CLINICAL REVIEW

Application Type	sNDA 21-008
Submission Number	018
Submission Code	SE5
Letter Date	10 November 2005
Stamp Date	10 November 2005
PDUFA Goal Date	10 May 2006
Reviewer Name	Eileen M. Craig, MD
Review Completion Date	3 May 2006
Established Name	octreotide acetate for injectable suspension
(Proposed) Trade Name	Sandostatin LAR® Depot
Therapeutic Class	somatostatin analogue
Applicant	Novartis Pharmaceuticals Corp.
Priority Designation	P
Formulation	IM depot injection
Dosing Regimen	40 mg IM every month
Indication	Hypothalamic Obesity
Intended Population	Pediatric patients, aged 6 through 17 years of age, inclusive

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve requested labeling, with revisions. The sponsor is not seeking a new indication for Sandostatin LAR depot use in children.

1.2 Recommendation on Postmarketing Actions

None

1.3 Summary of Clinical Findings

Novartis has submitted this supplemental new drug application for Sandostatin LAR Depot (SAS-LAR, octreotide acetate for injectable suspension) seeking to fulfill the Pediatric Written Request and gain pediatric exclusivity. Sandostatin is an analogue of the natural hormone somatostatin. Secreted by multiple tissues including the hypothalamus and pancreas, somatostatin inhibits a variety of hormones including growth hormone, insulin, glucagon, cholecystokinin, secretin, gastrin and vasoactive intestinal peptide.

Study SMS995B 2403 was conducted in order to fulfill the Written Request to evaluate the efficacy, safety and tolerability of 40mg Sandostatin LAR Depot as a weight loss agent in pediatric patients with hypothalamic obesity. Hypothalamic obesity is thought to occur as a result of damage to the ventromedial nucleus of the hypothalamus. As a result, the brain can not appropriately process hormonal satiety signals and instead perceives a starvation state. The weight gain associated with hypothalamic obesity does not respond to traditional weight reduction methods or therapies. Prior small studies have shown some success using subcutaneous (sc) octreotide three times daily to decrease insulin secretion, decrease food intake, increase physical activity, and either stabilize weight gain or promote weight loss in pediatric patients with hypothalamic obesity. Therefore, it was hypothesized that SAS-LAR may be beneficial for weight control in the pediatric hypothalamic obesity population.

1.3.1 Brief Overview of Clinical Program

Study 2403 was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study in children with hypothalamic obesity treated with 40mg of Sandostatin LAR® Depot or saline control administered as intramuscular injections monthly for 6 months.

In Study 2403, 62 patients were randomized into the study and 60 patients received study drug, had at least one post-baseline assessment and were included in the ITT and safety populations for analysis. Four patients in the safety population prematurely discontinued treatment (two in each treatment group) with two patients, one in each group, discontinued due to adverse events, after having received 4 months of treatment. The treatment groups were generally well balanced at

baseline for demographic and disease characteristics. The mean age in this study was 13.6 years with a range of 6 to 17 years, inclusive. Twenty-five percent were < 12 years and 75% were ≥ 12 years of age. Within the < 12 year group: nine were on SAS-LAR and six were on placebo. Within the ≥ 12-year group: 21 were on SAS LAR and 24 were on placebo. All patients had a history of cranial insult, trauma or treatment of a cranial tumor, with subsequent abnormal weight gain faster than 2 standard deviations (SDs) above the mean for their age for at least one year leading to a diagnosis of hypothalamic obesity. The only relevant differences between treatment groups were in weight, where the saline control group were slightly heavier at baseline (89.0 kg vs. 81.7 kg in the SAS-LAR group), and for Tanner staging, where a slightly younger profile in the SAS-LAR group was evident.

The primary efficacy endpoint was change in BMI. The secondary efficacy endpoints included:

- Change from baseline in weight
- Change from baseline in waist to hip ratio
- Change from baseline in key biochemical and metabolic parameter, leptin (measured at screening, Month 3, and Month 6)
- Change from baseline in insulin dynamics (insulin, C-peptide, amylin and glucose) versus time profiles during the OGTT
- Change from baseline in body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans and in visceral and subcutaneous fat in the abdomen by quantitative CT scan
- Change from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity
- Pharmacokinetic/Pharmacodynamic (PK/PD) relationships between octreotide concentration and insulin levels
- Pharmacokinetic (PK) parameters of SAS-LAR in pediatric patients
- Proportion of patients who show no increase in BMI (Δ BMI ≤ 0)

After a screening period in which patients were administered a single injection of subcutaneous octreotide to check for tolerability, patients were randomized to receive SAS-LAR 40 mg/month or saline control by intragluteal injection monthly for 6 months.

Exposure to study medication was similar in the two treatment groups. The majority of patients received study medication for at least 120 days (4 months) and all these patients also completed the full course of injections administered at Months 0, 1, 2, 3, 4 and 5 in the double-blind treatment period. Overall, 43% of SAS-LAR-treated patients and 60% of control-treated patients received study medication for >150 days in Study 2403.

There was limited long-term drug exposure in the open-label extension study. Only three patients received 12 months of treatment. Only six out of 19 (32%) subjects who received placebo in Study 2403 and SAS-LAR in the OLE received study drug for 6 months.

1.3.2 Efficacy

The data presented do not demonstrate efficacy for use of SAS-LAR in pediatric patients aged 6 to <18 years with hypothalamic obesity. After 6 months of treatment with SAS-LAR or placebo, no difference in change from baseline in BMI was seen between treatment groups (0.1 kg/m^2 in the SAS-LAR-treated group vs. 0.0 kg/m^2 in the placebo-treated group, p=0.74). Mean weight gradually increased in both treatment groups from baseline to the end of the study (1.9 kg in the SAS-LAR-treated group vs. 1.8 kg in the placebo-treated group, p=0.93). The waist to hip ratio decreased in the SAS-LAR group whereas it increased in the control group (-0.014 in the SAS-LAR-treated group vs. +0.025 in the placebo-treated group, p=0.012). However this isolated efficacy improvement is of questionable clinical relevance due to measurement imperfections. There was a statistically significant decline in insulin response and C-peptide AUC in favor of SAS-LAR treatment, but this did not correlate with a significant decrease in dietary intake. There was a trend toward a positive correlation (p=0.065) with physical activity scores in favor of SAS-LAR, while no correlation with changes in body fat was found.

Overall, Study 2403 failed to provide substantial evidence of effectiveness to support the use of SAS-LAR in the indication of pediatric hypothalamic obesity.

1.3.3 Safety

Adverse events that have been reported with Sandostatin LAR® Depot treatment in adults include gallbladder abnormalities (gallstones, sludge without stones, biliary duct dilatation), cardiac conduction abnormalities, and gastrointestinal symptoms (diarrhea, abdominal pain, flatulence, constipation, nausea, vomiting), hypoglycemia or hyperglycemia (due to alteration in the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone), hypothyroidism, and depressed vitamin B12 levels (due to altered absorption of dietary fats). In Study 2403, a higher proportion of patients receiving SAS-LAR experienced AEs (SAS-LAR 93%, control 70%). The most frequent AEs during SAS-LAR treatment were diarrhea (SAS-LAR 37%, control 7%), cholelithiasis (SAS-LAR 33%, control 0%), and abdominal pain (SAS-LAR 13%, control 3%), while nasopharyngitis occurred with similar frequency in both arms (SAS-LAR 30%, control 27%).

Eleven patients (11/30, 37%) were found to have new or worsened abnormalities of the gallbladder by the end of Study 2403. All cases involving gallstones (10 patients) were reported in the SAS-LAR group. Nine cases were asymptomatic and were detected by ultrasound at the end of the study. One of these patients developed severe gallstones associated with pancreatitis about 3 months after the last dose of study drug. In Study 2403, there were no cardiac conduction abnormalities reported. There was one case (1/30, 3%) of pericardial effusion in the SAS-LAR treatment group. The incidence of gastrointestinal disorders was 47% for the SAS-LAR group and 20% for the placebo group, with diarrhea (37% SAS-LAR, 7% placebo) and abdominal pain (13% SAS-LAR, 3% placebo) as the most common symptoms.

There were no episodes of hypoglycemia reported in the study. Three subjects (10%) in the SAS-LAR group and 2 subjects (7%) in the placebo group developed impaired glucose tolerance. One

subject (3%) in the SAS-LAR group was diagnosed with diabetes mellitus during the study. Two subjects, both in the SAS-LAR group, developed abnormalities in thyroid function tests – one with a suppressed thyroid stimulating hormone level and one with a decrease in free thyroxine. There was no evidence of decrease vitamin B12 levels or increased methylmalonic acid levels with SAS-LAR therapy.

The sponsor initiated, but did not complete, the 6-month open-label extension study (OLE). It was the unanimous recommendation of the Data Safety Monitoring Board that the OLE be terminated as soon as possible due to the lack of efficacy and the high risk of gallstone formation. All subjects received SAS-LAR in the OLE with subjects receiving SAS-LAR for both core and extension phases of the study identified as the C + E group and subjects receiving placebo in the core phase and SAS-LAR in the OLE phase identified as the SAS-LAR OLE group. A total of 32 subjects participated in the OLE (13 in the C + E group and 19 in the SAS-LAR OLE group) with 9 (28%) subjects completing the full 6 month extension phase (3 in the C + E group and 6 in the SAS-LAR OLE group). Serious adverse events (SAEs) were reported for nine (28%) patients (three (23%) in the C+E group and six (32%) in the SAS-LAR OLE group. Four of the nine (44%) SAEs were related to cholelithiasis, three (33%) to biliary tract abnormalities, and two (22%) to gastrointestinal disorders. Eleven patients (34%) were found to have new or worsened abnormalities of the gallbladder by the end of the extension study.

The safety profile of SMS-LAR in pediatric patients was consistent with the known safety profile of sandostatin as seen in adults in other indications. The incidence of diarrhea in clinical trials of adult patients with acromegaly is 36%, which is similar to the incidence of 37% seen in this trial. The incidence of abdominal pain or discomfort in clinical trials of adult patients with acromegaly is 29%, which is higher than the incidence of 17% for abdominal pain and upper abdominal pain seen in this trial. However, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%).

1.3.4 Dosing Regimen and Administration

The dose selected for use in Study 2403 was primarily based on data from the two previously conducted pediatric studies. Sandostatin LAR® Depot was given as two 20 mg intragluteal injections per month for a total dose of 40mg/month for 6 months.

1.3.5 Drug-Drug Interactions

Not applicable in this submission.

