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

Statistical Review and Evaluation

CLINICAL STUDY

NDA / Seq Number:	sNDA 22051 / Seq 0030
Drug Name:	Veramyst® Nasal Spray (fluticasone furoate)
Supplement Topic:	Pre-pubescent growth velocity
Current Indication:	Seasonal and perennial allergic rhinitis in adults and children ≥2 years of age
Applicant:	GlaxoSmithKline
Date(s):	Received: 10-25-2011 PDUFA Due Date: 08-25-2012
Review Priority:	Standard
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Keywords: NDA review, Clinical Studies

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1. EXECUTIVE SUMMARY

GlaxoSmithKline has submitted a post-marketing study to evaluate the effects on pre-adolescent growth of Veramyst® Nasal Spray, a fluticasone furoate suspension approved in 2007 by the Agency for the treatment of seasonal and perennial allergic rhinitis in adults and children ≥2 years of age. The recommended starting dosage is 55 mcg fluticasone (1 spray per nostril) once daily (qd) for patients less than 12 years of age, and 110 mcg fluticasone (2 sprays per nostril) qd for patients 12 or more years of age, to be reduced to 55 mcg qd if possible after symptoms have been controlled. Recommended dosage for patients less than 12 years of age whose initial response is inadequate increases to 110 mcg qd, to be reduced to 55 mcg qd after symptoms have been controlled.

The submission examined the effects of Veramyst on pre-adolescent growth in a single randomized, placebo controlled, parallel arm, international Phase IV trial, FFR101782, which randomized 186 males 5 to 8.5 years of age and females 5 to 7.5 years of age to receive either placebo or 110 mcg fluticasone qd for 1 year. Randomization ratio was 1:1, stratified by country and gender.

The point estimate for growth velocity was 0.27 cm/year less among patients treated with Veramyst compared to patients treated with placebo, with the 95% confidence interval ranging from 0.064 to 0.476 cm/year. No subgroup specific differences (age, gender, region) were seen in treatment effects.

Compared to placebo, Veramyst was not associated with reduced 24-hour urinary cortisol. Compliance did not differ by treatment.

2. INTRODUCTION

2.1 Overview

2.1.1 History of Drug Development

Veramyst® Nasal Spray, a fluticasone furoate suspension was approved on 27 April 2007 by the Agency for the treatment of seasonal (SAR) and perennial allergic rhinitis (PAR) in adults and children at least 2 years of age. A detailed account of twelve dose ranging, effectiveness, and safety studies in the submission for approval is provided in the statistical review by Feng Zhou, submitted to DARRTS on 23 February 2007.

Discussions between the sponsor and the Agency concerning potential HPA axis suppression by Veramyst began under IND 048647. At a PIND meeting on 08 August 2003, the Agency recommended HPA axis testing be conducted on the to-be-marketed delivery device rather than the phase 2 delivery device. The sponsor proposed that the pediatric program contain a single six

week HPA axis study in subjects between 2 and 11 years of age. The Agency replied that, because growth may be a more sensitive indicator of systemic corticosteroid effect, a growth study should be conducted. Further, if the growth study was to be conducted after approval, knemometry and HPA axis studies should be performed before approval. The Agency recommended that the HPA axis study include an active comparator arm approved for pediatric use, as recommended by the then current version of the FDA guidance for industry (GFI) "The Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteriods on Growth in Children[1]."

In a meeting between the Agency and the sponsor on 19 July 2004 concerning the clinical development plan, the Agency informed the sponsor that development plans should address potential suppression of hypothalmic/pituitary/adrenal (HPA) axis in pediatric patients. On 03 December 2004, the Agency provided comments on the pediatric HPA axis protocol FFR100012, noting that, if the sponsor did not include an active control arm for ethical reasons, evidence of patient compliance should be supplied, and would be carefully evaluated, since assay sensitivity would otherwise not be assured. On 07 January 2005, the sponsor submitted protocol FFR100012 as a randomized, double blind, placebo controlled parallel group, six week HPA axis study concerning the effect of Veramyst 110 mcg QD on PAR patients 2 to 11 years of age. The protocol did not include an active control arm due to ethical concerns, and the Agency on 29 March 2005 reminded the sponsor of it's position on the need for an active control to confirm assay sensitivity.

