and, in subjects able to perform the testing, demonstrate a ≥12% reversibility of forced expiratory volume in 1 second (FEV1) within approximately 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol. Subjects were required to demonstrate the ability to use the study provided inhalers under supervision of their parent. Subjects could not have had a history of life-threatening asthma, have experienced an asthma exacerbation requiring the use of systemic corticosteroids for at least 3 days or a depot corticosteroid injection within 3 months prior to screening or required hospitalization for asthma within 6 months prior to screening, have had evidence of concurrent respiratory disease, or have had any other clinically significant medical conditions.

Subjects eligible for randomization had to have a pre-bronchodilator PEF of ≥60% to ≤90% of their best post-bronchodilator value, have demonstrated symptoms of asthma and/or daily use of albuterol/salbutamol on at least 3 of the last 7 consecutive days of the run-in period, have demonstrated compliance with daily controller run-in medication on at least 4 of the last 7 consecutive days of the run-in period and have demonstrated compliance with completion of the Daily Diary reporting. Subjects could not have had any changes in asthma medication since screening, have a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or requiring hospitalization or emergency department visit for since screening, have evidence of concurrent respiratory disease, have had any unresolved clinically significant laboratory results from screening, or have had other clinically significant medical conditions.

As shown in Table 3, subjects' demographics were similar between treatment groups with the mean (SD) age 8 years (1.9), male (62%), White (42%), and non-US (86%). Of note, 39% of the subjects were aged between 5 and 7 years suggesting an adequate representation of younger children in the study; however, there were a lower proportion of this age group in the FF 50 OD treatment group compared to placebo (26% vs. 41%, respectively). Additionally, it should be noted that only 82/593 (14%) of the subjects were from the US, while the remainder of subjects were from outside the US, namely Bulgaria, Georgia, Germany, Japan, Latvia, Peru, Poland, the Russian Federation, and Ukraine. The inclusion of the larger number of non-US participants

should not affect the ability to reach conclusions from the data given the degree of disease similarity of asthma worldwide.

Subjects' baseline disease characteristics were similar between treatment groups (data not shown). Screening lung function tests demonstrated mean pre-bronchodilator PEF of 188 L/min, mean post-bronchodilator PEF of 241 L/min and a mean percentage of pre- to post-bronchodilator PEF of 78%. The majority (81%) of enrolled subjects had a diagnosis of asthma ≥2 years and ≤6% of subjects had asthma less than 1 year. Prior to screening approximately 54% of subjects were receiving SABA therapy with a concomitant ICS, 34% of subjects were receiving SABA therapy alone and 13% were receiving SABA therapy and a leukotriene modifying drug.

The median exposure to study drug was similar across all treatment groups and ranged between 83 and 85 days; however due to the differences in the incidence of early withdrawal between treatment groups, a greater proportion of subjects had an exposure of 56 day in the placebo group (34%) and the FF 100 OD group (24%) compared to the other treatment arms, FF 25 OD (14%), FF 50 OD (19%), FP 100 BD (14%). Further analyses examining drug exposure by subpopulation between treatment arms was performed by the Sponsor, and although limited by sample size, did not reveal significant differences that should impact the interpretability of the data.

Table 3. Study HZA106855: Summary of Demographic Characteristics (ITT)