1.3.6 Special Populations

The study was performed in a pediatric population between the ages of 6 and 17, inclusive.

2 INTRODUCTION AND BACKGROUND

Hypothalamic obesity, characterized by severe obesity with hyperphagia, is a devastating complication seen in children after therapy for craniopharyngioma and other tumors of the hypothalamic area. Hyperinsulinemia and insulin resistance routinely accompanies hypothalamic obesity. Previous attempts at controlling hypothalamic obesity through behavioral or pharmacologic interventions have proven generally unsuccessful.[1] This form of obesity often leads to comorbid conditions such as hypertension, obstructive sleep apnea, dyslipidemia, and psychosocial dysfunction.

Damage to the ventromedial hypothalamus is the suggested mechanism for the weight gain in these children and insulin hypersecretion and hyperphagia are components of this disease process. The reported incidence of this syndrome is 1,000 patients per year internationally. Octreotide is known to bind to the somatostatin receptor on the pancreatic beta cell and thereby to attenuate insulin release. This pharmacology is hypothesized to contribute to potential therapeutic efficacy of octreotide in hypothalamic obesity.

Lustig, RH et al. reported the use of octreotide to promote weight loss in children with hypothalamic obesity.[2] This prospective, open-label study (Study 2408) included eight patients aged 10 to 18 years with hypothalamic obesity secondary to treatment for brain tumors and/or following cranial irradiation. Patients were evaluated for 6 months prior to, then for 6 months during treatment with, up to 15µg/kg/day of octreotide administered subcutaneously in three divided doses.

Compared to the 6-month pre-study observation period, patients treated with octreotide experienced significant weight loss (-4.8 ± 1.8 kg vs. +6.0 ± 0.7 kg) and decrease in body mass index (-2.0 ± 0.7 kg/m2 vs. +2.1 ± 0.3 kg/m2). Of the 8 patients, 3 lost more than 10% of initial body weight, 2 lost approximately 5% initial body weight and 3 were stabilized. At the beginning of the study, 5 of 8 patients demonstrated impaired glucose tolerance on OGTT. At the end of the study, 2 of 7 patients showed impaired glucose tolerance. Weight change correlated with insulin response and plasma leptin.[3]

A second trial, Study 2409, enrolled 20 children with hypothalamic obesity randomized to 6 months of s.c. octreotide (5µg/kg/d up to 15µg/kg/d) vs. placebo (saline). After 6 months, all patients received s.c. octreotide for the subsequent 6 months. Nine patients in each group completed the trial. Efficacy data showed that compared to baseline, mean increases in weight and BMI at Month 6 were significantly higher in placebo than in octreotide-treated patients, as summarized in the table below. [3]

Table 2.1 Summary of Changes in Weight and BMI in SMS995B2409

	Placebo (n=9)	Sandostatin (n=9)
Weight	9.2± 1.5 kg	1.6±0.6 kg
BMI	2.3± 0.5 kg/m2	-0.1±0.1 kg/m2

Suppression of growth rate by octreotide occurred only in the first 6 months. Patients with open growth plates and receiving octreotide had a reduced growth rate of 1.9cm in 6 months, but in the second six months, this rate rose to a normal 2.7cm in 6 months.

Thus, octreotide administration in patients with pediatric hypothalamic obesity shows potential to improve insulin response and attenuate weight gain. Without treatment, these children continue to gain weight even after final height is reached. Sandostatin LAR® Depot is injected monthly and potentially has an improved safety profile over Sandostatin sc, and was therefore chosen to further evaluate the efficacy and safety of this treatment in children with hypothalamic obesity.

2.1 Product Information

Sandostatin (octreotide acetate) Injection is a synthetic, long acting, octapeptide analogue of the natural hormone, somatostatin. Like somatostatin, Sandostatin exerts inhibitory effects on the release of pituitary and gastroenteropancreatic hormones (i.e. GH, TSH, insulin, glucagons, CCK, CIP and gastrin) including inhibition of gastric acid secretion, pancreatic enzyme secretion and bile flow; prolongs intestinal time, and decreases gall bladder contractility. Sandostatin is a specific and potent somatostatin-receptor type 2 agonist. Relative to native somatostatin, Sandostatin is 45 times more potent in terms of inhibition of growth hormone (GH) secretion, 11 times more potent in inhibition of glucagon, but only 1.3 times as active in inhibition of insulin secretion.[4] Sandostatin (octreotide acetate) is normally administered subcutaneously (s.c.), either twice or three times per day.

Sandostatin LAR® Depot is a long-acting formulation that was developed for patients requiring long-term octreotide therapy. It consists of octreotide acetate microencapsulated by a biodegradable polymer, poly (DL-lactide-co-glycolide) D-(+) glucose. Drug release occurs slowly as cleavage of the polymer takes place primarily through tissue fluid hydrolysis.[4]

Sandostatin LAR® Depot and Sandostatin® Injection are approved in the US for the treatment of acromegaly and for the treatment of symptoms of malignant carcinoid syndrome, VIPoma, and in some countries for other gastroenteropancreatic (GEP) neuroendocrine tumors.

Adverse events that have been reported with Sandostatin LAR® Depot include gallbladder abnormalities (gallstones, sludge without stones, biliary duct dilatation), hypoglycemia or hyperglycemia (due to alteration in the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone), hypothyroidism, depressed vitamin B12 levels (due to

altered absorption of dietary fats), cardiac conduction abnormalities, and gastrointestinal symptoms (diarrhea, abdominal pain, flatulence, constipation, nausea, vomiting).

2.2 Currently Available Treatment for Indications

Many other pharmacologic agents with differing mechanisms of action have been used for primary pediatric obesity but not specifically for hypothalamic obesity.[5]

Dextroamphetamine was used for 24 months in five patients with craniopharyngioma, a subset of children with hypothalamic obesity[6]. Body mass indices stabilized during the treatment period. Bariatric surgery is considered in morbidly obese adolescent children, including genetically normal patients and those with Prader Willi Syndrome, weighing over 200% of their ideal body weight.[7] In a study of ten obese adolescents followed more than five years post-operatively, weight loss was more than 30 kg. While obesity related comorbidities improved, there were complications of the surgery such as anemia (50%), folate deficiency (30%), cholecystectomy (20%), incisional hernia (10%), and small bowel obstruction (10%). Despite its efficacy, in light of these considerable complications, gastric bypass is a last resort for severely obese adolescents.

Other therapies have been studied in obese children not diagnosed with hypothalamic obesity. Metformin was given to 19 obese patients aged 10-18 years. These patients had experienced significant weight gain while taking psychotrophic drugs. Study duration was up to 12 weeks and was an open-label design. Fifteen of nineteen patients lost weight while 3 gained and one maintained weight. Mean weight change was –2.93 kg and mean BMI change was –2.22kg/m^2. In the four patients followed beyond the 12- week study protocol, weight loss continued (losses of 4.1, 4.6, 8.2, and 13.1 kg). The mechanism for the metformin mediated weight loss is unknown.

In another randomized study of 29 obese adolescents (without hypothalamic injury) using 500 mg BID of metformin versus placebo without dietary therapy, there was a 1.3 % decrease in BMI after 6 months in the active group compared with a 2.3 % increase in the placebo group. Lactic acidosis, particularly seen in patients with compromised renal function, is a serious but very rare complication of metformin therapy. More common side effects of metformin therapy include nausea, bloating and diarrhea predominately at the start of treatment.

Orlistat was used in 11 obese prepubertal children (without hypothalamic injury) age 8.3- 12.3 years for 12 weeks in an open-label treatment. Median weight loss was 4.0 kg (range –12.7 to +2.5 kg, p=0.016). These children were able to avoid fatty foods and this study suggests a role for orlistat in conjunction with behavioral modification. Side effects of orlistat therapy include decreases in vitamin D and other fat-soluble vitamins, fecal incontinence and steatorrhea. These symptoms tend to be mild to moderate and diminish over time. Orlistat was also studied in a randomized, double-blind, placebo-controlled 52-week study of 539 obese adolescents, aged 12 to 16 years. All enrolled patients had a baseline body mass index (BMI) that was at least 2 units greater than the U.S. weighted mean for the 95th percentile based on age and gender. The patient

population enrolled was anticipated to grow during the time of the study; therefore, the change in BMI rather than the change in body weight was used as the primary efficacy endpoint.

In a LOCF analysis, the orlistat-treated group had a decrease in the mean BMI of 0.55 kg/m2 (which was in the range of weight loss that the diet alone should have caused), while the placebo-treated subjects had an increase in the mean BMI of 0.31 kg/m2 (p=0.001). In a responder analysis, 27% of the orlistat-treated patients and 16% of placebo-treated subjects had a decrease of at least 5% in baseline BMI. The orlistat group had a mean increase in body weight of 0.5 kg; whereas the placebo group had a mean increase in weight of 3.1 kg (nominal p<0.001). There was no evidence that the efficacy of the drug was significantly different in males vs. females. In a subgroup of subjects who had DEXA assessment of body composition, orlistat-induced weight loss was due primarily to a reduction in body fat. There was no evidence that fat-free mass declined following weight loss.[8]

Protein-sparing modified fast (PSMF) hypocaloric diets have resulted in weight loss when used in children and adults but follow-up after one year has shown similar weight loss in active vs. control patients. Risks of this regimen include cholelithiasis, hyperuricemia, diarrhea, and decreased plasma protein levels.

Sibutramine as treatment for adolescent obesity was evaluated in a randomized, double-blind, placebo-controlled trial of 82 obese children (without hypothalamic disease) age13-17 years. Patients received behavior therapy + either sibutramine or placebo for 6 months. During months 7-12, all patients received sibutramine open-label. During months 7-12, children initially treated with sibutramine gained 0.8 kg with continued use of the medication and patients switched to active drug from placebo lost an additional 1.3kg. Medication dose was reduced in 23 children and discontinued in 10 others to manage increases in BP or pulse rate. Sibutramine was also studied in a randomized, double-blind, placebo-controlled 12- month trial to assess the efficacy and safety of 10 mg and 15 mg once-daily sibutramine in obese adolescents.

Adolescents aged 12 to 16 years with a BMI lower limit of inclusion 2 units above the U.S. weighted mean for the 95th percentile based on age and gender, to a BMI upper limit of 44 kg/m2, were eligible for participation in the study. At baseline, subjects were randomized 3:1 to sibutramine 10 mg or placebo once daily. All patients were to receive instructions in lifestyle modification to include healthy eating behavior, exercise, and bodyweight control. At Month 6, all subjects randomized to sibutramine who had not lost > 10% of their initial BMI were up-titrated to 15 mg once-daily sibutramine. Subjects randomized to placebo who did not lost >10 % of their baseline BMI by Month 6 were also up-titrated to 15 mg once-daily placebo. Subjects were seen weekly for the first 2 weeks, then every 2 weeks for the next 10 weeks, and then monthly thereafter.

