Medical Officer Review
Division of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

Application:	NDA 22-051	Trade Name:	Veramyst
Sponsor:	GlaxoSmithKline	USAN Name:	Fluticasone furoate
Medical Officer:	Sofia Chaudhry, MD		
Team Leader:	Susan Limb, MD	Category	Corticosteroid
Review Date:	July 17, 2012	Route:	Intranasal

Submissions Reviewed In This Document

Document Date	CDER Stamp Date	Submission	Comments
October 25, 2011	October 25, 2011	SDN 413	CSR FFR101782 for PMC #1 (growth study)

Review Summary:

This is a medical officer review of a prior approval labeling supplement submitted by GlaxoSmithKline to NDA 22-051 for Veramyst® (fluticasone furoate nasal spray; FFNS; Approval: April 27, 2007). This labeling supplement includes the completed study report for FFR101782, a growth study in pre-pubescent patients that was conducted to satisfy the post marketing commitment (PMC) # 1 outlined in the April 27, 2007, approval letter.

PMC #1:

- To conduct a one-year linear growth study in children with fluticasone furoate using a dose that is relevant to the proposed fluticasone furoate nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation. Submit a labeling supplement reflecting the results of the study.

The growth effect of 52 weeks of FFNS was measured using stadiometry in children 5 to 8.5 years of age. FFNS demonstrated a statistically significant difference from placebo of -0.270 cm/year (95% CI: -0.476, -0.064). In addition, the magnitude of the mean difference falls within the range observed for other intranasal corticosteroids: fluticasone propionate (-0.14; 95% CI -0.54, 0.27), budesonide (-0.25; 95% CI -0.59, 0.08), mometasone furoate (+0.61 cm/year; 95% CI 0.11, 1.10), and beclomethasone (–1.45 cm/year difference from placebo; P<0.01).

The design for this pediatric growth study is adequate and the results appear reliable. Therefore, this reviewer recommends that this study be considered adequate to fulfill PMC #1. Overall, the sponsor's proposed language regarding the pediatric growth study is factually accurate and includes language similar to that in the currently approved labels of other intranasal products. The following text will be included in Section 8.4, Special Populations, Pediatrics:

- "A randomized, double-blind, parallel-group, multicenter, 1-year placebo-controlled clinical growth study evaluated the effect of 110 mcg of VERAMYST Nasal Spray once daily on growth velocity in 474 prepubescent children (girls aged 5 to 7.5 years and boys aged 5 to 8.5 years) with stadiometry. Mean growth velocity over the 52-week treatment period was lower in the patients receiving VERAMYST Nasal Spray (5.19 cm/year compared with placebo (5.46 cm/year). The mean treatment difference was -0.270 cm/year [95% CI: -0.476 to -0.064]. *[see Warnings and Precautions (5.7)]"*

Consultation with OSE and DDMAC, and recommendations from the consultants were incorporated where relevant. The final label is pending at the time of this review.

Recommended Action: Approval of labeling supplement and fulfillment of PMC #1.

1. Introduction

Veramyst (fluticasone furoate nasal spray; FFNS) was approved for the treatment of symptoms of SAR and PAR in adults and children ≥ 2 years of age on April 27, 2007 (NDA 22-051). The recommended dose for patients ≥12 years is 110 mcg (2 sprays per nostril) once daily. The dose for patients 2 to 11 years of age is 55 mcg (1 spray per nostril) once daily. Given the known class effect of growth inhibition by corticosteroids, the current label includes a Warnings and Precautions statement regarding a potential reduction in growth velocity. In addition, the sponsor was required to conduct a growth study as outlined in PMC #1 to further characterize this effect.

- To conduct a one-year linear growth study in children with fluticasone furoate using a dose that is relevant to the proposed fluticasone furoate nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation. Submit a labeling supplement reflecting the results of the study.