	Number (%) Subjects					
Demographic	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118	Total N=593
Sex, n (%)						
Female	49 (41)	41 (35)	46 (38)	48 (41)	39 (33)	223 (38)
Male	70 (59)	77 (65)	74 (62)	70 (59)	79 (67)	370 (62)
Age, years						
Mean (SD)	8.0 (1.91)	7.9 (2.08)	8.4 (1.62)	7.8 (2.04)	7.9 (1.87)	8.0 (1.92)
Min, Max	5, 11	5, 11	5, 11	5, 11	5, 11	5, 11
Age, n (%)						
5 years	17 (14)	19 (16)	6 (5)	26 (22)	15 (13)	83 (14)
6 years	10 (8)	21 (18)	13 (11)	8 (7)	19 (16)	71 (12)
7 years	22 (18)	8 (7)	12 (10)	21 (18)	17 (14)	80 (13)
8 years	21 (18)	24 (20)	24 (20)	21 (18)	20 (17)	110 (19)
9 years	19 (16)	10 (8)	31 (26)	7 (6)	22 (19)	89 (15)
10 years	15 (13)	18 (15)	24 (20)	23 (19)	13 (11)	93 (16)
11 years	15 (13)	18 (15)	10 (8)	12 (10)	12 (10)	67 (11)
Age Group, n (%)						
5 to 7 years	49 (41)	48 (41)	31 (26)	55 (47)	51 (43)	234 (39)
8 to 11 years	70 (59)	70 (59)	89 (74)	63 (53)	67 (57)	359 (61)
Body Size, mean (SD)						
Height (cm)	131.2 (12.56)	132.3 (13.61)	134.2 (11.30)	130.1 (13.21)	130.6 (13.01)	131.7 (12.80)
Weight (kg)	32.0 (11.00)	33.2 (12.68)	33.2 (9.36)	30.7 (10.53)	31.0 (9.63)	32.0 (10.72)
Race, n (%)						
White	48 (40)	57 (48)	51 (43)	52 (44)	43 (36)	251 (42)
Mixed Race	35 (29)	33 (28)	40 (33)	39 (33)	40 (34)	187 (32)
American Indian or Alaskan Native	24 (20)	17 (14)	16 (13)	17 (14)	21 (18)	95 (16)
African American/African Heritage	4 (3)	4 (3)	7 (6)	8 (7)	7 (6)	30 (5)
Asian	8 (7)	7 (6)	6 (5)	2 (2)	7 (6)	30 (5)
Ethnicity, n (%)						
Hispanic/Latino	64 (54)	55 (47)	57 (48)	60 (51)	65 (55)	301 (51)
Not Hispanic/Latino	55 (46)	63 (53)	63 (53)	58 (49)	53 (45)	292 (49)
Geographical Region						
USA[1]	15 (13)	18 (15)	16 (13)	19 (16)	14 (12)	82 (14)
Non-USA[2]	104 (87)	100 (85)	104 (87)	99 (84)	104 (88)	511 (86)

*Source: Sponsor's Summary of Clinical Efficacy, Table 4, page 21

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was the mean change from baseline in daily pre-dose AM PEF from the patient daily diary averaged over the 12-week treatment period. A statistically significant difference from placebo was reported for the average of the FF 50 OD and FF 100 OD treatment groups (Table 4). A distinct dose-response relationship was not demonstrated. A statistically significant difference was detected in the gatekeeper comparison of the two higher doses of FF allowed for statistical inference to be made for the comparisons of FF 100 OD versus placebo and FF 50 OD versus placebo. Since both treatment comparisons of FF 100 OD versus placebo and FF 50 OD versus placebo were statistically significant, inference could be made on the treatment comparison of FF 25 OD versus placebo. A statistically significant difference from placebo was observed for the treatment comparison of FF 25 OD versus placebo.

Table 4. Study HZA106855: Primary Endpoint Analysis: Change from Baseline in AM PEF (L/min) Averaged Over Weeks 1 to 12 (ITT)

	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
n	119	117	118	118	117
LS mean	198.9	217.5	218.4	211.3	212.9
LS mean change (SE)	3.3 (2.63)	21.9 (2.66)	22.8 (2.65)	15.8 (2.64)	17.3 (2.64)
Treatment vs. Placebo					
Difference		18.6	19.5	12.5	14.0
95% CI		11.3, 26.0	12.1, 26.9	5.1, 19.8	6.7, 21.4
p-value		<0.001	<0.001	<0.001	<0.001

*Source: Sponsor's Summary of Clinical Efficacy, Table 13, page 32

The Sponsor conducted sensitivity analyses as a result of the high withdrawal rate from the placebo group that resulted in a greater proportion of subjects in the placebo group missing change from baseline in AM PEF data at each week during the study compared to subjects in the FF treatment groups an active control group.