On 07 June 2005 the sponsor submitted the reporting and analysis plan (RAP) for protocol FFR20002, a six week double blind placebo and active (prednisone) controlled HPA study in adults and adolescents with PAR. On 10 August 2005, the Agency responded that the RAP was adequate from a statistical perspective.

On 11 August 2005, the sponsor submitted the RAP for the pediatric HPA axis study FFR100012. After evaluation, the Agency on 03 November 2005 requested that the sponsor thoroughly justify the noninferiority margin chosen for comparison of placebo to Veramyst for the 24 hour weighted mean of serum cortisol.

On 02 December 2005, the sponsor submitted a protocol and RAP for the 52 week adult/adolescent HPA axis study FFR102123.

Veramyst was approved on 27 April 2007. Regarding the NDA submission, the clinical team leader memo of 03 March 2007 noted that none of the studies assessing HPA axis (six week study FFR20002 in adults/adolescents, six week study FFR10012 in pediatric patients, 12 week study FFR30008 in pediatric patients, 52 week study FFR102123 in adults) via urinary cortisol suggested significant HPA axis suppression by Veramyst.

[1] The current version of this GFI, released in 2007, reverses this recommendation because of ethical concerns, and instead suggests use of a placebo control.

2.1.2 Current Submission

The current submission includes a one year growth velocity study to assess HPA axis suppression in pre-pubescent patients as well as a two year ocular safety study (Table 1). This review focuses on the growth velocity study, FFR101782, a placebo controlled, parallel arm, international phase 4 trial which randomized 474 pre-adolescent males (5 to 8.5 years of age) and females (5 to 7.5 years of age) to receive either placebo or 110 mcg fluticasone qd for 1 year. Randomization to treatment was 1:1, stratified by country and gender.

One year growth velocity study FFR101782 was conducted at 59 sites within the United States, Canada, France, Argentina, Chile, and Peru. It was intiated on 26 November 2007 and completed on 17 March 2011.

Table 1. Phase IV studies in current submission.

Study	Design	Population	Variables
FFR101782	Placebo F 110 mcg qd 1 Year DB: 52W treatmnt SB: 16W baseline 8W followup	Male: age 5 to 8.5 yr Female: age 5 to 7.5 yr PAR N=474 1F:1P	*Pre-Pubescent Growth Velocity*
FFR110537	Placebo F 110 mcg bid 2 Year DB: 104W treatmnt SB: 1-2W baseline 1W followup	age ≥ 12 y PAR N=550 2F:1P	*Ocular Safety* Primary: time to first event of Δ LOCS III posterior subcapsular opacity ≥ 0.3 Δ IOP ≥ 7mm

DB – double blind, SB – single blind, Δ – change from baseline, LOCS - lens opacities classification system
IOP – Intraorbital pressure

2.2 Data Sources

Data evaluated in this review was accessed at \\Cdsesub1\evsprod\NDA022051\0030 .

3. STATISTICAL EVALUATION

3.1 Evaluation of Growth Velocity

3.1.1 Study Design and Endpoints

Growth velocity was evaluated in study FFR101782, a placebo controlled, parallel arm, international phase 4 trial which randomized 474 pre-adolescent males (5 to 8.5 years of age) and pre-adolescent females (5 to 7.5 years of age) to receive either placebo or 110 mcg fluticasone qd for 1 year. The randomization ratio was 1:1, stratified by country and gender.

Randomization was conducted after a 16 week period to assess baseline growth velocity. Double blinded treatment was administered for 52 weeks, with a subsequent 8 week follow up. During each period, clinic visits were scheduled every 28 ±4 days.

The primary comparison of interest (or safety endpoint) was mean difference in growth velocities between subjects treated with Veramyst fluticasone furoate (F) and saline placebo (P). Stadiometric assessments were conducted at each visit, regardless of whether subjects discontinued treatment.

Secondary safety endpoints included frequency and type of adverse events, routine clinical laboratory tests, 24 hour urinary cortisol, and nasal examinations.

