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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205-625
Supplement #:	0041
Drug Name:	ARNUITY ELLIPTA (fluticasone furoate inhalation powder), for oral inhalation
Indication(s):	Treatment of asthma in patients aged 5 to 11 years: 1 inhalation of ARNUITY ELLIPTA 50 mcg once daily
Applicant:	GlaxoSmithKline
Date(s):	Stamp Date: 7/21/2017 PDUFA date: 5/21/ 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Mingyu Xi, Ph.D.
Concurring Reviewers:	Yongman Kim, Ph.D. (Acting Team Lead, DB II)
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Keith Hull, M.D., Nikolay Nikolov, M.D.
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Keywords: pediatric study, ANCOVA, sensitivity analyses & subgroup analyses

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1 EXECUTIVE SUMMARY

This review considers fluticasone furoate (FF) inhalation powder (ARNUITY), an inhaled corticosteroid, administered using a dry powder inhaler (DPI) ELLIPTA device for treatment of asthma in patients aged 5 to 11 years. We focus in this review on one phase 2b/3 study. The study was a multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study to evaluate the efficacy of ARNUITY ELLIPTA 50 mcg once daily (OD) with respect to pulmonary function over 12 week treatment period.

There was a statistical evidence of benefit for ARNUITY ELLIPTA 50 mcg OD with respect to the primary endpoint, mean change from baseline in daily pre-dose AM peak expiratory flow (PEF) averaged over the 12-week treatment period.

Treatment with ARNUITY ELLIPTA 50 mcg OD provided 19.5 L/min (95% confidence interval [CI]: 12.1, 26.9; $p<0.001$) mean improvements over placebo in PEF over the 12 week treatment period.

Evaluation of secondary endpoints of mean change from baseline in PM PEF compared to placebo and change from baseline in percentage of rescue-free 24-hour periods over the 12 week treatment period compared to placebo demonstrated efficacious results.

We think that the evidence of efficacy of active treatment for the pediatric population is substantial and robust considering statistically highly significant results for the primary endpoint supported by positive results for the clinically relevant secondary endpoints.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Asthma is a chronic disease of the lungs. Symptoms include coughing, wheezing, chest tightness and shortness of breath. Inhaled corticosteroids (ICS) are considered effective treatments for all severities of persistent asthma. Some of the benefits of ICS are control of asthma symptoms and improvement in lung function.

ARNUIT ELLIPTA was approved at doses of 100 mcg and 200 mcg for the treatment of asthma in adults and adolescents (>=12 years of age) on August 20, 2014.

This review considers ARNUIT ELLIPTA once daily 50 mcg for treatment of asthma in patients aged 5 to 11 years.

2.1.2 History of Drug Development

During both IND 077855 and IND 070297 development and the pre-NDA meeting, statistical advice regarding the design and analysis of the phase 3 trials was given to the applicant. Advice and comments from the Division were delivered through face-to-face meeting and written responses. Table 1 lists the key correspondences and meeting minutes during the drug development.

Table 1: List of Key Correspondences and Meeting Minutes

Document	Meeting Date/ Document Date	Topic	Reference Number
Meeting Minutes	11 May 2012/ 18 May 2012	pediatric asthma programs for FF and FF/VI	IND 077855
Meeting Minutes	21 July 2015/ 11 Aug 2015	pediatric asthma programs for FF and FF/VI	IND 077855 & IND 070297
Written Response	06 June 2016	FF dose for the pediatric asthma sNDA and on the52-week pediatric growth study.	IND 070297
Meeting Minutes	3 Oct 2016/ 14 Oct 2016	pre-submission meeting for the FF pediatric asthma sNDA	IND 077855
Written Response	10 Feb 2017	Additional feedback on the content and format of the FF pediatric asthma sNDA.	IND 070297

Source: Reviewer

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

1. The agency agreed to conduct single study for the pediatric population considering the evidence of efficacy from the adult and adolescent program.
2. The agency agreed using change from baseline pre-dose AM PEF averaged over the 12-week treatment period as the primary endpoint.
3. The sponsor agreed to include change from baseline FEV_1 at the end of the 12-week treatment period as one of the secondary endpoint despite the concern that some of the patients may not be able to use the spirometry.

2.1.3 Specific Studies Reviewed

This review focuses on one phase 2b/3 study, Study HZA106855.