Three hundred and sixty-three subjects were randomized to sibutramine and 127 to placebo. The baseline demographic characteristics were well matched between groups. The mean age was ~14 years; 65% were female; 57% Caucasian; and the average BMI was 36 kg/m^2. Seventy-six percent of the sibutramine subjects and 62% of the placebo subjects completed the one-year study. Lost to follow up and withdrawal of consent were the most common reasons for not

completing the trial. Thirty-four percent of the sibutramine-treated subjects and 50% of the placebo-treated patients did not lose at least 10% of their baseline weight by Month 6 and were titrated up to 15 mg.

In an analysis of mean change in BMI from baseline to Endpoint, the sibutramine group had a reduction in BMI of 3.0 and the placebo group had a reduction of 0.4 ($p<0.001$). Up-titration of sibutramine from 10 mg to 15 mg in those subjects who did not lose at least 10% of their baseline BMI did not lead to appreciably more weight loss during Months 6 through 12. The mean absolute and percent changes in body weight in the sibutramine subjects were approximately -6.2 kg vs. 1.1 kg in the placebo subjects.

However, during the review of this application, it was noted that approximately one third of the serial height measurements did not change or actually decreased during the study. This represented an obvious measurement error when height is recorded as having decreased. While there was no reason to believe that sibutramine would not produce weight loss in obese adolescents, the fact that up to 30% of the height data from this pediatric study appeared to be erroneous raised serious concern about the validity of the efficacy and perhaps the safety data. The results of the study were not approved for inclusion in the label.

Additional, because Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants, there was concern for an increased risk for suicidal behavior or thinking as is seen in some patients receiving antidepressants. [9]

Children with hypothalamic obesity are a very small subset of obese children in the population and, as such, available treatment options are limited. This syndrome is characterized by hyperphagia and impaired response to satiety signals. Octreotide administration has been associated with voluntary caloric restriction, increased physical activity and an improved sense of well-being. Octreotide may provide these children with another option to reduce obesity-related morbidities.

2.3 Availability of Proposed Active Ingredient in the United States

Sandostatin LAR® Depot is available by prescription in the United States.

2.4 Important Issues With Pharmacologically Related Products

Concerns regarding a possible class effect of somatostatin analogues in association with abnormalities of cardiac valves originated in a NDA review for lanreotide.[5] Lanreotide is a somatostatin analogue that was being developed for the treatment of acromegaly. The clinical development program included a cardiac substudy to evaluate whether the reductions in IGF-1 and GH levels associated with lanreotide improved ventricular function and wall thickness. Abnormalities in these parameters are cardinal features of acromegalic heart disease. A subset of 22 patients with acromegaly was noted to have valvular incompetence after 18 months of

lanreotide therapy. These findings were not reported on baseline Echo studies. The majority of these patients were asymptomatic and the degree of regurgitation was described as trace to mild. This was an open-label study. There was no comparator group and there was no standardization of the performance or the interpretation of these echocardiograms. In sum, the study was inconclusive with regard to an effect of lanreotide on cardiac valve function.

While none of the cardiac safety issues raised in the lanreotide database could be discussed specifically with Novartis, the Agency did allude to safety concerns with this class of drugs and required the sponsor to submit cardiac safety data for octreotide. The sponsor submitted an updated clinical safety database for all cardiac adverse events reported between December 23, 2000 and April 17, 2003. Case reports included patients treated for diabetic retinopathy, hepatic carcinoma, post menopausal breast cancer, endstage ovarian carcinoma, glucagonoma, carcinoid and acromegaly. There were approximately 38,900 patients treated with Sandostatin or Sandostatin LAR during this period. There were just fewer than 2800 safety reports of which 170 were cardiac related. Of all these reports, only 4 involved cardiac valves.

The pediatric protocol submitted in this application included echocardiograms at baseline, month 3 and month 6/early termination. ECGs were done at baseline and at study completion. The sponsor committed to instituting a data safety monitoring board (DSMB) comprised of a pediatrician, a pediatric cardiologist and a statistician, all independent of the company. If patients developed cardiac problems, a "discontinuation rule" is included. Thus, the protocol attempted to address the concern of a potential cardiac valvular effect of octreotide.

2.5 Presubmission Regulatory Activity

This study was performed in response to a Written Request Letter from the FDA in January 2004 for Sandostatin LAR® Depot safety and efficacy information in the pediatric patient population.

History of the Sandostatin Proposed Pediatric Study Request (PPSR) [5]

PPSR submitted 1/31/00 to IND 23,796
In this submission, the sponsor identified pediatric hypothalamic obesity as a condition with an unmet medical need that merited further evaluation with octreotide acetate. The rationale for this PPSR was based on a 6-month, open-label, uncontrolled study of 8 patients treated with octreotide acetate subcutaneously at 5 to 15µg/kg/d. The study reported both suppression of insulin secretion and weight reduction compared to pre-study data. The PPSR was an 8-month, blinded study in 40 children with hypothalamic obesity.

FDA response:
A denial letter was issued 5/9/00 based on concerns for the potential growth and pubertal suppressive effects of octreotide in pediatric patients not receiving concomitant growth hormone or gonadotrophin.

2nd PPSR submitted 6/29/00:

In response to the 5/9/00 Written Response denial letter, preliminary safety and efficacy results from a 6-month, placebo-controlled study were provided with this submission. Preliminary data were summarized for 18 patients (octreotide n=9, placebo n=9). The sponsor proposed a 6-month placebo-controlled, double-blinded comparison of 42 pediatric patients with hypothalamic obesity randomized to placebo, 7.5g/kg/d or 15µg/kg/d of octreotide.

FDA response:
On 11/13/00, a denial letter was sent requesting Pharmacokinetic/Pharmacodynamic (PK/PD) dose finding studies in patients with pediatric hypothalamic obesity using the subcutaneous octreotide followed by a bridging study with the depot formulation of octreotide. These studies would need to determine optimal dose and frequency of administration to reduce body mass index and body weight. Development of an algorithm for the use of Actigall (ursodeoxycholic acid) and incorporation of gallbladder ultrasound in the protocol was required in addition to periodic monitoring of stool fat, ECG, serum FT4, TSH and HbA1C. It was recommended that patients enrolled in the study and not on growth hormone should be periodically assessed by plasma IGF-1 levels and arginine-Ldopa growth hormone stimulation tests. Linear height by stadiometry and monitoring of bone age was advised for all patients.

During a **Teleconference on 1/8/01**, further information on cardiac safety and cardiac valvular abnormalities was requested.

3rd PPSR submitted on 7/23/02:
This PPSR proposed to evaluate Sandostatin LAR in pediatric patients with obesity and primary insulin hypersecretion. Sponsor stated that a PK/PD study was no longer relevant as the PPSR proposes to use the depot formulation.

FDA response:
A denial letter was sent 11/19/02 citing safety concerns on suppression of growth and progression of puberty in the pediatric population, modest effects of Sandostatin on weight, and safety of somatostatin analogues on cardiac valve function in adults.

Meeting between DMEDP and Novartis 6/4/03:
The sponsor invited two consultants, Dr. Robert Lustig, a pediatric endocrinologist who was the investigator on both clinical studies submitted to the FDA, and Dr. Justina Wu, a cardiologist. During this meeting, the sponsor and consultants presented evidence that there was a scientific rationale to further evaluate the efficacy of octreotide in pediatric patients with hypothalamic obesity and that there was no evidence that octreotide causes valve regurgitation.

4th PPSR submitted on 6/27/03:
A PPSR was submitted to IND 37,768 to conduct a six-month clinical trial comparing Sandostatin LAR to saline-control in 50 patients with pediatric hypothalamic obesity.

The Division drafted a Written Request in response to this PPSR and presented it to the Pediatric Implementation Team (PdIT) on October 1, 2003. Full support from PdIT was not obtained due to lingering concerns that Sandostatin may cause valvular regurgitation based on a finding as part

of the review of NDA 21,296 (lanreotide), another somatostatin analogue. A Written Request was eventually issued by the FDA to Novartis on 7 January 2004 to conduct pediatric studies using Sandostatin LAR® Depot for the treatment of pediatric hypothalamic obesity.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to the review by Janice Brown, PhD.

3.2 Animal Pharmacology/Toxicology

Please refer to the review by Dylan Yao, PhD.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Three studies submitted by the applicant are the source of data for this review of Sandostatin LAR® Depot (abbreviated to SAS-LAR) in the treatment of pediatric hypothalamic obesity:

- Study 2408: An open-label, non-randomized, pilot study of the use of sandostatin s.c. injection in reducing weight gain in 8 patients (9 patients recruited but data present for 8 patients).
- Study 2409: A double-blind, placebo-controlled study of the efficacy of sandostatin s.c. injection for weight loss in 20 patients over a 6-month period.
- Study 2403: A randomized, multicenter, double-blind trial of SAS-LAR (40 mg) versus saline control in 60 patients over 6 months. Twenty centers enrolled patients in 5 countries: Belgium (1), Canada (2), Poland (2), Russia (3), USA (12). Primary objectives were to compare changes in body mass index (BMI) with SAS-LAR (40mg) vs. saline control and to evaluate the safety and tolerability of SAS-LAR in pediatric patients with hypothalamic obesity.