As detailed by Xi Mingyu, PhD in the Biostatistician review, the Sponsor conducted four separate sensitivity analyses using multiple imputation methods for missing data that produced similar, and statistically significant, results to the averaging repeated measures analysis and therefore supported the primary endpoint analysis. The averaged treatment effect and treatment comparisons across Weeks 1 to 12 from the repeated measures analysis supported the findings of the primary endpoint analysis of change from baseline in AM PEF averaged over Weeks 1 to 12 with a statistically significant treatment difference compared with placebo observed for all FF doses and the active control, FP 100 BD.

Major Secondary Endpoints Analyses

Major secondary endpoint analyses prespecified by the Sponsor included change from baseline in AM PEF and PM PEF, change in the percentage of rescue-free and symptom-free 24-hour periods and change from baseline in Trough FEV1.

The Sponsor's prespecified analysis of the change from baseline in AM PEF at Week 12 using an LOCF methodology for imputing missing data demonstrated a statistically significant difference between placebo and each of the FF treatment groups and the active control group further supporting the primary endpoint.

Similarly, statistically significant changes in the Least Squares mean change were reported from baseline to Week 12 in all FF treatment groups compared to placebo. Analysis of PM PEF at Week 12 using an LOCF methodology for imputing missing data also demonstrated a larger increase in the Least Squares mean change from baseline for the FF 25 OD and FF 50 OD treatment groups compared with the placebo group (11 L/min and 13 L/min vs. 5 L/min, respectively).

A dose-dependent increase in the change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment periods was reported. Over the 12-weeks, a small dose-ordered increase in the LS mean change from baseline was shown in the FF 25 OD, FF 50 OD, FF 100 OD treatment groups (25%, 26%, and 29%, respectively) compared to the placebo group (17%). The adjusted treatment

differences from placebo for the FF 50 OD and FF 100 OD treatment groups were statistically significant.

The change from baseline PM clinic visit FEV1 was assessed in those subjects able to perform the testing, which comprised 508/593 (86%) of subjects. At Week 12, all subjects showed an increase in the in trough FEV1 at Week 12. A statistically significant difference from placebo was reported for the FF 25 OD treatment group but not for FF 50 OD, FF 100 OD, or FP 100 BD treatment groups (data not shown). The lack of a significant difference between treatment arms may reflect a high placebo response rate or as an effect of the greater proportion of subject withdrawal from the placebo arm.

Study HZA107112

Study HZA107112 was a single-center, randomized, double-blind, placebo-controlled, two-way crossover, non-inferiority study designed to assess the effect of two weeks of treatment with daily inhaled FF versus placebo on short-term lower leg growth using a knemometer.

The study consisted of five phases:

- Phase 1: Run in Period (2 weeks)
- Phase 2: Treatment Period 1 (2 weeks)
- Phase 3: Wash-out Period (2 weeks)
- Phase 4: Treatment Period 1 (2 weeks)
- Phase 5: Follow-up Period (1 week)

Subjects meeting eligibility criteria were entered into a 2-week run-in period during which time they were given a placebo ELLIPTA inhaler to familiarize themselves with the correct use of technique. During Phase 2, subjects were randomized to one of two treatment arms: inhaled placebo OD in Treatment Period 1 followed by FF 50 mcg OD in Treatment Period 2, or vice versa. Treatment periods one and two were separated by a 2-week washout period. Knemometry measurements were performed at Screening and the start of each Treatment Period.

A total of 60 subjects were screened and met criteria for enrolment in the study with a total of 58 (97%) of subjects completed the study and were included in the primary analysis. Inclusion and exclusion criteria were similar to that of Study HZA106855 and the baseline demographics and disease characteristics were similar between treatment arms.