GSK submitted its proposed growth study to the Division on August 24, 2007, for review and comments. The Divison's review of the protocol (see review by Dr. Anthony Durmowicz; October 2, 2007) noted that the proposed study closely adhered to the FDA Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of Effects of Growth in Children (2007). However, as this was a multinational trial and a potential for regional differences in growth velocity exists, the Division recommended that the sponsor include a regional subpopulation analysis.

One year growth studies, as measured by stadiometry, have previously been conducted on multiple intranasal corticosteroid products in children. To place the FFNS results in context, these results are provided in Table 1: Effect of Intranasal Corticosteroids on Growth Rate (cm/year). Growth studies for intranasal beclomethasone HFA, intranasal ciclesonide HFA aerosol, intranasal ciclesonide, intranasal triamcinolone AQ, intranasal triamcinolone HFA aerosol, or intranasal flunisolide have not yet been completed.

Table 1: Effect of Intranasal Corticosteroids on Growth Rate (cm/year)

Drug	Age (years)	Dose Mcg/day	N	Change from placebo (cm/year)	95% CI
Beclomethasone dipropionate[1,2]	6-9.5	336	49	-1.45	(P<0.01)
		0	49		
Budesonide[3]	4-8	64	141	-0.25	-0.59, 0.08
		0	67		
Fluticasone propionate[4t]	3-9	200	56	-0.14	-0.54, 0.27
		0	52		
Mometasone furoate[2,5]	3-9	100	42	+ 0.61	0.11,1.10
		0	40		

[1] Beconase prescribing information
[2] Data from Dr. Starke, Pulmonary and Allergy Drugs Advisory Committee meeting, March 24, 2005
[3] Rhinocort Aqua prescribing information
[4] Flonase prescribing information
[5] Nasonex prescribing information

2. Protocol Design

The inclusion/exclusion criteria (including age, size and sexual maturity of children enrolled), use of concomitant medications, study design, treatment doses, and compliance assessments follow the recommendations of the FDA Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects of the Growth in Children (2007). However, as noted by the Division during the original protocol evaluation, growth velocity for children in different regions may differ from children in the United States. Therefore, during the original study design, GSK proposed to stratify the data into appropriate subpopulations. This approach was acceptable to the Division. The data, stratified by gender, race and ethnicity, are located in Table 9: Summary of growth velocity by gender, race and ethnicity.

Details of the protocol design follow below.

Primary Growth Endpoint:

- mean difference in growth velocities between subjects treated with FFNS 100 mcg once daily and placebo as determined by stadiometry
    - triplicate stadiometry measurements collected at each clinic visit, due to diurnal variation in height, all visits scheduled to measurements taken at same time of day within a 3 hour am or pm window

Additional Safety Endpoints:

- frequency and type of AE
- results of routine clinical lab tests (chemistry, hematology, urinalysis)
- results of 24-hour urinary cortisol excretion assessments (24 hour urine samples were collected by the parent/guardian with 7 days of randomization, at the end of the treatment period and end of the 8 week follow up period in an urinary cortisol subpopulation)
- result of nasal examination

Population:

Key Inclusion Criteria:

- ≥ 5 but < 7.5 years old for females, and ≥ 5 but < 8.5 years old for males at screening
- pre-pubescent at Tanner stage 1 for all classifications during the 5 baseline visits
- bone age within 1 year of chronological age
- diagnosis and history of PAR
- during baseline period have rTNSS ≥ 5 on any 4 of the last 7 days prior to Visit 2
- current height, weight, and BMI within 3rd and 97th percentile
- ability to comply with study procedures, have parent/guardian consent

Key Exclusion Criteria:

- history of abnormal growth, or prior/current use of medication/treatment that may affect growth
- history of asthma with exception of mild intermittent asthma controlled by PRN SABA
- history of nasal or sinus surgery, septal perforation, severe nasal obstruction including polyps
- any other significant medical condition per investigator discretion
- use of corticosteroids within 6 weeks of Visit 1 or during baseline period, or use of systemic corticosteroids within 12 weeks of Visit 1 or during baseline period,
- immunotherapy initiated or adjusted within 30 days of Visit 1
- use of immunosuppressive medications during baseline period
- use of any medications that inhibit cytochrome P450 CYP3A4