2.1.4 Statistical Issues

There were potential statistical issues such as sufficiency of the single pivotal study, robustness of efficacy data to missing data, and multiple endpoints as labeling claims; we will discuss these issues in section 5.1.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, and study reports were accessed under the network path \\CDSESUB1\evsprod\NDA205625\205625.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

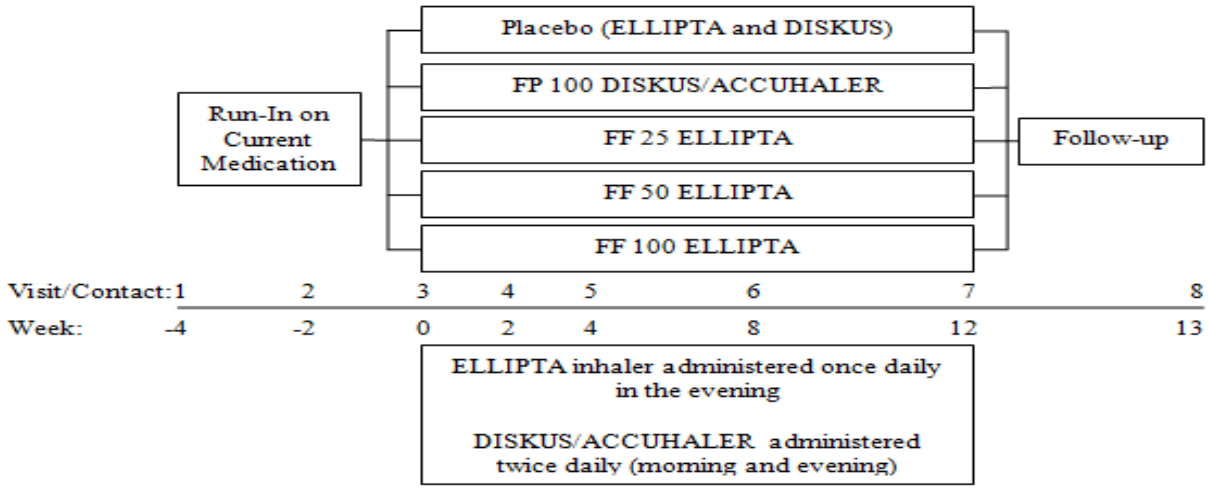
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study HZA106855 was a dose-response, efficacy and safety study. This study served as a dose-ranging study for FF/VI pediatric program; it also served as a pivotal phase 3 efficacy and safety study for pediatric program for FF monotherapy, which is the focus of this review.

Study HZA106855 was a multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study in children aged 5 to 11 years with persistent uncontrolled asthma. It consisted a 4-week run-in period, a 12-week treatment period and a 1-week follow-up period. Figure 1 presents the design scheme for Study HZA106855.

Figure 1: Design Scheme for Study HZA106855



Source: Figure 1 in Applicant's Study Report of Study HZA106855.

Subjects who qualified for the studies were randomized in a double-blind manner in a 1:1:1:1:1 ratio to the five treatment arms:

- FF 25 OD in the PM via the ELLIPTA inhaler PLUS placebo BD via the ACCUHALER/DISKUS (AM and PM).
- FF 50 OD in the PM via the ELLIPTA inhaler PLUS placebo BD via the ACCUHALER/DISKUS (AM and PM).
- FF 100 OD in the PM via the ELLIPTA inhaler PLUS placebo BD via the ACCUHALER/DISKUS (AM and PM).
- Placebo OD in the PM via the ELLIPTA inhaler PLUS placebo FP 100 BD via the ACCUHALER/DISKUS (AM and PM).
- Placebo OD in the PM via the ELLIPTA inhaler PLUS placebo BD via the ACCUHALER/DISKUS (AM and PM).

Randomization in the study was stratified by pre-screening ICS use (had used ICS/had not used ICS).

The patients in the trials were male or pre-menarchial females with uncontrolled asthma, aged between 5 and 11 years, with at least a 6-month history of asthma and who had been receiving stable asthma therapy for at least 4 weeks prior to screening.

The treatment duration was 12 weeks. Albuterol/salbutamol inhalation aerosol was used as rescue medication throughout the study.

Table 2 lists the key endpoints used in Study HZA106855.

Table 2: Primary and Secondary Endpoints of Study HZA106855

Primary Endpoint	mean change from baseline in daily pre-dose AM PEF from the patient electronic daily diary averaged over the 12-week treatment period
Key Secondary Endpoints	change from baseline in evening clinic visit (pre-bronchodilator and pre-dose) FEV_1 at the end of the 12-week treatment period in children who could perform the maneuver
	the change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period
	change from baseline in daily pre-dose PM PEF averaged over the 12-week treatment period

Source: Reviewer

3.2.2 Statistical Methodologies

The efficacy analyses were conducted on the ITT population, defined as all subjects randomized to treatment and who received at least one dose of study medication.

