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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-008 / SE5-018

Drug Name: Sandostatin (octreotide acetate depot) LAR
Indication(s): Pediatric hypothalamic obesity
Applicant: Novartis
Date(s): Submitted November 10, 2005

Review Priority: Priority (6-month review cycle)

Biometrics Division: Division of Biometrics 2 (HFD-715)
Statistical Reviewer: J. Todd Sahlroot, Ph.D., Team Leader

Medical Division: Division of Metabolic and Endocrine Products (HFD-510)
Clinical Team: Eileen Craig, M.D., primary reviewer
Mary Parks, M.D. , acting Division Director
Project Manager: Enid Galliers

Keywords: NDA submission, clinical studies, pediatric exclusivity

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study failed to provide adequate statistical evidence that Sandostatin LAR Depot is superior to placebo (saline control) in reducing body mass index (BMI) in pediatric patients with hypothalamic obesity. Table 1 shows the primary analysis results.

Table 1. Change from baseline in BMI (ITT- LOCF)

	Treatment group		Treatment difference [1]
	Sandostatin LAR Depot (40 mg) n=30	Saline control n=30	LS mean (95% CI) p-value
BMI (kg/m^2)			
Baseline mean (SD)	33.8 (5.4)	34.8 (6.6)	
LS mean change at Month 6	+0.1	-0.0	0.2 (-0.8, 1.1) p=.74

[1] Least square (LS) mean and confidence interval based on ANCOVA with treatment group as a factor and baseline BMI as covariate.

1.2 Brief Overview of Clinical Studies

Novartis submitted Study 2403, a randomized, multi-center, double-blind 6-month trial of Sandostatin (SAS) LAR Depot (40 mg per month) versus saline control in the treatment of pediatric hypothalamic obesity in males and females ages 6 to 18. The study was conducted in response to an FDA Written Request (WR) dated January, 2004.

1.3 Statistical Issues and Findings

Study 2403 was a failed efficacy study. There were no noteworthy statistical issues.

2. INTRODUCTION

2.1 Overview

The primary objectives of Study 2403 were:

- to compare changes in BMI with SAS-LAR (40mg) and saline control in pediatric patients with hypothalamic obesity
- to evaluate the safety and tolerability of SAS-LAR in pediatric patients with hypothalamic obesity

Height and weight were measured at monthly visits. The trial tested the null hypothesis that the mean changes from baseline in BMI (weight in kg/(height in meters)^2) at 6 months were equal in the two treatment groups versus the alternate hypothesis that the mean changes from baseline in BMI at 6 months were not equal.

The primary analysis population was the ITT population consisting of patients who were treated and had BMI data after randomization. Treatment groups were compared using contrasts from an ANCOVA with treatment as a factor and baseline BMI as covariate. Statistical testing was performed at the 2-sided 5% significance level. At 30 patients per group, the study had greater than 95% power to detect a 1.25 kg/m^2 difference in BMI change from baseline between groups assuming a SD of 1.22 kg/m^2.

An independent Data Safety Monitoring Board (DSMB) was convened after approximately 25 patients were enrolled In order to monitor the safety of SAS-LAR. It met twice more during the study and again at the end of the study.

2.2 Data Sources

The final report and raw data were located in, respectively,

\\Cdsesub1\n21008\S_018\2005-11-10\clinstat

\\Cdsesub1\n21008\S_018\2005-11-10\crt\datasets\2403\derived

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Sixty-two (62) subjects were randomized in approximately numbers to SAS-LAR and saline (Table 2). Fifty-six (56) patients completed the 6-month study. The study enrolled similar numbers of males and females as required by the WR.

Table 2. Patient disposition

	Sandostatin LAR	Saline control	Total
# pts randomized	32 (100%)	30 (100%)	62 (100%)
Exposed	31 (97%)	30 (100%)	61 (98%)
ITT population	30 (94%)	30 (100%)	60 (97%)
# females/ITT	16/30 (53%)	17/30 (57%)	33/60 (55%)
Completed	28 (88%)	28 (93%)	56 (90%)

Sixty (60) patients (30 SAS-LAR, 30 saline) were included in the ITT-LOCF analysis as specified in the WR. One excluded patient was randomized but not treated and withdrew because of "administrative problems". A second excluded patient received only one dose of study drug and did not return for post-baseline assessments and withdrew consent.

Most patients were Caucasian (93%) and aged ≥12 years (75%) with mean age 13.6 years. About half of the patients were from the United States (48%) and 27% were from Russia. Patients in the SAS-LAR group were on average a year younger than the saline-treated patients and therefore were smaller and weighed less. These differences did not translate into statistical differences for BMI at baseline (p=.34), as expected, since BMI partially adjusts for weight differences related to age.

Table 3 shows the primary analysis results. Both groups showed very little change from baseline in BMI over the 6-month treatment period. The difference between treatment groups was not statistically significant (p=.74).

Table 3. Change from baseline in BMI (ITT- LOCF)

	Treatment group		Treatment difference [1]
	Sandostatin LAR Depot (40 mg) n=30	Saline control n=30	LS mean (95% CI) p-value
BMI (kg/m^2)			
Baseline mean (SD)	33.8 (5.4)	34.8 (6.6)	
LS mean change at Month 6	+0.1	-0.0	0.2 (-0.8, 1.1) p=.74

[1] Least square (LS) mean and confidence interval based on ANCOVA with treatment group as a factor and baseline BMI as covariate.

Patients in each group gained an average of about 2 kg over 6 months (treatment difference p=.93).

3.2 Evaluation of Safety

This reviewer did not perform any safety evaluations.

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

/s/

Todd Sahlroot

4/28/2006 03:50:41 PM

BIOMETRICS