The sNDA and study report are in the FDA electronic document room via the network path \\CDSESUB1\N21008\S_018\2005-11-10

4.2 Tables of Clinical Studies

Table 4.2: Table of Clinical Studies of Sandostatin LAR in the Pediatric Population

Study	Title	Size	Design	Treatment Groups	N
2403	A randomized, multicenter, double-blind trial of Sandostatin LAR® Depot (40mg) versus saline control in the treatment of pediatric hypothalamic obesity	60 children with hypothalamic obesity; age:6 to <18 years race: 56W:1B:3O gender: 27M:33F	Randomized, placebo-controlled, multicenter, double-blind trial to compare changes in body mass index with Sandostatin LAR® Depot (40mg) and saline control	Form: Sandostatin LAR® Depot vs. saline placebo Duration: 6 months Doses: 40 mg/month (sandostatin) vs. 2mL/month (saline)	30:octreotide 30:placebo
2408	Hypothalamic obesity caused by cranial insult in children: Altered glucose and insulin dynamics and reversal by a somatostatin agonist. **publ.:** Lustig RH, Rose SR, Burghen GA, et al (1999) J Pediat; 135(2) (Pt1): 162-8	9 children with hypothalamic obesity; age: > 4 years race: unknown gender: unknown	Open-labeled, non-randomized pilot study in which all patients received study drug	Form: Octreotide s.c Duration: 6 months Doses: 5 to 15 µg/kg/d every 8 hours	9:octreotide 0: placebo
2409	Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab, 88(6):2586-92 **publ.:** Lustig RH, Hinds PS, Ringwald-Smith K,et al (2003)	20 children with hypothalamic obesity; age: 8 to 21 years race: unknown gender: unknown	Double-blind, placebo-controlled, randomized study; patients were stratified by tumor category	Form: Octreotide s.c versus saline Duration: 6 months Doses: 5 to 15 µg/kg/d every 8 hours *Note: 6 months of double-blind octreotide or placebo (saline) was followed by 6 months of octreotide for all patients.	10:octreotide 10:placebo

4.3 Review Strategy

All reviewers conducted independent reviews, but collaborated on areas of controversy and individual questions. The focus of the review is study 2403. The published studies 2408 and 2409 are reviewed in Section 10.1.

4.4 Data Quality and Integrity of Study 2403

4.4.1 Provisions to Enhance Data Integrity
Study bias was minimized by independent data monitoring by Novartis, multiple investigators participating in the studies, and double-blind placebo-controlled trial design.

Data items were entered directly into the study database or indirectly from source data documents by designated Novartis-trained investigator staff using single data entry with electronic verification. Novartis staff reviewed the data for completeness and accuracy and instructed the site personnel to make any required corrections or additions.

In order to monitor the safety of SAS-LAR in children during the conduct of the study, an independent Data Safety Monitoring Board (DSMB) was convened when approximately 25 patients had been enrolled. It met twice more during the study and again at the end of the study. The DSMB reviewed, evaluated and categorized any serious case reported in association with SAS-LAR. All relevant safety data available from this study were provided to each committee member for this review.

4.4.2 Potential Risks to Data Integrity

- Canada and Poland only agreed to enter patients aged ≥10 and ≥13 years, respectively, into the study.
- Thirteen patients were found to be too large to fit on the table (table limit is 300 lbs.) for DEXA body composition measurements and therefore had to have measurements taken excluding either their right or left arm. The value for the "missing arm" was imputed, based on the results from the measured arm, in the reports for the body components (i.e. left arm, right arm, left leg, right leg, etc.). Imputed values were not part of total body composition measurements and, therefore, were not included in the analyses of changes from baseline in total body composition of fat, fat free mass (lean tissue) and bone.
- Evaluation of quantitative abdominal CT scans was performed at local centers and a central facility. For consistency when analyzing the data, the central readers' results were used and local results were used only for those few patients whose scans were not available to the central facility readers.
- Holter monitoring was intended to be conducted at a single center (number 0512) where the site investigator was to sponsor these assessments in his sub-set of patients. However, this procedure was not performed due to technical difficulties.
- C-peptide analyses were affected by a change of test kit at the CRL Medinet USA central laboratory performing the assays. Pre-change values were transformed so that C-peptide results could be compared across the study

4.4.3 Division of Scientific Investigations (DSI)

The Division of Scientific Investigations was not consulted and did not conduct an audit or site visit for this application.

4.5 Compliance with Good Clinical Practices in Study 2403

4.5.1 Ethics

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC and US Code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

4.5.2 Informed Consent
Patients had to provide written informed consent according to the legal requirements of their respective countries.

4.5.3 Protocol Violations
The majority of protocol deviations were minor and not expected to affect the study results. Those that were considered major and led to exclusion of the patients from the PP (per-patient population) efficacy analysis are below:

1. POL/0602/00003 (SAS-LAR): Patient violated dose administration schedule more than once. Dosing interval was <25 or >42 days since prior dose.
2. USA/0502/00004 (SAS-LAR): Patient violated dose administration schedule more than once. Dosing interval was <25 or >42 days since prior dose.
3. USA/0512/00001 (SAS-LAR): Treatment assignment revealed to site staff prior to final study visit
4. USA/0502/00006 (saline control):Patient did not complete first 4 months of treatment
5. USA/0507/00004 (saline control): Patient administered weight loss medications

The treatment code was broken before database lock for 2 patients who received SAS-LAR:

1. Patient USA/0512/00001 (SAS-LAR) was unblinded, in error, during the double-blind treatment period when the study coordinator and investigator received the drug shipment ticket instead of the designated site personnel. Therefore, this patient was classified as a major protocol violator.
2. Patient CAN/0202/00002 (SAS-LAR) was unblinded after she completed the study when her parents insisted on knowing her treatment before deciding whether or not she should enter the extension study. This patient was found to have gallstones and did not enroll in the extension.

4.6 Financial Disclosures

No clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the clinical investigators participating in the trials.

5 CLINICAL PHARMACOLOGY

Pharmacokinetic and pharmacodynamic evaluations were incorporated into Study 2403. Serum samples were collected for octreotide concentration measurement using a population pharmacokinetic approach after the first dose in 26 out of 30 patients receiving Sandostatin LAR®. In addition, serum samples were collected for octreotide trough concentration

measurement (C_{trough}). Serum insulin concentrations were measured at the same time points as octreotide concentrations were measured.

5.1 Pharmacokinetics

Blood samples for octreotide serum concentrations were taken after a ≥8 h fast prior to each Sandostatin LAR® dose over the 6-month evaluation period. After the first and prior to the second Sandostatin LAR® dose, 3 additional fasting blood samples were taken, respectively within 1 to 10 days, 11 to 20 days, and 21 to 30 days post first dose.

Of the 60 patients qualified for inclusion in the intent to treat analysis population, 30 received saline control, and 30 received Sandostatin LAR® Depot, with 26/30 patients providing octreotide concentration data for PK analysis. Following monthly i.m. injection of Sandostatin LAR® Depot, accumulation of octreotide concentrations was observed. A steady-state concentration appeared to be achieved after the 3rd dose and was maintained throughout the remaining treatment period. Mean trough octreotide concentrations increased from 1396 pg/mL prior to the 2nd dose to 2973 pg/mL at steady state, representing an approximately 2-fold accumulation. Steady-state octreotide concentrations (in log-scale) were not correlated with either age or BMI, but moderately correlated with body weight ($p = 0.03$) and significantly correlated with gender ($p = 0.005$). Female patients had a mean octreotide concentration which was 16.6% higher than that in males. The correlation with body weight became statistically non-significant when the gender effect was included in the analysis. Mean body weight between the male patients (86.6 ± 24.0 kg) and female patients (84.4 ± 21.5 kg) was not significantly different ($p = 0.3$).

5.2 Pharmacodynamics

Blood samples for fasting serum insulin assessments were taken at the same time points as the blood collections for octreotide concentrations.

Insulin levels were significantly correlated with steady-state octreotide concentrations ($p=0.004$) and treatment ($p = 0.001$). No significant relationship with steady-state octreotide concentration was observed when considering only Sandostatin LAR® Depot treated patients ($p = 0.93$). Thus, the significant correlation between octreotide concentration and insulin appeared to be solely due to the treatment difference.

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Study 2403 was performed in response to a Written Request to study the safety and efficacy of Sandostatin LAR® Depot in the pediatric patient population. The primary objectives are to compare changes in body mass index (BMI) with SAS-LAR (40mg) and saline control and to evaluate the safety and tolerability of SAS-LAR in pediatric patients with hypothalamic obesity.

6.1.1 Methods

Study 2403 was a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial in children with hypothalamic obesity treated with 40mg SAS-LAR or saline control administered as intramuscular injections once a month for 6 months.

During the 2-week screening period, patients were given a single 100µg subcutaneous injection of Sandostatin® sc to test for tolerability. Eligible patients were randomized, in a 1:1 ratio, to receive either:

1. SAS-LAR given as 2 intragluteal injections of 20mg each (40mg total per month), or,
2. saline control given as 2 intragluteal injections of 2mls each (4ml total per month).

The study design is summarized below.

Table 6.1.1 Study 2403 Design (sponsor's table 3-1)

	Screening Randomization	Base -line	Double-blind treatment						Extension study †
Month	-0.5	0	1	2	3	4	5	6	7-12
Visit	1	2	3	4	5	6	7	8	
SAS sc	Test dose 100µg/mL	-	-	-	-	-	-	-	-
SAS-LAR		2 x 20mg SAS-LAR intragluteal injections per month						-	SAS-LAR 40mg per month
Saline		2 x 2mL saline intragluteal injections per month						-	

6.1.2 General Discussion of Endpoints

6.1.2.1 Efficacy Endpoints

6.1.2.1.1 Primary Efficacy Endpoint

- The primary efficacy endpoint is change in BMI.

6.1.2.1.2 Secondary Efficacy Endpoints

The secondary efficacy variables include:

- Change from baseline in weight
- Change from baseline in waist to hip ratio
- Change from baseline in key biochemical and metabolic parameter, leptin (measured at screening, Month 3, and Month 6)
- Change from baseline in insulin dynamics (insulin, C-peptide, amylin and glucose) versus time profiles during the OGTT
- Change from baseline in body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans and in visceral and subcutaneous fat in the abdomen by quantitative CT scan
- Change from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity
- Pharmacokinetic/Pharmacodynamic (PK/PD) relationships between octreotide concentration and insulin levels
- Pharmacokinetic (PK) parameters of SAS-LAR in pediatric patients
- Proportion of patients who show no increase in BMI (Δ BMI ≤ 0)

Details on the special tests performed as part of the efficacy assessment were provided in Novartis' Clinical Study Report, pages 28-29 and 76-82.

6.1.3 Study 2403 Design

6.1.3.1 Criteria for adequate and well-controlled studies

6.1.3.1.1 Minimization of bias

Study Blinding:
This was a double-blind study. To minimize bias, the patient's assigned treatment group was not known to the patient, investigator, study coordinator and study monitors. Study monitors were unblinded at database lock in order to perform full drug accountability.

Randomization:
Randomization was performed by Novartis Drug Supply Management. The randomization scheme was reviewed by the Biostatistics Quality Assurance Group in Novartis Biostatistics and Statistical Reporting Department and locked by them after approval. Randomization data were kept strictly confidential; accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any emergency code breaks was determined after return of all code break reports and unused drug supplies to Novartis. Only when the study had been completed, the data file verified, and the protocol violations determined were the drug codes broken and made available for data analysis.