Primary Clinical Endpoint Analysis

The primary clinical endpoint was prespecified as the mean growth rate (mm/week) in lower leg growth as determined by knemometry. Analysis of the Least Squares mean growth rate was 0.31 mm/week during treatment with FF 50 OD versus 0.36 mm/week during treatment with placebo. The difference in the model adjusted LS mean growth rate between the treatment groups was -0.05 mm/week with a 95% CI of -0.12, 0.02. the lower limit of the CI was greater than the pre-specified non-inferiority margin of -0.20 mm demonstrating that FF 50 OD is non-inferior to placebo. Overall, the data suggest that there was no clinically significant growth retardation in subjects treated with FF compared to placebo.

Study HZA107118

Study HZA107112 was a randomized, double-blind, placebo-controlled, stratified, parallel group, non-inferiority study designed to compare the effects of 6-weeks treatment with daily inhaled FF versus placebo on the HPA axis system of children aged 5 to 11 years. Subjects meeting entry criteria entered a 7 to 14 day run-in period and were treated with open-label montelukast and a SABA as needed. Eligible subjects were randomized to receive FF 50 mcg OD or placebo via the ELLIPTA inhaler. Subjects received treatment for 6-weeks and attended two domiciled treatment visits at Weeks 1 and 6. Inclusion and exclusion criteria were similar to that of Study HZA106855 and the baseline demographics and disease characteristics were similar between treatment arms.

A total of 156 subjects were screened and 111 met criteria for enrolment in the study. Inclusion and exclusion criteria were similar to that of Study HZA106855 and the baseline demographics and disease characteristics were similar between treatment arms.

Primary Clinical Endpoint Analysis

The primary clinical endpoint was the changes from baseline in 0-24 hour weighted mean serum cortisol at the end of the 6-week treatment period tested using the non-inferiority of FF 50 OD to placebo. The non-inferiority margin was selected based on the FDA Guidance for Industry Statistical Approaches to Establishing Bioequivalence using the bioequivalence limit (i.e., 90% CI for the ratio of the averages should fall within a limit of 80-125%). The serum cortisol (SC) population was the prespecified population for the primary analysis.

Analysis of the SC population demonstrated non-inferiority of FF 50 OD compared to placebo based on the derived serum cortisol weighted mean (0-24 hour) as the lower limit of the 95% CI for the geometric mean treatment ratio of FF 50 OD versus placebo was greater than 0.80 (95% CI: 0.81, 1.1). Analysis of the ITT population also demonstrated non-inferiority of FF50 OD to placebo, supporting the primary analysis. Detailed analyses are discussed in Dr. Grimstein's review; however, overall, the data suggest that there was no clinically significant effect on HPA axis in subjects treated with FF compared to placebo.

Study HZA102942

Study HZA102942 was a randomized, double-blind, placebo-controlled, two-way crossover 14-day study designed to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of repeat dose inhaled FF 100 mcg in children 5 to 11 years with persistent asthma. Each subject participated in two 14-day treatment periods: one in which they received FF and the other placebo. The washout period between treatment periods was a minimum of seven days. Subjects attended a post-study follow-up visit within 7-14 days of their last dose.

A total of 27 subjects were randomized with 22 subjects completing the study. The reasons for withdrawal included protocol deviation (n=2), Investigator discretion (n=2) and AE (n=1). The average subject was 8 years of age and white with a balanced distribution of male and females. Inclusion and exclusion criteria were similar to those of Study HZA106855 and were deemed reasonable for the study objective.

Inhaled FF 100 mcg or matching placebo was administered once daily in the morning using the DPI inhaler. The primary objective of the study was completed through examination of the safety and tolerability data. No formal hypothesis testing or statistical analyses were performed. Results are discussed in Dr. Grimstein's review.