The primary efficacy endpoint was change from baseline in AM PEF averaged over the 12-week treatment period. It was analyzed by analysis of covariance (ANCOVA) model. It included effects due to baseline AM PEF, region, sex, actual pre-screening ICS use, age, and treatment group. For the ANCOVA model, it used Kenward-Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects.

For the primary endpoint, the primary comparison of interest was the comparison of the average of the higher two FF dose (FF 100 and FF 50) versus the placebo. This comparison was performed first. Provided this test was statistically significant, inference then was made on treatment comparison of FF 100 versus placebo and of FF 50 versus placebo. Furthermore, if both treatment comparisons of FF 100 versus placebo and FF 50 versus placebo were statistically significant, inference will be made on the treatment comparison of FF 25 versus placebo.

Statistical significance was evaluated using a two-sided hypothesis test at the 5% significance level.

Analyses of secondary efficacy endpoints of change from baseline in trough FEV_1 at the end of the 12-week treatment period, change from baseline in percentage of rescue-free periods over the 12-week treatment period, and change from baseline in PM PEF averaged over the 12-week treatment period were similar to the analyses of primary endpoint. The model included the baseline value, region, sex, actual pre-screening ICS use, age, and treatment group.

There was no multiplicity control among the secondary endpoints.

The applicant did not impute missing data for the primary endpoint in the primary analysis. In order to assess impact of missing data on the primary results, they conducted four sensitivity analyses using multiple imputation methods for missing data (Missing at Random [MAR], Copy Increment from Reference [CIR], Jump to Reference [J2R] and Copy Reference [CR]).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

In this application, about 71% subjects completed the study. Subject withdrawal was higher in the placebo group (45%) than the FF treatment groups (20% to 28%) and the active control group, FP 100 BD (25%). The main reason for withdrawal was lack of efficacy. There were about 35% subjects in placebo group withdrawal due to lack of efficacy and 14% to 19% in FF treatment group.

Table 3 presents patient disposition of Study HZA106855.

Table 3: Patient Disposition of Study HZA106855

	Number (%) Subjects					
	PBO N = 119	**FF 25 OD N = 118**	**FF 50 OD N = 120**	**FF 100 OD N = 118**	**PF 100 BD N = 118**	**Total N = 593**
Completed	66 (55)	94 (80)	87 (73)	85 (72)	89 (75)	421 (71)
W/D	53 (45)	24 (20)	33 (28)	33 (28)	29 (25)	172 (29)
Reasons for W/D						
Lack of efficacy	42 (35)	16 (14)	23 (19)	21 (18)	19 (16)	121 (20)

Inv.[1] discretion	3 (3)	5 (4)	2 (2)	4 (3)	2 (2)	16 (3)
W/D consent	4 (3)	1 (<1)	3 (3)	4 (3)	3 (3)	15 (3)
Prot.[2] 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[3]	1 (<1)	0	0	0	0	1 (<1)

[1]: Investigator
[2]: Protocol
[3]: Reached protocol defined stopping criteria
Source: Reviewer

3.2.3.2 Patient Demographic and Baseline Characteristics

Demographics and baseline characteristics data for the ITT population are summarized in Table 4. As expected, due to the random treatment assignment, the treatment arms are fairly balanced with respect to each factor considered.

Table 4: Patient Demographic and Baseline Characteristics of Study HZA106855

		Number (%) Subjects					
		PBO N = 119	**FF 25 OD N = 118**	**FF 50 OD N = 120**	**FF 100 OD N = 118**	**PF 100 BD N = 118**	**Total N = 593**
Sex							
	F	49 (41)	41 (35)	46 (38)	48 (41)	39 (33)	223 (38)
	M	70 (59)	77 (65)	74 (62)	70 (59)	79 (67)	370 (62)
Age (yrs)							
	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 Group (yrs)							
	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)
Race							
	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/Africa 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)
Ethnic Group							
	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	15 (13)	18 (15)	16 (13)	19 (16)	14 (12)	82 (14)
	Non-USA	104 (87)	100 (85)	104 (87)	99 (84)	104 (88)	511 (86)