Identification of Endpoints:
Data from all participating centers were combined so that an adequate number of patients was available for statistical analysis. Data from patients who completed at least one post-baseline

assessment were included in the intent-to-treat and per-protocol analyses using last observation carried forward (LOCF) methodology as appropriate.

For the primary efficacy variable (change from baseline in BMI), change was calculated such that negative change values indicate improvements. For primary safety variables and all secondary variables, positive values of change indicate increases from baseline.

The following definitions were used for assessments:

Baseline assessment: The last assessment made at or before randomization.
Unscheduled assessment: Assessments made in response to events during the course of the trial, for example, premature termination from the study, adverse event, etc.

The safety population consisted of all randomized patients who were administered at least one dose of study medication.

The intent-to-treat population (ITT**)** consisted of all randomized patients who were administered at least one dose of study medication and had at least one post-baseline assessment. The per-protocol population (PP) consisted of all randomized patients who had at least one post-baseline assessment, who completed at least the first four months of the study and had no major protocol violations.

Prospective Statistical Analytic Plan

The trial tested the null hypothesis that the mean changes from baseline in BMI 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.

Treatment groups were compared using contrasts from an ANCOVA with treatment as a factor and baseline BMI as covariate. Testing was performed at the 2-sided 5% significance level.

Summary statistics (sample size, mean, median, standard deviation, minimum and maximum).were reported for the primary endpoint and all continuous secondary endpoints during baseline and treatment periods.

The sample size calculation for the hypothesis of the primary objective was based on the requirement that all comparisons should have at least 90% power to detect the anticipated differences in reductions from baseline of BMI between the active treatment group and the saline controls. Based on previous study results for an ITT population, it was estimated that the active treatment arm compared with the saline control arm would reduce BMI by at least 1.25 kg/m^2 and the reductions would have a common standard deviation of 1.22 kg/m^2 at the end of the 6-month study. Having used these estimates and assuming 0.05 level of significance of a two-sided two-sample t-test, the sponsor estimated that at least 22 evaluable patients would need to be enrolled on each trial arm.

Efficacy analyses:

The primary efficacy analysis was performed on the intent-to-treat and per-protocol populations in order to take into account the response of patients who prematurely withdrew from the study for any reason. The primary efficacy result is the change from baseline to last post-baseline assessment of BMI. BMI was calculated as the patient's weight (in kilograms) divided by the square of the patient's height (in meters). Patient listings of BMI were provided. All secondary efficacy evaluations were performed on the ITT population.

Safety analyses:
Safety parameters were presented by treatment group using descriptive statistics for continuous variables, and frequencies with percentages for categorical variables. All safety analyses were performed on the safety population only.

6.1.3.2 Assessment of benefit

6.1.3.2.1 Adequacy of duration of controlled studies

The duration of the study was 6 months. This provided an adequate time for an assessment of efficacy and safety.

6.1.3.2.2 Entry criteria

Inclusion Criteria:
Patients were eligible for inclusion if they met criteria 1-4, 7, 8; and at least one of criteria 5 and 6, as follows:

1. Male or female patients ages 6 to less than 18 years
2. Patients who had experienced any form of cranial insult related to cranial trauma, or to a tumor or its treatment (i.e. surgery, radiation, and/or chemotherapy)
3. Patients who were at least one year following therapy for their tumor
4. Patients may be pre-pubertal (Tanner 1) through adult (Tanner 5)
5. Patients who were normal weight for height within a year of diagnosis of their cranial insult or tumor, but were greater than 120% of their ideal body weight for height, or Body Mass Index >27 kg/m^2 at screening
6. Patients who had gained weight faster than 2 standard deviations (SDs) above the mean for their age for at least one year following all tumor therapy
7. Patients had to have documented stabilized pituitary function tests (thyroid function tests (TFTs), growth hormone (GH) levels within normal limits) prior to enrollment into the study. Patients taking thyroid medications, growth hormone etc. must have been on the medication for a minimum of 30 days and have documented evidence of stabilization.
8. Patients had to provide written informed consent according to the legal requirements of their respective countries.

Exclusion Criteria:
Patients were excluded if any of the following criteria were met:

1. Patients who had severe cardiovascular dysfunction (for example cardiomyopathy, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation)
2. Patients with severe neurologic handicaps, which precluded normal physical activity, or patients who were confined to bed or wheelchair bound preventing them from performing activities of daily living or normal physical activity i.e. walking
3. Patients currently receiving any antineoplastic therapy
4. Patients with a history of gallstones
5. Patients who had previously received Sandostatin (octreotide)
6. Patients who could not tolerate the Sandostatin sc test injection
7. Patients with clinically active cardiac diseases, valvulopathy included
8. Patients who could not tolerate the OGTT test or patients who were glucose intolerant

The sponsor's exclusion criteria did not specifically include "patients who are post-menarcheal females not using an acceptable form of contraception" as requested in the Pediatric Written Request. However, the case report form did include questions inquiring about menses and sexual activity. No pregnancies occurred during study treatment.

6.1.3.2.3 Adequacy of dose regimen

A dose of 40mg was selected for the pivotal study 2403, as it is roughly equivalent to 10µg/kg/day of octreotide s.c. as utilized in study 2409. However, the sponsor notes that the significant reduction in body weight and body mass index was more notable at the maximum dose investigated, 15µg/kg/day sc octreotide, compared to the starting dose of 5µg/kg/day. Over a 30-day period, the sponsor calculates a cumulative dose of 42.75 mg octreotide. Using an average relative bioavailability of Sandostatin LAR® Depot of 60%, approximate 71 mg of Sandostatin LAR Depot would be required. Therefore, the proposed 40 mg Sandostatin LAR® Depot dose represents the highest dose specified in the drug label, but corresponds to only one half of the 15µg/kg/day dose that was found to be effective in study 2409.

6.1.4 Efficacy Findings

6.1.4.1 Primary Efficacy Endpoints

As outlined in the table below, analyses of the primary efficacy endpoint mean change from baseline in BMI, comparing SAS-LAR and saline-control at the end of the study (LOCF) showed no statistically significant differences between treatments, in the ITT or PP populations.

Table 6.1.4.1 BMI (kg/m2) mean change from baseline to end of study: treatment comparisons (ITT and PP populations, LOCF)
(Sponsor's Table 9-1)

Population Treatment	n	Baseline mean	mean change	LSM change †	95% CI †	SAS-LAR vs. saline control p-value †
ITT						
SAS-LAR	30	33.9	0.1	0.1	-0.5, 0.8	0.735
Saline control	30	34.8	0.0	0.0	-0.7, 0.6	
PP						
SAS-LAR	27	34.3	-0.1	-0.1	-0.8, 0.6	0.846
Saline control	28	34.2	0.0	0.0	-0.7, 0.7	

n is the number of patients with observations at baseline and at least one visit post-baseline.
† ANCOVA with treatment as a factor and baseline value as covariate. P-value is from the ANCOVA model F-test on treatment. LSM = least squares mean, LOCF = last observation carried forward

6.1.4.2 Secondary Efficacy Endpoints for the ITT Population

6.1.4.2.1 Change from baseline in weight

Mean weight gradually increased in both treatment groups from baseline to the end of the study (1.9 kg in the SAS-LAR-treated group vs. 1.8 kg in the saline-control-treated group, p=0.93). There was no statistically significant difference between treatments in the ITT and PP populations.

6.1.4.2.2 Change from baseline in waist to hip ratio

Mean waist to hip ratio decreased in the SAS-LAR group whereas it increased in the saline control. Analyses comparing mean change from baseline in waist to hip ratio between SAS-LAR and saline control at Month 6 (no LOCF) showed a statistically significant difference between treatments in favor of SAS-LAR, in the ITT (-0.014 in the SAS-LAR-treated group vs. +0.025 in the saline-control-treated group, LSM difference -0.039, p=0.012,) and PP populations (-0.018 in the SAS-LAR-treated group vs. +0.025 in the saline-control-treated group, LSM difference -0.043, p=0.008).

6.1.4.2.3 Change from baseline in leptin (measured at screening, Month 3, and Month 6)

Mean leptin rose higher between baseline and Month 6 in the saline control group than in the SAS-LAR group, indicating increasing adiposity. The difference between the two groups in mean change of leptin from baseline to Month 6 was suggestive of statistical significance in favor of SAS-LAR treatment to prevent an increase in adipose tissue, p=0.062.

6.1.4.2.4 Change from baseline in insulin dynamics (insulin, C-peptide, amylin and glucose) versus time profiles during the OGTT

In the SAS-LAR group, mean insulin AUC decreased significantly between baseline and Month 6 but remained about the same in the saline control group showing a lower insulin response to a glucose load during SAS-LAR treatment compared with saline control. The difference between the two treatments in mean change of insulin AUC from baseline to Month 6 was statistically significant ($p<0.001$).

C-peptide AUC analysis was affected by limitations of the AUC calculation which excluded values >2.32 nmol/L, therefore reducing the number of patients contributing to the analysis to 13 SAS-LAR and 19 saline control patients. Mean C-peptide AUC tended to decrease between baseline and Month 6 in the SAS-LAR group but did not so in the saline control group. The difference between the two groups in mean change of C-peptide AUC from baseline to Month 6 was suggestive of statistical significance ($p=0.067$).

Mean amylin AUC decreased between baseline and Month 6 in the SAS-LAR and saline control groups by a similar amount. There was no statistically significant difference between the two groups.

Mean glucose AUC increased between baseline and Month 6 in the SAS-LAR group but decreased in the saline control group, so that the difference between the two groups in mean change of glucose AUC from baseline to Month 6 was statistically significant ($p=0.009$). The higher glucose AUC suggests a lesser metabolic capacity to handle a glucose load during SAS-LAR treatment.

6.1.4.2.5 Change from baseline in body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans and in visceral and subcutaneous fat in the abdomen by quantitative CT scan

DEXA total lean tissue weight increased between baseline and Month 6 in both groups and there was no significant difference between the groups, $p=0.81$. No other body composition variable changed significantly in either group although mean CT subcutaneous fat thickness increased in the saline control group (mean change of 19.9 cm^2) but fell slightly in the SAS-LAR group (mean change of -0.7 cm^2). However, the difference between the two groups was not significant, $p=0.151$.

6.1.4.2.6 Change from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity

In the SAS-LAR and saline control groups, mean 24h total calorie and total fat intakes were lower at Month 6 compared with baseline. However, there were no statistically significant differences between the two groups in the mean changes from baseline to Month 6 for any of the dietary intake variables. Physical activity scores showed a mean increase in the SAS-LAR group and a mean decrease in the saline group. This approached statistical significance, $p=0.065$.