Study HZA112777

Study HZA112777 was a randomized, double-bind, repeat dose, two period crossover study to evaluate the safety and tolerability, pharmacokinetics, and pharmacodynamics of inhaled FF/VI 100/25 mcg in children aged 5 to 11 years with persistent asthma. Subjects were enrolled into one of two cohorts based on age. Subjects in the younger cohort were enrolled only after a review of the safety and pharmacokinetic data of at least six subjects from the older subject cohort. Eligible subjects were randomized to one of the two possible treatment sequences FF/VI or FF in an alternating sequence and received treatment for 14 days followed by a washout period of at least seven days. Blinded safety and pharmacokinetic data from at least six subjects aged 8 to 11 years were required to be reviewed before subjects aged 5 to 7 years entered the study. Data from a total of 10 subjects aged 8 to 11 years was reviewed prior to dosing the younger children aged 5 to 7 years (of the 10 total subjects, seven subjects had completed treatment periods 1 and 2; and three had completed treatment period 1). Subjects attended a post-study follow-up visit within 7 to 14 days of their last dose, and the duration of the study was up to 11 weeks for each subject.

A total of 26 subjects were randomized with 23 completing the study. The reasons for withdrawal included two protocol deviations and one subject who reached protocol-defined stopping criteria. The average subject was 8 years of age and white and a higher proportion of males (58%). Inclusion and exclusion criteria were similar to those of Study HZA106855 and were deemed reasonable for the study objective. The primary endpoint was safety and tolerability. Results are discussed in Dr. Grimstein's review.

SAFETY ANALYSIS

As noted above and shown in Table 5, the majority of FF exposure occurred during Study HZA106855. Data from the supportive and clinical pharmacology studies are discussed in the representative sections.

Table 5. Summary of Exposure by Study

Study	Number of Subjects[1]								
	Placebo	Placebo + MONT	FF 25 OD	FF 50 OD	FF 50 OD + MONT	FF 100 OD	FP 100 BD	FF/VI 100/25 OD	Total
Pivotal Study									
HZA106855	119	-	118	120	-	118	118	-	593
Supportive Studies									
HZA107112	60	-	-	58	-	-	-	-	60
HZA107118	-	55	-		56	-	-	-	111
Clinical Pharmacology Studies									
HZA102942	25	-	-	-	-	26	-	-	27
HZA112777	-	-	-	-	-	25	-	25	26

*Source: Sponsor's Summary of Clinical Safety, Table 3, page 16

A total of 596 subjects were randomized and 593 subjects received at least one dose of study drug in Study HZA106855. The planned duration of treatment was 84 days (12 weeks) and the median exposure across all treatment arms ranged from 83 to 85 days; however, due to the differences in the incidence of early withdrawal between the treatment arms, a greater proportion of subjects had an exposure of 56 days or less in the placebo arm (34%) and the FF 100 OD arm (24%) than in the other treatment arms (14% to 18%). Median exposure across all treatment arms was similar between subjects ages 5 to 7 years and subjects ages 8 to 11 years, sex, and racial subgroups.

As outlined above, the supportive Studies HZA107112 and 107118 contributed a total of 171 subjects to the safety database. Study HZA107112 randomized 60 subjects and all received at least one dose of study drug with 58/60 (97%) subjects completing the study. Study HZA107118 randomized a total of 111 studies with 107 (96%) subjects completing the study. The clinical pharmacology studies contributed a total 53 subjects to the safety database. Study HZA102942 randomized 27 subjects and Study HZA112777 randomized 26 subjects.

The Sponsor prespecified an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A serious AE (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonged hospitalization, resulted in disability or incapacity, was a congenital anomaly or birth defect, or was associated with livery injury and impaired liver function.

Deaths

No deaths were reported during the five completed studies included in this review. Additionally, there have been no reported deaths from the ongoing study HZA114971.

Serious Adverse Events

A total of four SAEs were reported during the studies. Two SAEs were reported during Study HZA106855: one subject in the FF 50 OD group reported syncope 75 days after starting study drug and one subject in the FF 100 OD group reported hepatitis A. Two placebo-treated subjects in Study HZA107112 reported SAEs of asthma exacerbation with one subject in the placebo group withdrawing from the study. No further SAEs were reported in the remainder of the studies and there have been no reported SAEs from the ongoing study HZA114971.