Height (cm)							
	Mean (SD)	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)							
	Mean (SD)	32.0 (11.00)	33.2 (12.68)	33.2 (9.36)	30.7 (10.53)	31.0 (9.63)	32.0 (10.72)
Baseline asthma therapy							
	SABA inhaler alone	40 (34)	43 (36)	38 (32)	38 (32)	41 (35)	200 (34)
	SABA inhaler with LMA	14 (12)	13 (11)	16 (13)	18 (15)	14 (12)	75 (13)
	SABA inhaler with ICS	65 (55)	62 (53)	66 (55)	62 (53)	63 (53)	318 (54)
Baseline Pre-bronchodilator PEF (L/min)							
	Mean (SD)	192.5 (67.1)	193.3 (60.8)	198.1 (54.0)	180.4 (59.7)	182.9 (57.2)	189.5 (60.1)
Baseline Pre-bronchodilator FEV_1 L							
	Mean (SD)	1.4 (0.5)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)

Source: Reviewer

3.2.4 Results and Conclusions

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

According to the statistical analysis plan, for the primary endpoint, the primary comparison of interest was the comparison of the average of the higher two FF dose (FF 100 and FF 50) versus the placebo. Table 5 presents this result. A statistically significant difference from placebo was observed for the average of the two higher doses of FF (FF 50 OD and FF 100 OD) with mean improvement of 16.0 L/min (95% CI: 9.6, 22.4) and p-value of less than 0.001.

Both treatment comparisons of FF 100 OD versus placebo and FF 50 OD versus placebo were statistically significant (12.5 L/min, 95% CI: 5.1, 19.8; $p<0.001$ and 19.5 L/min, 95% CI: 12.1, 26.9; $p<0.001$, respectively). Treatment comparison of FF 25 OD versus placebo was also statistically significant (18.6 L/min, 95% CI: 11.3, 26.0; $p<0.001$). Table 6 presents the results of endpoint AM PEF. There was no dose-response observed in the primary endpoint results.

Table 7 presents the results of endpoint PM PEF. Results were similar to the AM PEF with slightly less improvement. Statistically significant differences from placebo were observed for all FF treatment groups, but there was no dose-response observed.

In the analysis of mean change from baseline in trough FEV_1 at Week 12 (last observation carry forward [LOCF]), LS mean increases from baseline were observed across all FF treatment

groups as well as placebo group. A statistically significant difference from placebo was observed for the FF 25 OD treatment group with improvement of 126 mL (95% CI: 51, 201) and p-value of less than 0.001, but not for the FF 50 OD and FF 100 OD treatment groups. For the active control group FP 100 BD, no statistically significant difference from placebo was observed. Table 8 presents the results of endpoint FEV_1.

For the endpoint of change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period, statistically significant improvements over placebo were observed for all FF treatment groups. Table 9 presents the result of endpoint of percentage of rescue-free 24-hour periods.

Table 5: Statistical Analyses of Change from Baseline in AM PEF (L/min) Averaged Over Weeks 1-12 Average of FF 50 OD and FF 100 OD doses versus Placebo (Study HZA106855, ITT Population)

	PBO N = 119	Average of FF 50 OD and FF 100 OD N = 238
LS Mean (SE): L/min	198.9	214.9
LS Mean change (SE): L/min	3.3 (2.63)	19.3 (1.86)
Difference from PBO: L/min (95% CI)		16.0 (9.6, 22.4)
p-value compare to PBO		<0.001

Source: Reviewer

Table 6: Statistical Analyses of Change from Baseline in AM PEF (L/min) Averaged Over Weeks 1 to 12 (Study HZA106855, ITT Population)

	PBO N = 119	FF 25 OD N = 118	FF 50 OD N = 120	FF 100 OD N = 118	PF 100 BD N = 118
LS Mean (SE): L/min	198.9	217.5	218.4	211.3	212.9
LS Mean change (SE): L/min	3.3 (2.63)	21.9 (2.66)	22.8 (2.65)	15.8 (2.64)	17.3 (2.64)
Difference from PBO: L/min (95% CI)		18.6 (11.3, 26.0)	19.5 (12.1, 26.9)	12.5 (5.1, 19.8)	14.0 (6.7, 21.4)
p-value compare to PBO		<0.001	<0.001	<0.001	<0.001

Source: Reviewer

Table 7: Statistical Analyses of Change from Baseline in PM PEF (L/min) (Study HZA106855, ITT Population)