6.1.4.2.7 Pharmacokinetic (PK) parameters of SAS-LAR in pediatric patients

A steady-state concentration appeared to be achieved after the 3rd dose and was maintained throughout the remaining treatment period. Mean trough octreotide concentrations increased from 1396 pg/mL prior to the 2nd dose to 2973 pg/mL at steady state, representing an approximately 2-fold accumulation. Steady-state octreotide concentrations (in log-scale) were not correlated with either age or BMI, but moderately correlated with body weight (p=0.03) and significantly correlated with gender (p-value= 0.005). Female patients had a mean octreotide concentration that was 16.6% higher than that in males. The correlation with body weight became statistically non-significant when the gender effect was included in the analysis. Mean body weight between the male patients (86.6 ± 24.0 kg) and female patients (84.4 ± 21.5 kg) was not significantly different (p=0.3).

6.1.4.2.8 Pharmacokinetic/Pharmacodynamic (PK/PD) relationships between octreotide concentration and insulin levels

Insulin levels were significantly correlated with steady-state octreotide concentrations (p=0.004) and treatment (p=0.001). No significant relationship with steady-state octreotide concentration was observed when considering only Sandostatin LAR® Depot treated patients (p=0.93). Thus, the significant correlation between octreotide concentration and insulin appeared to be solely due to the treatment difference.

6.1.4.2.9 Proportion of patients who show no increase in BMI ($\Delta BMI \leq 0$)

Thirty six percent of patients treated with SAS-LAR and 48% of patients in the saline control group responded to treatment as evidenced by no change or a decrease in BMI. There was no statistically significant difference between treatments (chi-square test p=0.350).

6.1.4.3 Study Subject Disposition

Sixty-two patients were randomized (32 SAS-LAR, 30 saline) and 56 patients completed the study. Patient disposition is summarized in Table 6.1.4.3.

Table 6.1.4.3 Patient disposition by treatment and overall (All patients)
(Sponsor's table 7-1)

	SAS-LAR N=32 n (%)	Saline control N=30 n (%)	Total N=62 n (%)
Patients:			
Screened			74
Randomized	32 (100)	30 (100)	62 (100)
Exposed	31 (96.9)	30 (100)	61 (98.4)
Completed	28 (87.5)	28 (93.3)	56 (90.3)
Discontinued	4 (12.5)	2 (6.7)	6 (9.7)
Main reason for discontinuation:			
Adverse event(s)	1 (3.1)	1 (3.3)	2 (3.2)
Patient withdrew consent	2 (6.3)	1 (3.3)	3 (4.8)
Administrative problems	1 (3.1)	0	1 (1.6)

Sixty patients (30 SAS-LAR, 30 saline) were correctly included in the ITT-LOCF analysis as defined in the Written Request. 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.

6.1.4.4 Demographics

As outlined in the table below, the majority of patients were Caucasian (93%), aged ≥12 years (75%) with mean age of 13.6 years. No patients reported themselves to be of Hispanic/Latino race or ethnicity.

Table 6.1.4.4 Baseline demographic characteristics
(Sponsor's Table 7-4)

		SAS-LAR N=30	Saline control N=30	Total N=60
Age (years)	Mean	12.9	14.2	13.6
	SD	3.38	2.43	2.99
	Median	13.5	14.0	14.0
	Range	6 – 17	9 – 17	6 – 17
Age group – n (%)	<12 years	9 (30.0)	6 (20.0)	15 (25.0)
	≥12 years	21 (70.0)	24 (80.0)	45 (75.0)
Sex – n (%)	Male	14 (46.7)	13 (43.3)	27 (45.0)
	Female	16 (53.3)	17 (56.7)	33 (55.0)
Race – n (%)	Caucasian	27 (90.0)	29 (96.7)	56 (93.3)
	Black	1 (3.3)	0	1 (1.7)
	Pacific islander	0	1 (3.3)	1 (1.7)
	Other	2 (6.7)	0	2 (3.3)
Country – n (%)	Belgium	3 (10.0)	3 (10.0)	6 (10.0)
	Canada	2 (6.7)	2 (6.7)	4 (6.7)
	Poland	3 (10.0)	2(6.7)	5 (8.3)
	Russia	8 (26.7)	8 (26.7)	16 (26.7)
	USA	14 (46.7)	15 (50.0)	29 (48.3)
Weight (kg)	Mean	81.72	89.02	85.37
	SD	21.236	24.459	23.006
	Median	84.50	85.20	85.10
	Range	47.4 – 127.0	42.0 – 147.5	42.0 – 147.5
Height (cm)	Mean	154.3	158.8	156.5
	SD	14.84	10.93	13.12
	Median	155.0	159.0	156.0
	Range	123 – 181	137 – 182	123 – 182
BMI (kg/m^2)	Mean	33.9	34.8	34.3
	SD	5.37	6.60	5.98
	Median	33.0	34.3	33.8
	Range	25.3 – 44.6	22.4 – 50.0	22.4 – 50.0

BMI results are taken from visit 2 (month 0).

At baseline, no gallbladder ultrasound or echocardiogram abnormalities were found in any of the patients. There was a slight imbalance in body composition at baseline for total lean tissue weight and visceral fat thickness which were lower in the SAS-LAR group, and the difference between treatment groups for visceral fat was suggestive of statistical significance (p=0.06).

For the majority of patients (54, 90%), neoplasms, most frequently craniopharyngiomas and their treatment by surgery and/or radiotherapy were responsible for the hypothalamic dysfunction and consequently, endocrine disorders were common. Four patients had head injury (reported as cranial trauma, 2 in each group), one patient had no posterior pituitary and one patient had idiopathic diabetes insipidus that caused the hypothalamic dysfunction. Three patients (2 in

SMS-LAR group, 1 in saline control group) had a history of non-insulin dependent diabetes mellitus reported to be transient in 2 of the 3 patients.

6.1.4.5 Prior and Concomitant Drug Therapies

Concomitant drug usage in the SAS-LAR and saline control groups reflected the patients' endocrine disorders and the medications required to treat these e.g. glucocorticoids (SAS-LAR, saline: 60%, 63% of patients), somatropin (SAS-LAR, saline: 33%, 53%), thyroid hormones (SAS-LAR, saline: 63%, 87%) and vasopressin (SAS-LAR, saline: 50%, 70%). There were some imbalances between the two treatment groups with respect to the use of these hormone replacement therapies.

Non-drug therapies and procedures including surgery were reported by a similar proportion of patients in each group (SAS-LAR, saline: 27%, 30%), as were analgesics and anti-inflammatory agents such as paracetamol (SAS-LAR, saline: 20%, 23%) and ibuprofen (17% in each group).

The use of forbidden concomitant medications was taken into consideration when identifying protocol violators. Only one patient was considered to be a major protocol violator because of use of forbidden therapy, (weight loss medication use by patient USA/0507/00004).

6.1.4.6 Review of effectiveness data for gender, age, and racial subgroups

The majority of patients were Caucasian (93%) and no patients reported themselves to be of Hispanic/Latino race or ethnicity. Thus, there are insufficient numbers of other racial groups to conduct a meaningful analysis for differences in safety or efficacy.

There was a significant difference between males and females in the PK parameters of SAS-LAR in pediatric patients. Steady-state octreotide concentrations (in log-scale) were not correlated with either age or BMI, but moderately correlated with body weight (p-value = 0.03) and significantly correlated with gender (p-value= 0.005). Female patients had a mean octreotide concentration that was 16.6% higher than that in males. The correlation with body weight became statistically non-significant when the gender effect was included in the analysis. Mean body weight between the male patients (86.6 ± 24.0 kg) and female patients (84.4 ± 21.5 kg) was not significantly different (p-value = 0.3).

6.1.4.7 Limitations of efficacy studies

The proposed 40 mg Sandostatin LAR® Depot dose represents the highest dose specified in the drug label, but corresponds to only one half of the 15μg/kg/day dose that was found to be effective in study 2409. Efficacy for Sandostatin LAR® Depot for hypothalamic obesity may have been shown if a higher dose of SAS-LAR had been given.

These studies are investigating the efficacy of SAS-LAR in a small population of children with obesity secondary to hypothalamic injury and cannot be generalized to the population of children with primary obesity (not associated with hypothalamic injury).

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

6.1.6.1 Primary Endpoint for the ITT and PP Population

The primary efficacy analysis of mean change from baseline in BMI comparing SAS-LAR and saline-control at the end of the study (LOCF) showed no statistically significant differences between treatments, in the ITT (p=0.735) or PP populations (p=0.846).

6.1.6.2 Secondary Endpoints for the ITT Population

There was a statistically significant difference between treatments in the following secondary efficacy endpoints:

- ✓ Change from baseline in waist to hip ratio
- ✓ Mean change of insulin AUC and glucose AUC from baseline to Month 6

Analyses comparing mean change from baseline in waist to hip ratio between SAS-LAR and saline control at Month 6 showed a statistically significant difference between treatments in favor of SAS-LAR. However, the sponsor states that this difference was not considered to be clinically relevant due to possible measurement imperfections.

In the SAS-LAR group, mean insulin AUC decreased significantly between baseline and month 6 but remained about the same in the saline control group showing a lower insulin response to a glucose load during SAS-LAR treatment compared with saline control. In the SAS-LAR group, mean glucose AUC increased significantly between baseline and Month 6 but decreased in the saline control group. The higher glucose AUC suggests a decreased metabolic capacity to handle a glucose load during SAS-LAR treatment.

There was no statistically significant difference between the two treatment groups in the following secondary efficacy endpoints:

- ✓ Change from baseline in weight
- ✓ Change from baseline in leptin
- ✓ Mean change of C-peptide AUC and amylin AUC from baseline to month 6
- ✓ Change from baseline in body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans and in visceral and subcutaneous fat in the abdomen by quantitative CT scan

- ✓ Change from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity
- ✓ Proportion of patients who show no increase in BMI ($\Delta BMI \leq 0$)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The primary safety endpoint was evaluation of the safety and tolerability of Sandostatin LAR® depot in pediatric patients with hypothalamic obesity.