Treatment compliance was also assessed, using daily e-diaries recording usage of nasal spray, change in weight of nasal spray from pior to dispensing until return to site, reflective total nasal symptom score (rTNSS), which is ordinal ranging from 0 to 3, and use of rescue medications.

The study was not powered to detect any treatment differences. Instead, the study was designed to provide an estimated mean treatment difference between F 110 mcg and placebo with a certain degree of precision on the 95% confidence interval in growth velocity, i.e., that the width of that confidence interval should be no greater than 0.5 cm per year.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 474 subjects were randomized and were included in the intent-to-treat population. Of these, 435 (92%) were included in the growth population and 342 (72%) in the urinary cortisol population. The majority of subjects (79%) completed the study. Numerical patterns of treatment continuation until week 52 did not contradict safety (Table 2).

Table 2. **Patient Disposition. N (%).**

Disposition	Fluticasone (N = 237)	Placebo (N=238)
Completed Treatment	186 (78)	187 (78)
Discontinued Treatment	51 (22)	51 (22)
Adverse Event	5 (2)	6 (3)
Treatment Failure	0 (0)	3 (1)
Lost to Followup	7 (3)	5 (2)
Protocol Deviation	15 (6)	12 (5)
Protocol Required	0 (0)	3 (1)
Withdrew Consent	20 (8.4)	20 (8)
Investigator Discretion	4 (2)	2 (1)

source: demog 2012 01 12.sas

Demographic characteristics were balanced at study baseline (Table 3).

Table 3. Demographic and baseline characteristics.

Parameter		Placebo (N=237)	Fluticasone (N=238)
Age			
	Mean (SD)	6.6 (0.9)	6.6 (1)
	Range	5 - 8.4	5 - 8.4
Sex N (%)			
	Male	162 (68.4)	165 (69.3)
	Female	75 (31.6)	73 (30.7)
Race N (%)			
	White	199 (84)	189 (79.4)
	Black	12 (5.1)	17 (7.1)
	Asian	5 (2.1)	7 (2.9)
	Mixed	3 (1.3)	6 (2.5)
	Native Amer	18 (7.6)	19 (8)
	Other	0 (0)	1 (0.4)
Country N (%)			
	USA	83 (35)	83 (34.9)
	non-USA	154 (65)	155 (65.1)
Ethnicit N (%)y			
	Latino	150 (63.3)	147 (61.8)
	Non-Latino	87 (36.7)	91 (38.2)
Height			
	Mean (SD)	119.8 (7.2)	119.7 (7.5)
	Range	102.3 - 134.8	102.1 - 140.4
Weight			
	Mean (SD)	24.1 (4.4)	24 (4.1)
	Range	15.4 - 37	15.2 - 42
BMI			
	Mean (SD)	16.6 (1.7)	16.6 (1.6)
	Range	13.6 - 21.5	13.8 - 21.7

source: demog 2012 01 12.sas

3.1.3 Growth Velocity

For the primary analysis, growth velocity for each subject was calculated using linear regression on measurements at each visit. Calculated growth velocity was then used as the response in an analysis of covariance (ANCOVA) with independent variables treatment, gender, country and baseline age which calculated 95% confidence intervals on the difference between treatments.

Patients included in growth analyses were randomized, received at least one dose of the double blind study medication, and had at least three height measurements from at least three post-randomization visits during the treatment period.

Fluticasone was associated with a mean growth velocity decrement of 0.270 cm/year in the primary analysis (Table 4). The 95% CI (-0.48, -0.06 cm/year) is below 0.5 cm.

Table 4. Growth Velocity (cm/year). Primary Analysis.

Analysis	F	Placebo	Diff	Lower_95	Upper_95
Primary	5.194 (217)	5.464 (218)	-0.270	-0.476	-0.064

A similar analysis including age by treatment interaction as a covariate showed no statistically significant effects of age on treatment (p=0.33).

Sensitivity analyses excluding questionable measurements, excluding patients after they began taking medications with the potential to affect growth, or excluding patients who reached Tanner stage 2 during the study supported the conclusion that mean growth velocity decreased by more than 0.270 cm/year over the 52 week trial period (Table 5). An additional analysis of growth velocity, based on a random coefficients repeated measures model with dependent variable height and independent variables treatment, baseline, age, sex, time since initiation of treatment, and treatment by time since initiation of treatment interaction, showed differences between fluticasone and placebo similar to the primary and other sensitivity analyses (Table 5).