	PBO N = 119	FF 25 OD N = 118	FF 50 OD N = 120	FF 100 OD N = 118	PF 100 BD N = 118
LS Mean (SE): L/min	210.3	221.5	223.7	218.7	218.3
LS Mean change (SE): L/min	5.1 (2.76)	16.3 (2.81)	18.5 (2.77)	13.5 (2.78)	13.1 (2.77)
Difference from PBO:		11.2	13.4	8.4	8.0

L/min (95% CI)		(3.4, 19.0)	(5.7, 21.1)	(0.7, 16.1)	(0.3, 15.7)
p-value compare to PBO		0.005	<0.001	0.033	0.042

Source: Reviewer

Table 8: Statistical Analyses of Change from Baseline in PM Trough FEV_1 (L) at Week 12 (LOCF) (Study HZA106855, ITT Population)

	PBO N = 119	FF 25 OD N = 118	FF 50 OD N = 120	FF 100 OD N = 118	PF 100 BD N = 118
LS Mean (SE): L	1.524	1.650	1.545	1.557	1.587
LS Mean change (SE): L/min	0.128 (0.0264)	0.254 (0.0272)	0.150 (0.0252)	0.162 (0.0272)	0.192 (0.0262)
Difference from PBO: L (95% CI)		0.126 (0.051, 0.201)	0.022 (-0.050, 0.094)	0.033 (-0.041, 0.108)	0.064 (-0.010, 0.137)
p-value compare to PBO		<0.001	0.551	0.379	0.089

Source: Reviewer

Table 9: Statistical Analysis of Change from Baseline in Percentage of Rescue-Free 24-Hour Periods (Study HZA106855, ITT Population)

	PBO N = 119	FF 25 OD N = 118	FF 50 OD N = 120	FF 100 OD N = 118	PF 100 BD N = 117
LS Mean change (SE)	16.5 (3.01)	24.9 (3.03)	26.3 (3.03)	28.7 (3.02)	22.7 (3.01)
Difference from PBO (95% CI)		8.4 (0.0, 16.9)	9.8 (1.3, 18.2)	12.2 (3.8, 20.5)	6.2 (-2.1, 14.6)
p-value compare to PBO		0.050	0.023	0.004	0.143

Source: Reviewer

3.3 Evaluation of Safety

Please refer to the evaluation of safety in the clinical review by Dr. Keith Hull.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this review, subgroup analyses were conducted for primary endpoints for sex, age, race and region using summary statistics of mean, standard deviation, median, minimum and maximum due to small number of subjects in each group. Table 10 presents these results. Figure 2 presents results of change from baseline in AM PEF by subgroups in FF 50 treatment group with 95% confidence interval.