Adverse Events Leading to Withdrawal

Adverse events leading to withdrawal was low across all studies. Seven subjects experienced AEs or SAEs leading to withdrawal from Study HZA106855: three subjects in the FF 100 OD treatment group (seasonal allergy/nasopharyngitis, stomatitis, and hepatitis A), two subjects in the placebo group (nasopharygitis and cough/dyspnea), and one subject each in the FF 50 OD group (syncope) and the FP 100 BD group (upper respiratory tract infection).

Two subjects from Study HZA107112 experienced an AE that led to withdrawal from the study. One placebo-treated subject reported an SAE of asthma during active treatment and another patient reported an AE of asthma during the wash-out period from placebo. One subject in Study HZA102942 experienced an AE of otitis externa and otitis media during active treatment with FF 100 OD and was withdrawn from the study. No subjects from Studies HZA107118 or 112777 reported withdrawal from study due to and AE.

Common Adverse Events

Overall, the most frequently reported AEs were consistent between studies and consistent with those reported in the current ARNUITY ELLIPTA USPI. No new safety signals were identified.

As shown in Table 6, a higher proportion of FF-treated subjects experienced an AE during treatment in Study HZA106855 compared to placebo. The most frequently reported AEs were cough, nasopharyngitis, rhinorrhea, pharyngitis, headache, oropharyngeal pain, bronchitis, and upper respiratory tract infection.

Table 6. Study HZA106855: Most Frequently Reported AE While on Study Drug (≥3%)

Adverse Event Preferred Term	Number (%) Subjects				
	Placebo N=119	FF 25 OD N=118	FF 50 OD N=120	FF 100 OD N=118	FP 100 BD N=118
Subjects with any AE	35 (29)	43 (36)	38 (32)	39 (33)	36 (31)
Subjects with most frequent events	28 (24)	30 (25)	25 (21)	31 (26)	26 (22)
Cough	6 (5)	7 (6)	1 (<1)	10 (8)	5 (4)
Nasopharyngitis	4 (3)	9 (8)	4 (3)	3 (3)	4 (3)
Rhinorrhoea	2 (2)	6 (5)	1 (<1)	6 (5)	5 (4)
Pharyngitis	4 (3)	2 (2)	7 (6)	5 (4)	1 (<1)
Headache	2 (2)	2 (2)	2 (2)	7 (6)	4 (3)
Oropharyngeal pain	1 (<1)	6 (5)	2 (2)	2 (2)	4 (3)
Bronchitis	1 (<1)	2 (2)	4 (3)	2 (2)	2 (2)
Upper respiratory tract infection	3 (3)	1 (<1)	0	4 (3)	3 (3)
Pyrexia	0	4 (3)	1 (<1)	2 (2)	1 (<1)
Body temperature increased	0	3 (3)	0	0	4 (3)
Rhinitis	3 (3)	1 (<1)	1 (<1)	0	2 (2)
Tonsillitis	3 (3)	1 (<1)	2 (2)	1 (<1)	0
Viral infection	2 (2)	0	3 (3)	1 (<1)	1 (<1)
Dyspnoea	3 (3)	0	0	1 (<1)	0
Respiratory tract infection	0	3 (3)	0	0	1 (<1)

*Source: Sponsor's Summary of Clinical Safety, Table 11, page 29

The two supportive studies and two clinical pharmacology studies reported similar types and frequencies of AEs. Although there were small differences between treatment arms, in general, the FF-treated subjects reported a greater frequency of AEs compared to placebo controls. No new safety signals were identified.

Adverse Events Related to Laboratory Abnormalities, Vital Signs, EKG, or Weight

A 10-year female in the FF 50 OD treatment group reported a post-treatment increase of ALT associated with borderline neutropenia and underlying viral infection. The ALT abnormality resolved after eleven days. No other AEs related to laboratory abnormalities, vital signs, EKG, or weight were reported in the other four studies.