- exposure to varicella or measles during the 3 week screening period or baseline period if not immune

Prohibited Medications

- intranasal cromolyn
- short acting antihistamines
- long acting antihistamines other than rescue loratadine syrup provided by GSK
- intranasal antihistamines
- corticosteroids: oral, intranasal, inhaled, injected, ocular or dermatological with exception of topical hydrocortisone 1% or less
- oral or intranasal decongestants
- LABA
- intranasal, oral and inhaled anticholinergics
- any intranasal medication other than study drug
- oral anti-leukotrienes
- immunotherapy, stable maintenance dose will be allowed for duration of the study
- immunosuppressive medications
- omalizumab
- CYP3A4 inhibitors
- tricyclic antidepressants

Withdrawal Criteria:

- chickenpox or measles
- noncompliance
- AE, in investigator opinion, that poses unacceptable risk for continued participation
- treatment blind broken
- GSK stops the study

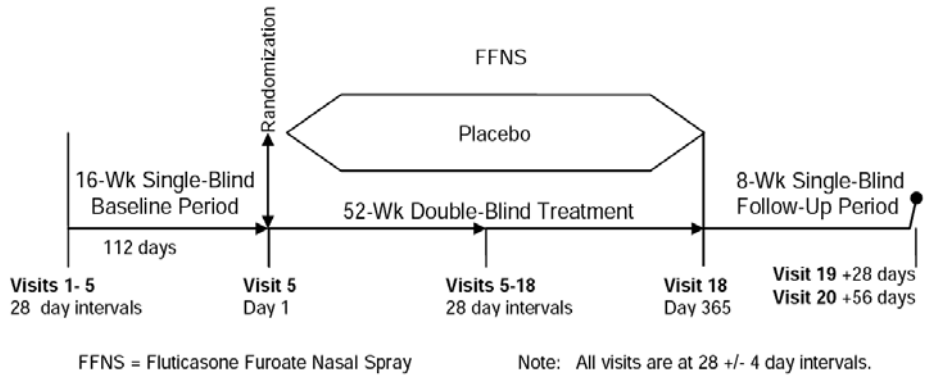
Study Design:

This was a phase IV, multinational, randomized, double-blind, placebo-controlled, parallel group 76 week study.

- Visit 1 Screening Visit:
- Visit 1 – 4: every 28 days: 16 week baseline period to assess baseline growth
- Visit 5: randomization visit to FFNS 100 mcg daily or placebo
- Visits 6-18: every 28 days: 52 week double-blind treatment period
- Visit 19 (28 days after treatment completion): single-blind follow-up period
- Visit 20 (56 days after treatment completion): single-blind follow-up period

Study Schematic:

Figure 1 FFR101782 Study Design



Source: CSR FFR101782 Figure 1

Study Treatments:

Subjects were randomized 2:1 into the following treatment groups:

- FFNS 110 mcg once daily x 104 weeks
- Placebo nasal spray x 104 weeks

Loratadine syrup was given to all study participants as a rescue medication.

Compliance Assessment:

Compliance was assessed with daily e-diary recordings, nasal spray device weights, nasal symptom assessments and rescue medication use.

3. Study Results

Disposition:

Overall the subject disposition and breakdown of protocol deviations were balanced between treatment groups.

A total of 910 subjects were screened. Of these, 474 subjects were randomized in a 1:1 ratio and included in the ITT population. Of the 474, 435 were included in the Growth Population and 342 in the Urinary Cortisol Population. A majority of subjects (N = 373, 79%) completed the study with withdrawal of consent being the main reason for premature withdrawal (N = 40, 8%).

The disposition data is summarized in Table 2: Summary of Subject Disposition and Protocol Deviations (ITT).