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, as well as regular measurement of vital signs, hematology, biochemistry, ECGs (measured and assessed locally) and the performance of physical examinations. Laboratory evaluations of hematology and biochemistry included the standard blood tests and a complete lipid profile (HDL, LDL, VLDL, chylomicrons, cholesterol and triglycerides), fasting glucose and insulin, HbA1c, vitamin A (beta-carotene), vitamin B12 (cyanocobalamine), methylmalonic acid, homocysteine levels, folic acid (folate), prothrombin time (PT), thyroid function tests (TFTs) and urinalysis. Details on the special tests performed as part of the safety assessment were provided in Novartis' Clinical Study Report, pages 30-31 and 77 and are summarized below.

Table 7.1.1 Evaluation and Visit Schedule for Study 2403

Evaluations	Screen -ing [1] Visit 1	Month 0 Baseline Visit 2				Mth 1 V3	Mth 2 V4	Mth 3 V5	Mth 4 V6	Mth 5 V7	Month 6 SC or ET Visit 8
Informed consent	X[2]										
Medical history/ Demographics	X										
Physical examination	X*										X
Tanner staging	X										X
Vital signs (standing and sitting), height, weight, BMI(calc)	X	X				X	X	X	X	X	X
Wrist X-ray		X									
ECG	X*										X
Echocardiogram	X*							X			X
Holter monitoring (single site only)	X*										X
DEXA scan [3]		X									X
U/S gallbladder	X*[4]										X
Quantitative CT scan		X									X
Pregnancy test (urine)	X[5]	X				X	X	X	X	X	X
Hematology, blood chemistry, & urinalysis	X*[5]							X			X
TFTs and HbA_{1C}	X	X				X	X	X	X	X	X
Insulin (2-hour OGTT)** [7]		X						X			X
Leptin**		X						X			X
Fasting serum glucose and insulin** [8]	X	X	D1-10	D11-20	D21-30	X	X	X	X	X	X
SAS-LAR PK analysis[9]		X	D1-10	D11-20	D21-30	X	X	X	X	X	X
SAS sc injection test dose [10]	X										
Spot stool fat analysis		X						X			X
Nutritional evaluation		X				X	X	X	X	X	X
Dietary analysis (3-day food record)		X						X			X
Physical activity analysis (3-day record of activity)[11]		X						X			X
Waist and hip circumferences		X						X			X
Study medication administration INTRA GLUTEAL		X				X	X	X	X	X	
Adverse events	<----------Every visit as needed---------->										
Conmeds	<----------Every visit as needed---------->										
SC Form											X

The safety section of final study report included data on:

- Body composition as monitored by CT scan (Months 0 and 6) and waist to hip ratio (Months 0, 3, and 6).
- Tanner staging (screening and end of study)
- Gallbladder imaging w/ ultrasound was performed at baseline and at end of study
- PT, routine blood chemistries, stool fat analysis at baseline, 3 months, and end of study
- beta carotene, homocysteine, B12, and methylmalonic acid levels were measured at baseline and at end of study
- OGTT, HbA1c, fasting blood glucose, and plasma insulin levels were obtained at baseline and at 6 months
- echocardiograms were performed at baseline, 3 months, and at end of study
- ECGs were obtained at baseline and at 6 months
- TFTs were performed at baseline and at 6 months

A DSMB was established to review safety data collected in an on-going manner in this pivotal clinical study. As discussed in Novartis' Clinical Study Report, pages 788-89, the DSMB was comprised of pediatricians and cardiologists.

Additional safety data were submitted from two previously conducted clinical studies using octreotide subcutaneous injectable formulation. These were provided in this submission as study reports for Studies SMS995B 2408 and SMS995B 2409. Study 2408 was an open-label pilot study that recruited 9 pediatric patients with data available from 8 patients out to 6 months. Study 2409 was a double-blind, placebo-controlled study in 20 patients for 6 months followed by an additional 6 months of open-label therapy.

The applicant initiated a 6-month open-label extension study to Study SMS995B 2403. This study was terminated by the DSMB due to lack of efficacy data from the controlled period and the apparent higher risk of gallstone formation.

Study 2408, 2409 and the 6-month open-label extension to Study 2403 are reviewed in Section 10.1.

7.1.1 Deaths

There were no deaths in this study.

7.1.2 Other Serious Adverse Events

There were 13 patients (10: SAS-LAR, 3: saline control) who experienced a serious adverse event.

Treatment group Sandostatin LAR® Depot: 10 patients (30%) with SAE

- Patient 201 0002: Biliary sludging/Cholelithiasis
- Patient 202 0002: Cholelithiasis
- Patient 501 0003: Cholelithiasis
- Patient 502 0004: Cholelithiasis
- Patient 510 0001: Cholelithiasis
- Patient 512 0001: Gallstone Pancreatitis, abdominal pain, nausea, vomiting, hypoactive bowel sounds, increased liver function tests, inflammation of the head of the pancreas
- Patient 515 0003: Gallstones
- Patient 602 0003: Cyst of maxillary sinus, cyst removal, thickening of the mucous membrane
- Patient 701-0008: Cholelithiasis
- Patient 704-0006: Cholelithiasis

Nine patients in the SAS-LAR group developed cholelithiasis reported as SAEs, suspected to be related to study drug and detected by ultrasound scan of the gallbladder performed at the end of the study. Two of the cases of gallstones were graded as severe or life threatening and the others were mild or moderate in severity. One patient (512 0001) subsequently developed gallstone pancreatitis reported as a severe study drug-related SAE about 3 months after the last dose of SAS-LAR and, after further investigation, she was to undergo laparoscopic cholecystectomy. All nine (30%) patients receiving SAS-LAR who developed cholelithiasis during the study were recorded in the clinical database as having SAEs regardless of the reported severity. A tenth SAS-LAR patient had a non-serious AE at the end of the study reported as gallbladder "sludge" but gallstones developed after the study and were reported as an SAE (patient 201-0002).

Treatment group Saline: 3 patients (10%) with SAE

- Patient 102 0002: Hypernatremic dehydration associated with enteritis, hypokalemia,
- Patient 507 0004: Back pain, spinal lipomas, hematuria, urinary tract infection, hematochezia
- Patient 518 0001: Hypernatremia, increased body temperature, confusion.

None of the SAEs in the control group were suspected to be related to study drug.

7.1.3 Dropouts and Other Significant Adverse Events

Specifically, patients were to discontinue if any of the following occurred:

1. severe or life-threatening hyperglycemia (e.g. diabetic ketoacidosis, hyperosmolar coma)
2. Type 2 diabetes mellitus, as determined by a rise in their HbA1c or by glycosuria. Patients were to be labeled a "treatment failure". Their data collection was to be continued in an intent-to-treat (ITT) model.
3. jaundice or hepatitis, or LFTs increased
4. renal dysfunction (i.e. elevated BUN or creatinine)
5. concurrent hormonal abnormality
6. newly developed cardiac dysfunction

7.1.3.1 Overall profile of dropouts

Table 7.1.3.1 Overall profile of deaths, SAEs, and dropouts (Safety population)
(Sponsor's table 10-4)

	SAS-LAR N=30 n (%)	Saline control N=30 n (%)
Patients with AE(s)	28 (93.3)	21 (70.0)
Serious or other significant events:		
Deaths	0	0
SAE(s)	9 (30.0)	3 (10.0)
Discontinued due to SAE(s)	0	1 (3.3)
Discontinued due to AE(s)	1 (3.3)	1 (3.3)
AEs requiring study drug dose adjustment or temporary interruption	1 (3.3)	0

7.1.3.2 Adverse events associated with dropouts

Only two patients discontinued from the study because of AEs, 1 in each group:

Patient 501-0002 – Elevated liver transaminases and impaired oral glucose tolerance test
Treatment group: Sandostatin LAR Depot
Event(s): 1. AE causing withdrawal from study (Elevated liver transaminases)
This 12-year-old Caucasian Female has a medical history of pilocytic astrocytoma and hypothalamic obesity. The patient commenced treatment on study drug on 27 Sep 2004. The patient's last dose of study treatment was administered on 20 Dec 2004. On 20 Dec 2004, the patient developed elevated liver transaminases.

Patient 507-0004: Back pain, spinal lipomas, hematuria, urinary tract infection, hematochezia
Treatment Group: Saline Control
Event(s): 1. SAE (Back pain, paraspinal lipomas, hemturia, hematochezia)

Both patients received 4 months of treatment before they discontinued

One patient in the SAS-LAR group had her fifth monthly study drug administration delayed by a few days because she had chicken pox.

7.1.3.3 Other significant adverse events

Patient USA/0514/00002 could not tolerate the 100µg SAS sc test dose. She experienced pain at the injection site and hypertension when first challenged and on re-challenge. These events were reported as SAEs but they are not included in the clinical database because the patient was not randomized and was classified as a screening failure due to SAS sc intolerance.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, was to be collected and recorded on the Adverse Event eCRF and followed as appropriate. An adverse event is defined by the sponsor as any undesirable sign, symptom or medical condition occurring after starting study drug even if the event is not considered to be related to study drug. Study drug includes the drug under evaluation, and any reference or saline drug given during the trial. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them.

A serious adverse event is an undesirable sign, symptom, or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any serious adverse event occurring in a patient after providing informed consent and until 8 weeks after stopping the trial was required to be reported. The period after discontinuing study drug could have been extended if there is a strong suspicion that the drug had not yet been eliminated.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and terms was standard and appropriate for this study. Coexistent diseases and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The safety variables are:

1. Adverse events
2. Serious adverse events

3. Laboratory and other safety evaluations (Hematology, Blood Chemistry, Urinalysis, TFTs, LFTs, HbA1c, Gallbladder ultrasound, ECG, and echocardiogram)

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges.

7.1.5.3 Incidence of common adverse events

As outlined in the section below, the overall number of subjects experiencing an adverse event was higher in the SAS-LAR group (28 (93%) of the SAS-LAR-treated subjects and 21(70%) of the saline-treated subjects). The most common adverse events were diarrhea (11 (37%) of the SAS-LAR-treated subjects and 2(7%) of the saline-treated subjects), cholelithiasis (10 (33%) of the SAS-LAR-treated subjects and none of the saline-treated subjects) and nasopharyngitis (9 (30%) of the SAS-LAR-treated subjects and 8(27%) of the saline-treated subjects).

Age subgroup:
The majority of children in the younger age group (<12 years) had AEs (SAS-LAR 89%, saline control 100%). These were most frequently infections and infestations, gastrointestinal and respiratory disorders. In the older age group (≥ 12 years old), a higher percentage of patients in the SAS-LAR group had AEs (SAS-LAR 95%, saline control 63%). These were most frequently infections and infestations, gastrointestinal, and hepatobiliary disorders. Diarrhea occurred more often in the younger children treated with SAS-LAR. All but one of the 10 children with cholelithiasis were in the older age group but the one younger child with gallstones subsequently developed gallstone pancreatitis.