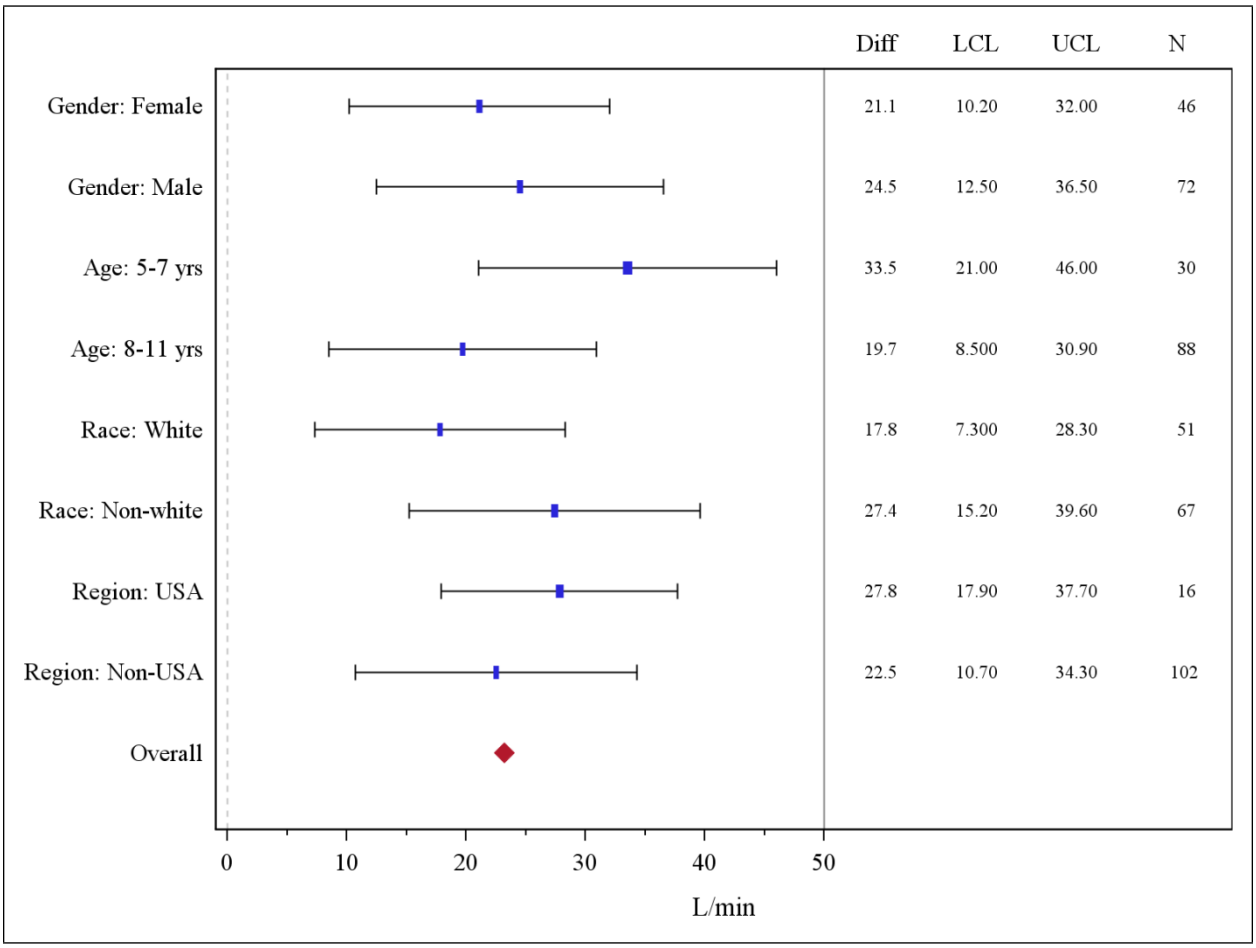
Subgroup analysis of sex, age, race and region using summary statistics demonstrated that the efficacy result of the primary endpoint is consistent across the subgroup considered.

Table 10: Summary Statistics of Primary Endpoint of Change from Baseline in AM PEF (L/min) by Subgroups

		Mean (SD) Median (Min, Max)				
Subgroups		**PBO N = 119**	**FF 25 OD N = 118**	**FF 50 OD N = 120**	**FF 100 OD N = 118**	**PF 100 BD N = 118**
Sex						
	Female	10.4 (35.3) 6.1 (-33, 178)	16.3 (38.28) 24.1 (-173, 74)	21.1 (30.72) 16.6 (-24, 118)	17.6 (24.61) 17.4 (-65, 63)	13.8 (29.69) 13.9 (-36, 87)
	Male	-2.9 (23.15) -1.0 (-53, 49)	20.2 (28.9) 14.9 (-41, 112)	24.5 (37.73) 15.1 (-42, 167)	16.9 (31.25) 15.5 (-45, 106)	22.0 (26.35) 20.8 (-24, 93)
Age Group (yrs)						
	5 to 7 years	3.8 (20.13) 6.1 (-53, 49)	17.4 (22.85) 15.9 (-41, 69)	33.5 (40.74) 18.4 (-10, 167)	11.3 (26.57) 8.7 (-65, 61)	23.7 (29.12) 21.7 (-36, 93)
	8 to 11 years	1.7 (34.54) -1.3 (-48, 178)	19.9 (37.63) 19.5 (-173, 112)	19.7 (32.42) 14.5 (-42, 138)	22.4 (29.55) 18.8 (-45, 106)	15.8 (26.16) 17.6 (-34, 69)