Table 2: Summary of Subject Disposition and Protocol Deviations (ITT)

	Placebo N = 237	FFNS N = 237
ITT Completion status, n (%)		
Completion	187 (79)	186 (78)
Withdrawn	50 (21)	51 (22)
Reason for Withdrawal, n (%)		
Consent withdrawn	20 (8)	20 (8)
Protocol deviation	12 (5)	15 (6)
Lost to follow up	5 (2)	7 (3)
Adverse event	5 (2)	5 (2)

	Placebo N = 237	FFNS N = 237
Investigator discretion	2 (<1)	4 (2)
Lack of efficacy	3 (1)	0
Protocol defined stopping criteria	3 (1)	0
Any Protocol Deviation, n (%)	30 (13)	26 (11)
Prohibited medication use	33 (14)	30 (13)
Other	4 (2)	3 (1)
Reported Incorrect treatment received	4 (2)	2 (<1)
Incorrect age stratification	0	1 (<1)

Source: CSR FFR101782: Table 1, Table 5.7, 5.8

Baseline Demographics:

Baseline demographics were balanced between the placebo and FFNS treatment groups. Subjects in both groups had a similar mean age, height, weight, and BMI and both groups were predominately Caucasian. In addition, allergy history between the two treatment groups was similar with most subjects sensitized to dust mite (placebo N = 169; FFNS N = 160).

An equal percentage (75%) of subjects in both treatment groups used concomitant medications during the study period. The most frequently used medications were salbutamol, lidocaine, prilocaine, and ibuprofen. As use was similar between treatment groups and none of the medications are known to be associated with significant growth restriction, use is unlikely to have impacted the data.

Table 3: Baseline demographics

	Placebo N = 237	FFNS N = 237
Age (yrs), mean (SD)	6.61 (0.969)	6.64 (0.933)
Gender, n (%)		
Male	164 (69)	162 (68)
Female	73 (31)	75 (32)
Race, n (%)		
White	189 (80)	199 (84)
American Indian or Alaska Native	19 (8)	18 (8)
African heritage	16 (7)	12 (5)
Asian	7 (3)	5 (2)
Other	6 (2)	3 (1)
Height (cm), mean (SD)	119.7 (7.47)	119.8 (7.24)
Weight (kg), mean (SD)	24 (4.13)	24.1 (4.37)
BMI (kg/m^2), mean (SD)	16.6 (1.58)	16.6 (1.67)

Source: CSR FFR101782 Table 7 and Dr. Robert Abugov's statistical review Table 3

All regions had equal percentages of participants randomized to the placebo and treatment groups. The United States had the largest number of enrollees followed by Chile. As noted earlier, the multinational nature of this study was an issue of concern for the Division. To address this, the statistical reviewer conducted a regional analysis of USA vs non-USA. The results of this analysis are discussed in Growth Velocity by Gender, Race, and Ethnicity Section of this review.

Table 4: Enrollment by Country

Country	Placebo	FFNS	Total

United States, n (%)	82 (35)	83 (35)	165 (35)
Non USA	154 (65)	155 (65)	309 (65)
Chile, n (%)	77 (32)	77 (32)	154 (32)
Argentina, n (%)	44 (19)	44 (19)	88 (19)
Peru, n (%)	19 (8)	18 (8)	37 (8)
France, n (%)	9 (4)	9 (4)	18 (4)
Canada, n (%)	6 (3)	6 (3)	12 (3)

Source: CSR FFR101782 Table 5.3 and Dr. Robert Abugov's statistical review Table 3

Compliance

Compliance was assessed by electronic diary card records (e-diary), nasal device weights, daily rTNSS scores, and rescue medication use. Overall, this study demonstrated reasonable rates of compliance and the study results are adequate for review.

Per the e-diary records, 82% of placebo subjects and 83% of FFNS subjects were compliant with daily treatment. In addition, both the placebo and FFNS treatment groups were similar and close to the benchmark weight (0.218 g) for the nasal device with respective mean and median values for the placebo group of 0.207 g and 0.20 g and 0.205 g and 0.212g for the FFNS group. Finally, the FFNS treatment group demonstrated improved efficacy over the placebo group with a change from baseline in rTNSS score of -1.288 versus the placebo group of -0.998. Both treatment groups demonstrated only a little change from baseline in rescue medication-free days: -2.23% for placebo and -2.96% for the FFNS treatment group.