Adverse Events of Special Interest

Adverse events of special interest (AESI) for FF were predefined as those AEs associated with known pharmacodynamic actions of inhaled corticosteroids and were identified using standard MedDRA queries and Sponsor-defined special interest terms where no MedDRA terms were available. These pre-defined AE of special interest included hypersensitivity, effects on glucose, pneumonia, lower respiratory tract infection, decreased bone mineral density, adrenal suppression, corticosteroid-related eye disorders, local corticosteroid effects and growth retardation in children.

No AESIs were reported in Study HZA106855 using standardized MedDRA queries; however, when using the Sponsor-defined special interest terms, cough, oropharyngeal pain, bronchitis, and dyspnea were reported to be the most commonly reported AESI in FF-treated subjects. None of the AESI met the definition of serious and there were no events of systemic corticosteroid effects.

A total of six subjects experienced an AESI during Study HZA107112 with two FF 50 ID subjects reporting oropharyngeal pain. Of the remaining four subjects, all received placebo and experienced oropharyngeal pain (n=3) and one case of dysphonia. Similarly, three subjects experienced AESI during Study HZA107118: two subjects reported oropharyngeal pain (FF 50 OD-treated, n=1; placebo, n=1) and a single case of allergic sinusitis in a placebo-treated subject.

A single AESI was reported in Studies HZA102942 and HZA112777 with one subject experiencing a lower respiratory tract infection following FF/VI 100/25 treatment.

Clinical Laboratory and Vital Sign Evaluations

There were no clinically significant abnormalities reported for clinical laboratories or vital sign evaluations, except as noted above.

Post-Marketing Data

Fluticasone furoate DPI at strengths of 100 mcg and 200 mcg was approved by the Agency for use in adults and adolescents for the maintenance treatment of asthma in August 2014. As of February 2017, FF DPI has been approved and marketed in eight other countries. The overall estimated cumulative patient exposure of inhaled FF in asthma since August 2014 is approximately 18,000 patient-years.

The Sponsor has reviewed post-marketing data received for inhaled FF since the product launch data and reports a small number of post-marketing events from spontaneous data in comparison with the cumulative patient exposure data. There has been no new safety signals identified during this period and the overall risk:benefit profile of inhaled FF remains favorable.

Dose Selection

The FF 100 mcg dose represents the lowest dose currently marketed for adults and adolescents as both FF monotherapy and in the FF/VI combination. The two lower doses, FF 50 mcg and 25 mcg, were selected as the doses to be progressed in HZA106855. The three FF doses were selected based on the data generated from a previous dose-ranging study in adults and adolescents as well as a repeat-dose study in pediatric subjects.

As discussed in Dr. Grimstein's review, subjects in Study HZA106855 who were treated with FF doses of 25, 50 and 100 mcg showed no evidence of a dose-response relationship for the clinical endpoints. No dose-ordering was apparent for the primary endpoint, i.e., AM PEF averaged over Weeks 1 to 12 or for the secondary endpoint, evening trough FEV1 at Week 12. At the proposed dosage of FF 50 mcg QD, no clinically relevant changes in adrenal function, as measured by 24-hour serum cortisol profiles, were observed. No dose adjustment is recommended for any intrinsic factor in pediatric asthma population. There was no apparent dose-dependent effects between treatment groups in the overall incidence of AEs during treatment, even though the incidence was slightly higher in the FF treatment groups compared with the placebo group.

The safety and efficacy data support the proposed dose of FF 50 mcg QD; however, the data may also support use of the lowest dose of FF 25 mcg OD as well.

Recommendations

Based on my review of the data, in conjunction with the analyses of the clinical pharmacology data by Dr. Grimstein, I recommend approval of the current NDA expanding the indication to include once daily maintenance treatment with FF 50 mcg QD in children ages 5 to 11 years of age who are diagnosed with asthma.

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

/s/

KEITH M HULL
03/26/2018

SALLY M SEYMOUR
03/26/2018