Table 5. Growth Velocity (cm/year). Sensitivity Analyses.

Analysis	F	Placebo	Diff	Lower_95	Upper_95
Excluding Questionable Measurements	5.193 (217)	5.465 (218)	-0.271	-0.478	-0.065
Excluding Growth Affecting Meds	5.201 (214)	5.473 (215)	-0.272	-0.481	-0.063
Excluding Tanner 2	5.185 (195)	5.467 (201)	-0.282	-0.503	-0.061
Random Coefficients Model	5.392 (217)	5.676 (218)	-0.284	-0.508	-0.060

An ANCOVA based analysis of change from baseline growth rate again showed a mean difference between fluticasone and placebo equal to approximately 0.27 cm/yr (Table 6).

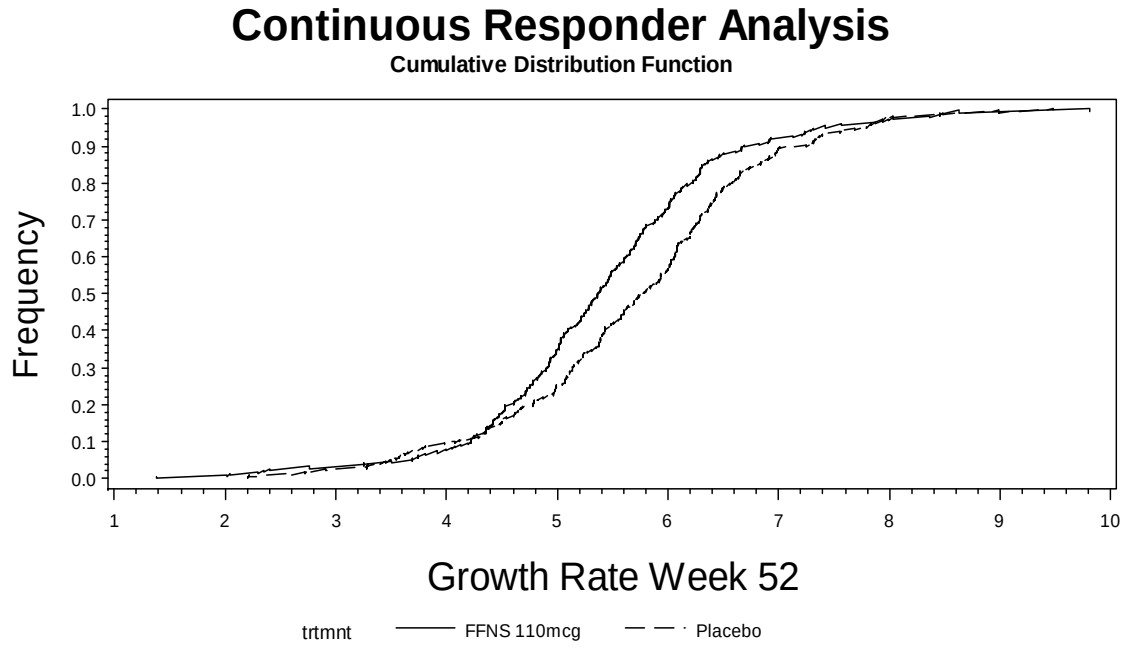
Table 6. Change from Baseline Growth Velocity (cm/year).