Safety Results:

Growth Velocity:

The primary study endpoint was the mean difference between FFNS and placebo in growth velocity (cm/year) as assessed by stadiometry. Baseline mean velocity growth was similar between the two treatment groups (placebo: 5.972 cm/year; FFNS: 5.935 cm/year). For the treatment period, the FFNS treatment group had a growth velocity of 5.19 cm/year versus 5.46 cm/year in the placebo group. This provided for a LS mean difference of -0.270 cm/year with a 95% CI of -0.48, -0.06. Therefore, a statistically significant effect on growth was demonstrated by FFNS. In addition, the magnitude of the mean difference is similar to the effect seen for other intranasal corticosteroids. The growth effect data for the other intranasal steroids is summarized in Table 1: Effect of Intranasal Corticosteroids on Growth Rate (cm/year).

Table 5: Summary of Change from baseline in growth velocity assessed by stadiometry

	Placebo		FFNS	
	Growth Velocity (cm/year)	Change from baseline (cm/year)	Growth Velocity (cm/year)	Change from baseline (cm/year)
Baseline				
N	218		217	
Mean	5.972		5.935	
SD	1.2161		1.2474	

Growth Velocity (cm/year)	Change from baseline (cm/year)	Growth Velocity (cm/year)	Change from baseline (cm/year)	Growth Velocity (cm/year)

	Placebo		FFNS	
Treatment				
N	218	218	217	217
Mean	5.686	-0.287	5.401	-0.534
SD	1.2295	1.5640	1.1864	1.5370
Follow up				
N	191	191	188	188
Mean	5.668	-0.367	5.082	-0.834
SD	3.0856	3.39	2.4791	2.4948

Source: CSR FFR101782 Table 13

Table 6: Primary Analysis of Growth

	Placebo	FFNS
Primary Analysis		
N	218	217
LS mean	5.464	5.194
LS mean difference		-0.270
95% CI		(-0.474,-0.064)

Source: Dr. Robert Abugov's statistical review Table 4

Sensitivity analyses of the primary safety endpoint

Additional sensitivity analyses, as listed below, were conducted by the statistical reviewer, Dr. Robert Abugov. In general, these results support the conclusion that the mean growth velocity decreased by 0.270 cm/year over the 52 week trial. The sensitivity analyses conducted included:

- excluding subjects with one post baseline Tanner stage assessment ≥ 2
- excluding subjects with questionable height measurements
- excluding height measurements taken after receiving medications known to affect growth (corticosteroids or oral CNS stimulants or all of the above)
- random coefficients model

These data are summarized in Table 7: Subgroup analyses of growth analyses (cm/year).

Table 7: Subgroup analyses of growth analyses (cm/year)

Population	Placebo	FFNS
Excluding subjects with Tanner Stage ≥ 2		
N	201	195
LS mean (SE)	5.467	5.185
LS mean difference		-0.282
95% CI		(-0.503,-0.061)
Excluding questionable height measurements		
N	218	217
LS mean (SE)	5.465	5.193
LS mean difference		-0.271
95% CI		(-0.478, -0.065)

Population	Placebo	FFNS
Excluding measurements after growth altering medication		
N	215	214
LS mean (SE)	5.473	5.201
LS mean difference		-0.272
95% CI		(-0.481, -0.063)
Random Coefficients Model		
N	218	217
LS mean (SE)	5.676	5.392
LS mean difference		-0.284
95% CI		(-0.508, -0.060)

Source: Dr. Robert Abugov's statistical review Table 5

Secondary analyses of the growth velocity

The sponsor conducted additional secondary analyses of growth. These included:

- growth velocity below the 3rd percentile
- shifts from baseline to endpoint in growth velocity quartile
- growth velocity over treatment weeks 1-12
- growth velocity by gender, race, and ethnicity
- SD scores for height
- growth velocity with random coefficients

In general, these results do not support the conclusion that FFNS had a clinically significant effect on growth compared to placebo. However, more weight is placed on the results of the primary endpoint as it is the more direct measure of a growth effect.