Race						
	White	-8.3 (21.91) -8.4 (-53, 45)	20.8 (28.78) 14.9 (-41, 112)	17.8 (28.71) 13.7 (-42, 92)	16.0 (25.84) 17.4 (-42, 75)	11.9 (19.53) 11.3 (-26, 45)
	Mixed Race	11.7 (37.93) 8.9 (-28, 178)	21.9 (24.22) 22.0 (-19, 69)	28.5 (43.47) 15.2 (-18, 167)	16.6 (29.41) 15.3 (-65, 87)	21.7 (28.3) 25.1 (-36, 87)
	American Indian or Alaskan Native	7.4 (23.57) 10.0 (-42, 46)	11.6 (55.01) 26.3 (-173, 78)	25.2 (34.89) 21.0 (-22, 118)	21.4 (39.9) 6.0 (-27, 106)	26.1 (28.72) 25.2 (-28, 93)
	African American/Africa Heritage	11.3 (33.21) 15.9 (-33, 47)	17.7 (28.65) 27.1 (-23, 40)	36.1 (21.42) 44.4 (12, 63)	19.1 (20.16) 20.0 (-14, 58)	6.7 (43.09) -12.0 (-34, 87)
	Asian	9.3 (25.46) 7.9 (-32, 51)	6.7 (30.55) 4.9 (-34, 55)	15.1 (36.9) 2.4 (-15, 88)	16.7 (13.48) 16.7 (7, 26)	43.0 (31.76) 53.0 (1, 81)
Geographical Region						
	USA	-1.0 (28.54) 6.1 (-42, 47)	15.7 (24.09) 16.1 (-25, 60)	27.8 (25.72) 18.3 (-6, 88)	15.2 (20.72) 17.3 (-14, 58)	16.5 (32.33) 17.2 (-34, 87)
	Non-USA	3.1 (29.60) 1.1 (-53, 178)	19.5 (33.65) 17.5 (-173, 112)	22.5 (36.36) 15.1 (-42, 167)	17.6 (29.97) 15.7 (-65, 106)	19.6 (27.11) 19.8 (-36, 93)