Analysis	F	Placebo	Diff	Lower_95	Upper_95
Baseline	5.915 (217)	5.949 (218)	-0.033	-0.261	0.195
Change From Baseline	-0.759 (217)	-0.49 (218)	-0.270	-0.476	-0.064

source: Growth 2012 01 12.sas

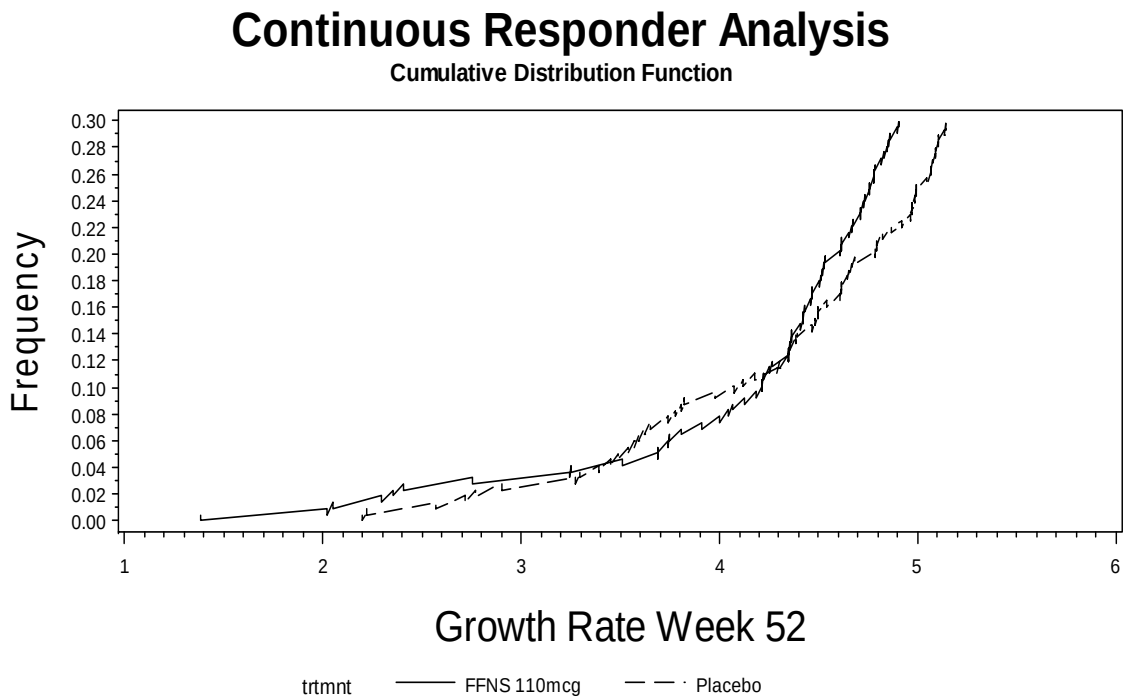
Although patients with the lowest growth rates were those treated with fluticasone, the difference between treatments in mean growth velocities was not driven by outliers. Overall, patients treated with fluticasone consistently showed a lower growth rate than patients treated with placebo (Figure 1). That the lower growth rate exhibited by patients treated with fluticasone was not due to patients at extremes is shown by the fact that patients receiving fluticasone did not show consistently lower growth rates until the 12th percentile of growth velocity (Figure 2) and that patients receiving placebo did not show consistently higher growth rates above the 95th percentile of growth velocity (Figure 3).

Figure 1. Growth Rate Cumulative Distribution Functions.