Growth velocity below the 3rd percentile

A similar number of subjects reported growth velocity < 3rd percentile in both the placebo and FFNS treatment groups (placebo: 21 subjects and FFNS: 20 subjects). This result supports the conclusion that the difference in growth velocity is subtle and of unclear clinical significance.

Change in growth velocity quartile from baseline to endpoint

The sponsor provided information regarding both increased and decreased shifts in growth velocity quartiles. However, the submission notes the following limitations with this data. The reference data is based on literature, as velocity data by quartiles is not available in the CDC database. In addition, this characterization requires transforming a continuous variable to a categorical variable.

The FFNS treatment group did not have a large percentage of subjects shifting into a lower growth velocity quartile and the results were similar to those of the placebo group (FFNS: 39%, placebo: 37%). These data do not support a clinically relevant growth effect. The table below summarizes these data.

Table 8: Change in growth velocity quartile

	Placebo N = 218	FFNS N = 217
Increase		
Any	44(24)	61(34)
1st to 2nd	3(2)	8(4)
1st to 3rd	3(2)	4(2)

1st to 4th	17(9)	19(10)
2nd to 3rd	1(<1)	4(2)
2nd to 4th	4(2)	15(8)
3rd to 4th	16(9)	11(6)
Decrease		
Any	68(37)	70(39)
4th to 3rd	6(3)	5(3)
4th to 2nd	4(2)	9(5)
4th to 1st	16(14)	34(19)
3rd to 2nd	3(2)	2(1)
3rd to 1st	15(8)	9(5)
2nd to 1st	14(8)	11(6)
No change	70(38)	50(28)

Source: CSR FFR101782 Table 16

Growth velocity during first 12 weeks of treatment
The LS mean growth velocity for the first 12 weeks of treatment was similar between both the placebo and FFNS group. The placebo group had a velocity of 5.64 cm/year compared to 5.66 cm/year for the FFNS treatment group. These data indicate that FFNS does not appear to have a strong impact on growth during the first 12 weeks of treatment.

Growth velocity by gender, race, ethnicity
Both genders, in both treatment groups, had mean growth velocity decrease during the treatment period. Overall, the change in mean growth velocity over the 52 week treatment was similar regardless of gender.

The evaluation of the data stratified by race and ethnicity is limited by the small sample sizes of races other than Caucasians. However, the growth effect does not appear to vary by race or ethnicity. In addition, no statistically significant interaction was seen by region (USA vs non-USA) in an analysis conducted by the statistical reviewer, Dr. Robert Abugov.

Table 9: Summary of growth velocity by gender, race and ethnicity

	Baseline	treatment	Change	Baseline	Treatment	Change
Gender						
Female						
N	67	67	67	68	68	68
Mean	6.161	5.883	-0.278	6.084	5.542	-0.542
SD	1.2203	1.1906	1.7321	1.2192	1.4405	1.6095
Male						
N	151	151	151	149	149	149
Mean	5.889	5.598	-0.291	5.867	5.337	-0.530
SD	1.2089	1.2401	1.4895	1.2582	1.0496	1.5083
Race						
White						
N	173	173	173	181	181	181
Mean	6.040	5.843	-0.197	5.971	5.531	-0.440
SD	1.2002	1.1063	1.4424	1.2351	1.1147	1.5245
African heritage						
N	15	15	15	11	11	11
Mean	5.385	5.569	0.184	5.836	5.475	-0.361