Source: Reviewer

Figure 2: Forest Plot of Summary Statistics of Primary Endpoint of Change from Baseline in AM PEF (L/min) by Subgroups



Source: Reviewer

5 SUMMARY AND CONCLUSIONS

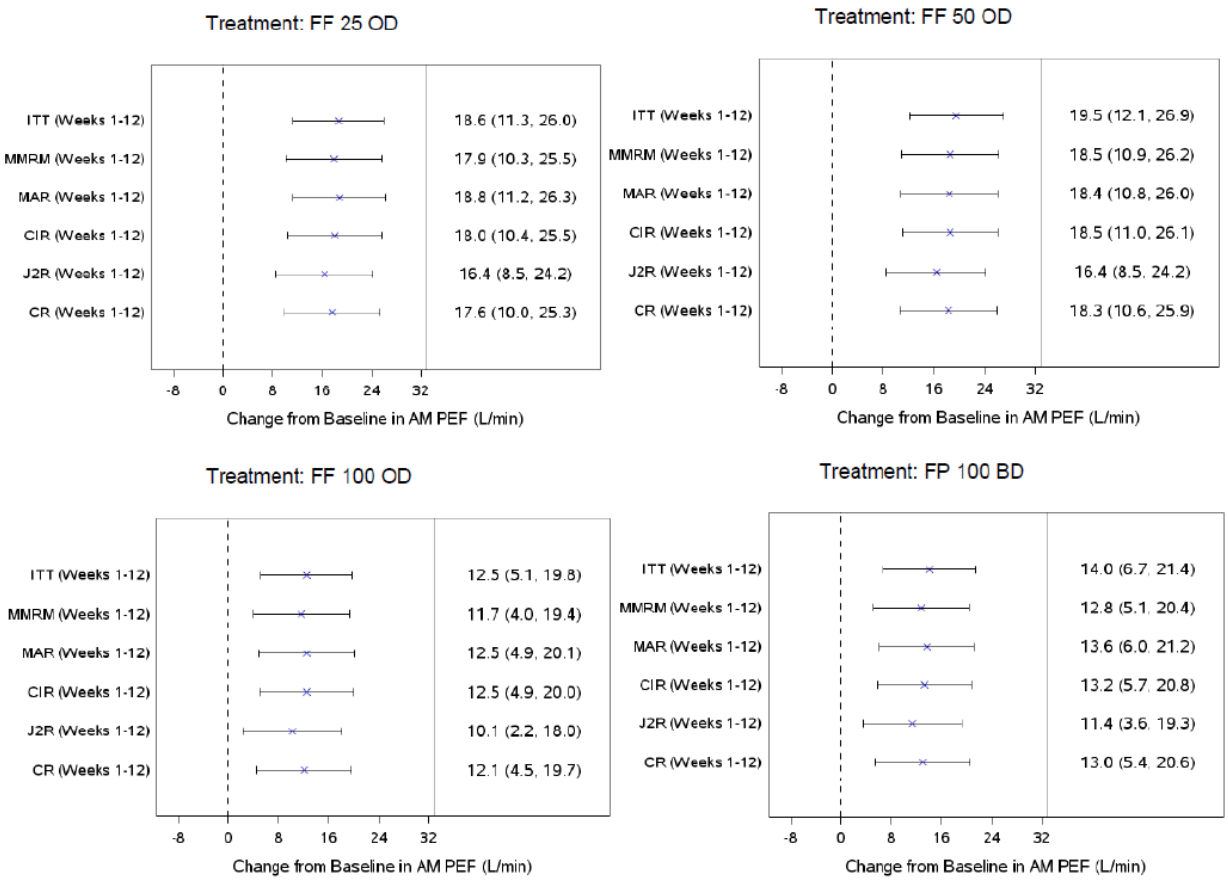
5.1 Statistical Issue

During the IND development, the agency has agreed to conduct single study due to the supportive evidence of efficacy from adult and adolescent program. Considering statistically highly significant results of the primary endpoint and positive results of the clinically relevant secondary endpoints, the evidence of efficacy is substantial.

There were 45% patients from placebo group withdrawal from the study. The most common reason for withdrawal was lack of efficacy (35%). There were 20~28% patients from FF treatment group withdrawal from the study, and 14~19% due to lack of efficacy.

Due to the high withdrawal rate from the placebo treatment group, a greater proportion of subjects in the placebo group were missing change from baseline in AM PEF data each week from week 1 to week 12. The applicant has conducted several sensitivity analyses to examine assumptions about missing AM PEF data. Multiple imputation methods assuming missing at random (MAR), copy increment from reference (CIR), jump to reference (J2R) and copy reference (CR) were used in these sensitivity analyses. Figure 3 presents these results along with the primary analysis results. Results from repeated measure analyses are also presented in Figure 3. These analyses produced similar and statistically significant results for all FF treatment group compare to placebo group. They supported the primary analyses.

Figure 3: Adjusted Mean Treatment Difference (95% CI) in Change from Baseline in AM PEF (L/min): Primary Analysis and Sensitivity Analyses Averaged Over Weeks 1 to 12 (Study HZA106855, ITT Population)



Source: HZA106855 CSR, Figure 6.10
AM=morning; BD=twice daily; OD=once daily; PEF=peak expiratory flow
Analyses: ITT=Intent-to-Treat Primary Analysis, MMRM=Mixed Model Repeated Measures, MAR=Missing at Random multiple imputation method, CIR=Copy Increment from Reference multiple imputation method, J2R=Jump to Reference multiple imputation method, CR=Copy Reference multiple imputation method.

The applicant also has conducted tipping point analyses allowing the assumptions about the missing data on the different arms to vary independently. Due to the large magnitude of efficacy,

in all scenarios considered, statistically significant differences from placebo were observed for all FF doses and the active control. Therefore, the tipping point analyses supported the primary analysis.

Therefore, the efficacy results of the primary endpoint are robust despite of large amount of missing data.

5.2 Collective Evidence

This review focused on a single phase 2b/3 study. Effectiveness of three different dosages was examined: FF 25 OD, FF 50 OD and FF 100 OD. Statistically significant and reliable (despite large amount of missing data) demonstration of efficacy of FF over placebo was achieved in change from baseline of AM PEF over the 12-week treatment period, but there was no dose-response observed. Improvement of FF over placebo was also observed in change from baseline of PM PEF over 12-week treatment period and change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period for all dosages. However, no benefits of FF 50 OD over placebo and of FF 100 OD over placebo were observed for endpoint of change from baseline FEV_1 at week 12 (LOCF).

Based on the primary endpoint AM PEF and secondary endpoint PM PEF results, both FF 25 OD and FF 50 OD have bigger improvements than FF 100 OD. FF 100 OD has already been approved for treatment of asthma in adult and adolescent asthma patients. Considering no major safety issues in FF 50 OD treatment group, FF 50 OD can be a good candidate dosage for approval.

5.3 Conclusions and Recommendations

GSK has proposed 1 inhalation of ARNUITY ELLIPTA 50 mcg once daily for treatment of asthma in patients aged 5 to 11 years. We think that the evidence of efficacy of active treatment for the pediatric population is substantial and robust considering statistically highly significant results for the primary endpoint supported by positive results for the clinically relevant secondary endpoints. Regarding the proposed labeling claims in the clinical studies section, we recommend keeping the results of AM PEF, the primary endpoint. (b) (4)

We recommend approval for expansion of the indicated population to include pediatric patients aged 5 to 11 years.

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/s/

MINGYU XI
04/02/2018

YONGMAN KIM
04/02/2018
I concur.