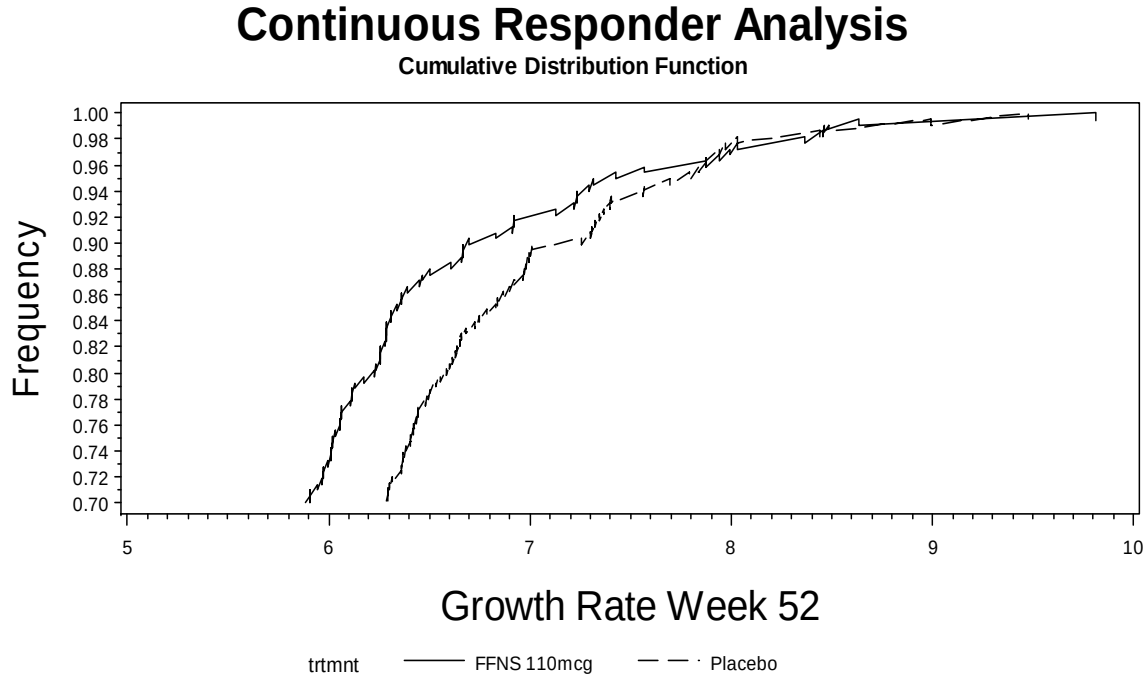
source: Growth 2012 01 12.sas

Figure 2. Growth Rate Cumulative Distribution Functions. Lower percentile detail.



source: Growth 2012 01 12.sas

Figure 3. Growth Rate Cumulative Distribution Functions. Upper percentile detail.



source: Growth 2012 01 12.sas

3.1.4 Urinary Cortisol

Change from baseline 24 hour urinary cortisol was examined after 52 weeks of treatment. Patients included in growth analyses were those who received at least one dose of the double blind study medication to which they were randomized, did not receive any steroids in addition to their randomized treatment, and who had measurable urine samples with interpretable results at the prescribed collection time.

Mean 24-hour urinary cortisol concentration increased from baseline to week 52 in both Veramyst and placebo treated patients (Table 7; mcg/24 hr, Table 8; nmoles/24 hr); the increase was numerically greater in patients treated with Veramyst.

Table 7. Change from Baseline 24-Hour Urinary Cortisol (mcg/24 hr).

Treatment	Geometric Mean (N)			Arithmetic Mean (N)
	Baseline	Week 52	W52/Baseline	Change from Baseline
Fluticasone	7.91 (172)	9.15 (169)	1.85 (168)	1.15 (168)
Placebo	8.24 (168)	9.21 (163)	1.52 (162)	1.11 (162)

source: Cortisol 2012 01 25.sas

Table 8. Change from Baseline 24-Hour Urinary Cortisol (nmoles/24 hr).

Treatment	Geometric Mean (N)			Arithmetic Mean (N)
	Baseline	Week 52	W52/Baseline	Change from Baseline
Fluticasone	21.82 (172)	25.24 (169)	1.15 (168)	5.10 (168)
Placebo	22.73 (168)	25.40 (163)	1.11 (162)	4.18 (162)

source: Cortisol 2012 01 25.sas

3.1.5 Compliance

Treatment compliance was assessed using daily e-diaries recording usage of nasal spray, change in weight of nasal spray from prior to dispensing until return to site, and reflective total nasal symptom score (rTNSS), which is ordinal ranging from 0 to 3, and use of rescue medications.

Compliance rates were similar in the two patient groups, and daily medication used differed by 0.002 grams per day (Table 9). Percent rescue free days among Veramyst treated patients during the treatment period was 4% less than among placebo treated patients (Table 9).