	Baseline	treatment	Change	Baseline	Treatment	Change
SD	0.9822	1.5492	1.9604	1.0438	1.0894	1.4340
Am. Ind./Al. native						
N	18	18	18	18	18	18
Mean	5.979	4.174	-1.805	5.484	4.221	-1.263
SD	1.4554	1.3165	1.7362	1.4807	1.3922	1.7295
Asian						
N	7	7	7	5	5	5
Mean	5.993	6.171	0.178	6.392	5.018	-1.374
SD	1.2795	0.8287	1.7014	1.3074	1.1516	1.0006
Mixed Race						
N	5	5	5	2	2	2
Mean	5.347	5.332	-0.015	6.104	4.777	-1.327
SD	1.2177	0.7699	0.7840	1.1899	0.7455	0.4444
Ethnicity						
Hispanic or Latino						
N	136	136	136	140	140	140
Mean	6.022	5.585	-0.437	6.035	5.377	-0.658
SD	1.1940	1.2489	1.5862	1.2517	1.2613	1.5637
Not Hispanic or Latino						
N	82	82	82	77	77	77
Mean	5.590	5.853	-0.038	5.752	5.445	-0.307
SD	1.2550	1.1851	1.5031	1.2264	1.0431	1.4701

Source: CSR FFR101782 Table 19, 6.15 and 6.16

Standard deviation score for height
The SD for height measurements by visit was similar between the two treatment groups.

Growth Velocity with random coefficients
The sponsor conducted a random coefficient analysis using an ANCOVA model with height as the dependent variable and baseline height, age, gender, treatment, time and treatment by time interaction as explanatory variables. The results were consistent with the primary endpoint. The placebo group had a growth velocity of 5.680 cm/year compared to 5.397 cm/year for the FFNS treatment group. This provides for a treatment difference of -0.283 cm/yr with a 95% CI of (-0.51, -0.06). These results are similar to the random coefficients sensitivity analysis conducted by Dr. Robert Abugov.

24 hour urinary free cortisol excretion
In general, the results from the urinary free cortisol excretion are not supportive of a clinically significant treatment effect of FFNS on the HPA axis. However as noted earlier, the primary endpoint of growth via stadiometry measurements is the more sensitive indicator of a growth effect.

A numeric difference was noted between the FFNS treatment group and placebo. However, as no subjects in either treatment group had a measurement below the normal range, the results are not clinically significant. The placebo group had a mean change from baseline in urinary cortisol excretion of 1.52 mcg/24hr compared to 1.85 mcg/24 hr for the FFNS treatment group after 52 weeks of treatment. The results are summarized in the two tables below. This is followed by a box and scatter plot obtained from the sponsor that demarcates the outlier results.

Table 10: Summary of 24-hour Urinary Cortisol Excretion (mcg/24hr)

	Placebo N = 162	FFNS N = 168
Change from baseline Week 52 endpoint Geometric Mean (mcg/24hr)	1.52	1.85

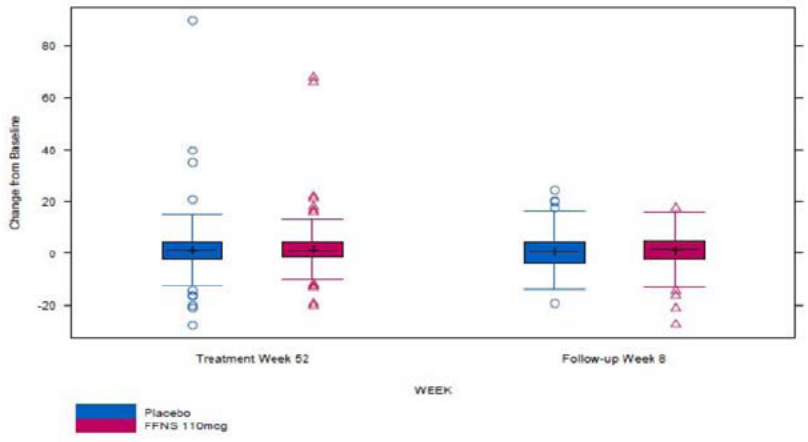
Source: Dr. Robert Abugov's statistical review Table 7