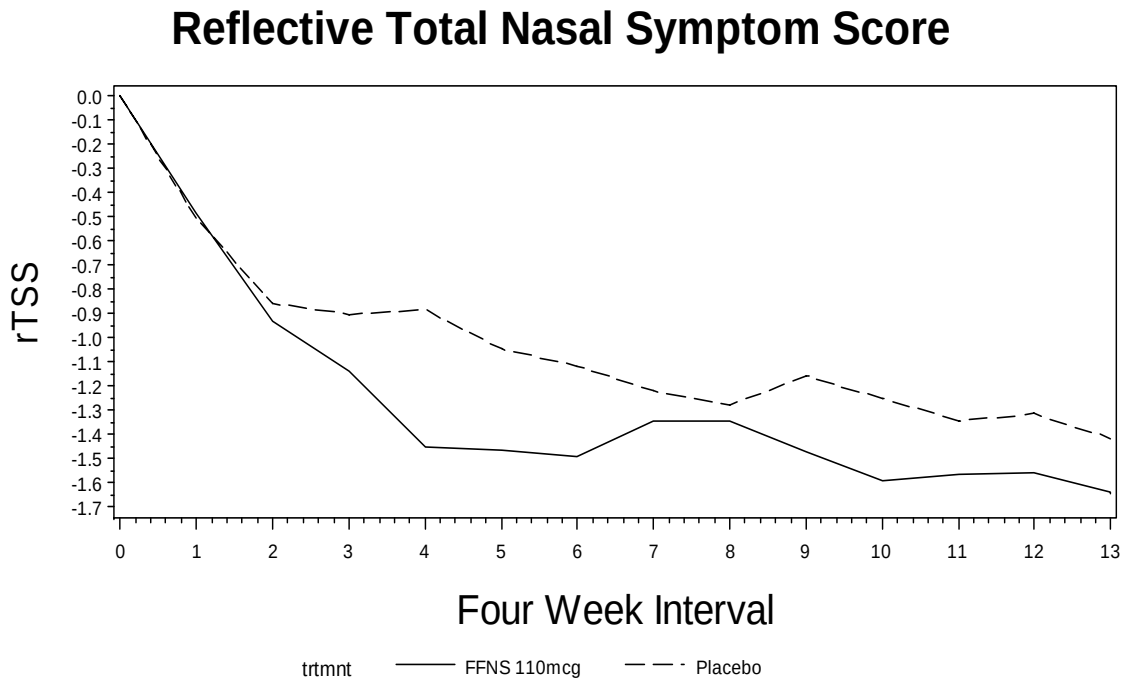
Table 9. Medication usage, by treatment group.

Variable	Mean (N)		
	Fluticasone	Placebo	Difference
Mean Compliance Rate	89.9% (237)	89.9% (237)	0.0%
Daily Medication Dispensed (grams)	0.205 (202)	0.207 (214)	0.002
Rescue Free Days	58.7% (237)	54.8% (237)	3.96%

source: Compliance 2012 01 19.sas

After two weeks of treatment, decreases from baseline reflective total nasal symptom score were numerically greater in magnitude among patients treated with Veramyst (Figure 4).

Figure 4. Reflective Total Nasal Symptom Score by Treatment, Four Week Intervals.



source: Compliance 2012 01 19.sas

3.2 Other Safety Parameters

Dr. Sofia Chaudhry reviewed the safety of Veramyst in detail. The reader is referred to Dr. Chaudhry's review regarding laboratory parameters and adverse event profiles.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Geographic Region

No statistically significant interactions (all p-values were greater than 0.20) were seen between treatment and race, gender, or region (USA vs non-USA). Models to assess these interactions were the same as those used to assess efficacy, with additional terms for the indicated subgroup and subgroup by treatment interaction. Country was not included as a covariate in the analysis for region.

5. SUMMARY AND CONCLUSIONS

The point estimate for growth velocity was 0.27 cm/year less among patients treated with Veramyst compared to patients treated with placebo, with a 95% confidence interval of width less than 0.5 cm., ranging from 0.064 to 0.476 cm/year No subgroup specific differences (race, gender, region) were seen in treatment effects.

Although randomization was not stratified by age, mean age was similar in both treatment groups age at randomization, and further analyses show no statistically significant effects of age on differences between treatments.

Compared to placebo, Veramyst was not associated with reduced 24-hour urinary cortisol. Compliance did not differ by treatment.

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/s/

ROBERT ABUGOV
05/16/2012

JOAN K BUENCONSEJO
06/12/2012
I concur with Dr. Abugov's review of the Growth Study.