Table 11: Summary of abnormalities in 24 hour urinary cortisol excretion

	Placebo	FFNS
Baseline		
Total N	169	173
Above normal range, n (%)	17 (10)	11 (6)
Within normal range, n (%)	152 (90)	162 (94)
Below normal range n (%)	0	0
Week 52 treatment		
Total N	163	170
Above normal range, n (%)	14 (9)	12 (7)
Within normal range, n (%)	149 (91)	158 (93)
Below normal range, n (%)	0	0
Baseline to week 52 shift		
Total N	163	170
Below normal range, n (%)	0	0
Normal to no change, n (%)	151 (93)	163 (98)
Above normal range, n (%)	12 (7)	7 (4)

Source: CSR FFR101782 Table 6.33

Figure 2: Box plot of change from baseline in 24-hour urinary



Source: CSR Figure 7

Adverse Events:

No new safety signals based on adverse event reporting were identified in this study. Various mild infections were the most frequently reported adverse events during the treatment period including cases of bronchitis, pyrexia, influenza, gastroenteritis. These infections, in addition to headache, occurred in a greater percentage of FFNS subjects and in > 3% of the population

and. These findings are consistent with the known safety profile of FFNS described in the current package insert.

There were no deaths and 6 SAEs reported during this study. Four SAEs were reported in the placebo group (myositis, head injury, osteomyelitis, atypical pneumonia/asthma) and 2 in the FFNS treatment group (appendicitis and gastroenteritis). Three subjects had nasal septal adverse events during the trial: 1 case of nasal ulcer was reported in both the placebo and FFNS treatment groups and one additional subject in the placebo group reported a nasal septal defect. Local nasal toxicity is a class effect of intranasal corticosteroids and is included in the current Warnings and Precautions section of the label.

The table below summarizes the most common adverse events reported in this study.

Table 12: Adverse Events > 3% during Treatment Period

	Placebo N = 237	FFNS N = 237
Any event	160 (68)	152 (64)
Infections and Infestations, n (%)		
Any event	137 (58)	134 (57)
Nasopharyngitis	41 (17)	37 (16)
Bronchitis	24 (10)	34 (14)
Pharyngitis	18 (8)	12 (5)
Respiratory tract infection viral	17 (7)	12 (5)
Sinusitis	14 (6)	11 (5)
Upper respiratory tract infection	11 (5)	13 (5)
Influenza	8 (3)	14 (6)
Acute sinusitis	13 (5)	3 (1)
Tonsillitis	7 (3)	8 (3)
Gastroenteritis	4 (2)	9 (4)
Gastroenteritis viral	9 (4)	3 (1)
Gastroenteritis	4 (2)	9 (4)
Gastroenteritis viral	9 (4)	3 (1)
Respiratory, thoracic and mediastinal disorders, n (%)		
Any event	56 (24)	43 (18)
Epistaxis	22 (9)	16 (7)
Cough	15 (6)	14 (6)
Asthma	9 (4)	7 (3)
General disorders & administration site conditions, n (%)		
Any event	15 (6)	22 (9)
Pyrexia	14 (6)	21 (9)
Nervous system disorders, n (%)		
Any event	7 (3)	9 (4)
Headache	5 (2)	8 (3)

Source: CSR FFR101782 Table 23

4. Discussion:

GSK has submitted the completed study report for trial FFR110537 to fulfill its post marketing commitment to evaluate the effects of FFNS on pediatric growth.

The study protocol follows the FDA Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects of the Growth in Children (2007) and fulfills the

intention of the PMC. In addition, a review of the study results including subject disposition and compliance indicates reasonable study conduct.

Based on the analysis of the primary endpoint, FFNS has a statistically significant impact on growth with the magnitude of the mean difference falling within the range observed for other nasal steroids. However, the growth velocity below the 3rd percentile and shift in growth quartile data are not suggestive of a clinically relevant effect on growth. Overall, inclusion of the results for the primary endpoint into the study label is reasonable.

5. Proposed Product Label:

Final labeling is pending at the time of this review.

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/s/

SOFIA S CHAUDHRY
07/17/2012

SUSAN L LIMB
07/17/2012