Gender subgroup:
Fewer boys in the saline control group had AEs (SAS-LAR 100%, saline 54%), whereas similar proportions of girls in both treatment groups had AEs (SAS-LAR 88%, saline 82%). Of the 10 children with cholelithiasis in the SAS-LAR group, 3 were boys and 7 were girls. The incidence of GI disorders was similar in the gender subgroups and higher in the SAS-LAR treatment group.

7.1.5.4 Common adverse event tables

Table 7.5.4.1 Number (%) of patients with AEs overall and by primary system organ class (Safety population)

	SAS-LAR N=30 n (%)	Saline control N=30 n (%)
Patients with AE(s)	**28 (93.3)**	**21 (70.0)**
Primary system organ class affected:		
Infections and infestations	18 (60.0)	16 (53.3)
Gastrointestinal disorders	14 (46.7)	6 (20.0)
Hepatobiliary disorders	11 (36.7)	0
Respiratory, thoracic and mediastinal disorders	7 (23.3)	6 (20.0)
Metabolism and nutrition disorders	5 (16.7)	4 (13.3)
Investigations	4 (13.3)	1 (3.3)
Endocrine disorders	3 (10.0)	1 (3.3)
General disorders and admin. site disorders	2 (6.7)	4 (13.3)
Skin and subcutaneous tissue disorders	2 (6.7)	4 (13.3)
Nervous system disorders	1 (3.3)	4 (13.3)
Neoplasms benign, malignant and unspecified	1 (3.3)	2 (6.7)
Injury, poisoning and procedural complications	1 (3.3)	1 (3.3)
Psychiatric disorders	1 (3.3)	1 (3.3)
Cardiac disorders	1 (3.3)	0
Immune system disorders	1 (3.3)	0
Renal and urinary disorders	1 (3.3)	0
Reproductive system and breast disorders	1 (3.3)	0
Surgical and medical procedures	1 (3.3)	0
Musculoskeletal and connective tissue disorders	0	3 (10.0)
Congenital, familial and genetic disorders	0	1 (3.3)
Ear and labyrinth disorders	0	1 (3.3)
Vascular disorders	0	1 (3.3)

Table 7.1.5.4.2 Number of patients with frequent AEs (≥10% of patients in either treatment group (Safety population)
(Sponsor's table 10-2)

	SAS-LAR N=30 n (%)	Saline control N=30 n (%)
Patients with AE(s)	28 (93.3)	21 (70.0)
AE preferred term:		
Diarrhea	11 (36.7)	2 (6.7)
Cholelithiasis	10 (33.3)	0
Nasopharyngitis	9 (30.0)	8 (26.7)
Abdominal pain	4 (13.3)	1 (3.3)
Glucose tolerance impaired	3 (10.0)	2 (6.7)
Cough	3 (10.0)	0
Pharyngitis	2 (6.7)	3 (10.0)
Upper respiratory tract infection	1 (3.3)	3 (10.0)

Preferred terms are listed in descending order of frequency in the SAS-LAR group.

7.1.5.5 Identifying common and drug-related adverse events

Based on experience with the patient populations receiving Sandostatin LAR® Depot for currently approved indications, adverse events of interest that may be related to study drug include gallbladder and related events; cardiac events including bradycardia and conduction abnormalities; gastrointestinal events including diarrhea, abdominal pain, flatulence, constipation, nausea and vomiting; hypoglycemia or hyperglycemia; hypothyroidism and injection site pain.

Gallbladder and Related Events:
In Study 2403, all cases involving gallstones (10 patients) were reported in the SAS-LAR group. Nine cases were asymptomatic and were detected by ultrasound at the end of the study. One of these patients developed severe gallstones associated with pancreatitis about 3 months after the last dose of study drug. Eleven patients (11/30, 37%) in the SAS-LAR group were found to have new or worsened abnormalities of the gallbladder by the end of Study 2403. No patients in the control group experienced new or worsened gallbladder abnormalities.

In Study 2408, four patients out of eight (50%) had asymptomatic gallbladder sludging/gravel or gallstones as determined by the Month 6 ultrasound.

In Study 2409, four patients out of nine (44.4%), treated with octreotide during the double blind phase, had gallstone or sludge formation at the time of the Month 6 ultrasound.

In the open-label extension to Study 2403, eleven subjects (11/30, 37%) experienced a new or worsened abnormality on the gallbladder ultrasound.

In clinical trials for the original Sandostatin NDA, 52% of acromegalic patients, most of whom received Sandostatin LAR® Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones. In clinical trials, 62% of malignant carcinoid patients who received Sandostatin LAR® Depot for up to 18 months developed new biliary abnormalities including gallstones, sludge and dilatation. New gallstones occurred in 24% of patients.[10]

Thus, in the trials with children with hypothalamic obesity, the number of subjects found to have new or worsened abnormalities of the gallbladder was comparable to that seen in the adult population. However, the incidence of new cholelithiasis is higher (approximately 33%) in the pediatric hypothalamic obesity population compared to that seen in the adult population (22 to 24%).

Cardiac:
In Study 2403, there were no conduction abnormalities. There was one case (1/30, 3.3%) of pericardial effusion in the SAS-LAR treatment group.

In clinical trials for the original Sandostatin NDA, in acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) Injection therapy. Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). In carcinoid syndrome patients sinus bradycardia developed in 19%; conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease.[8]

Gastrointestinal:
In Study 2403, the incidence of gastrointestinal disorders was 46.7% for the SAS-LAR group and 20% for the saline-control group, diarrhea was 36.7% for SAS-LAR and 6.7% for saline-control, constipation was 6.7% for SAS-LAR and 0% for saline-control, nausea was 0% for SAS-LAR and 3.3% for saline-control, vomiting was 3.3% for SAS-LAR and 0% for saline-control, and abdominal pain was 13.3% for SAS-LAR and 3.3% for saline-control. These rates are comparable, and for some parameters better, than that seen in the adult population.

In clinical trials for the original Sandostatin NDA, the incidence of gastrointestinal symptoms in clinical trials of adult patients with acromegaly is diarrhea (36%), abdominal pain or discomfort (29%), flatulence (26%), constipation (19%), nausea (10%), and vomiting (7%). In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR® Depot.

7.1.5.6 Additional analyses and explorations

None

7.1.6 Less Common Adverse Events

None

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory evaluations of hematology and biochemistry included the standard blood tests and a complete lipid profile (HDL, LDL, VLDL, chylomicrons, cholesterol and triglycerides), fasting glucose and insulin, HbA1c, vitamin A (beta-carotene), vitamin B12 (cyanocobalamin), methylmalonic acid, homocysteine levels, folic acid (folate), prothrombin time (PT), thyroid function tests (TFTs) and urinalysis.

Laboratory assessments of hematology, biochemistry and urinalysis were performed at screening, Month 3 and Month 6 or end of study.

The safety section of the final study report included data on:

- Body composition as monitored by CT scan (Months 0 and 6) and waist to hip ratio (Months 0, 3, and 6).
- Tanner staging (screening and end of study)
- Gallbladder imaging with ultrasound was performed at baseline and at end of study
- PT, routine blood chemistries, stool fat analysis at baseline, 3 months, and end of study
- Beta carotene, homocysteine, vitamin B12, and methylmalonic acid levels were measured at baseline and at end of study
- Oral glucose tolerance test (OGTT), HbA1c, fasting blood glucose, and plasma insulin levels were obtained at baseline and at 6 months
- Echocardiograms were performed at baseline, 3 months, and at end of study
- ECGs were obtained at baseline and at 6 months
- Thyroid function tests were performed at baseline and at 6 months

The criteria for clinically notable laboratory abnormalities are:

- Alkaline Phosphatase > 2.5 x ULN
- Bilirubin > 1.5 x ULN
- AST > 3 x ULN
- ALT > 3 x ULN
- HbA_{1c} > 2 x ULN
- FT_4, TSH > 2.0 x ULN

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The primary study selected for analysis of laboratory data is Study SMS995B 2403.

Additional safety data were submitted from two previously conducted clinical studies using octreotide subcutaneous injectable formulation. These were provided in this submission as study reports for Studies SMS995B 2408 and SMS995B 2409. Study 2408 was an open-label pilot study that recruited 9 pediatric patients with data available from 8 patients out to 6 months. Study 2409 was a double-blind, placebo-controlled study in 20 patients for 6 months followed by an additional 6 months of open-label therapy (see Section 10.1).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Hematology

Descriptive statistics of changes from baseline are based on local lab data without normalization to correct for the different methodologies and normal ranges. Therefore, the magnitude of the changes is not meaningful, but the direction of the changes from baseline may give an indication of overall trends.

There were no clinically relevant differences between the two groups for changes from baseline of any hematology parameter (absolute and % of basophils, eosinophils, lymphocytes, monocytes, and neutrophils; hematocrit; hemoglobin; platelet count; prothrombin time; RBC; and total WBC).

7.1.7.3.2 Biochemistry

As for hematology, no normalization was performed to correct for the different methodologies and normal ranges. Thus, the magnitude of the changes is not meaningful, but the direction of the changes from baseline may give an indication of overall trends in each group.

For most of the biochemistry parameters, descriptive statistics did not show any clinically relevant differences between the two treatment groups. However, there was a trend toward the following:

- mean increases in AST, ALT and vitamin B12 in the SAS-LAR group,
- mean increases in leptin in the saline control group
- mean decreases in C-peptide in the SAS-LAR group
- mean glycosylated hemoglobin (HbA1c) increased slightly at the 3 and 6 month timepoint with SAS-LAR but decreased in the saline control group
- mean TSH decreased slightly in both groups at the 3 and 6 month timepoint
- Insulin levels showed a shift from high values at baseline to normal values post-baseline in the SAS-LAR group (46% high at baseline, 23% high at month 6). However, in the control group, fewer patients shifted from high to normal and more patients shifted from

normal to high so that overall there was little change in the proportion of patients with high levels (42% high at baseline, 46% high at month 6).

Hypo/Hyperglycemia:
In Study 2403, there were no episodes of hypoglycemia. There were 3 subjects (10%) in the SAS-LAR group and 2 subjects (6.7%) in the saline-control group who experienced impaired glucose tolerance. There was one subject (3.3%) in the SAS-LAR group and no subject in the saline-control group who experienced diabetes mellitus.

In clinical trials for the original Sandostatin NDA, in acromegaly patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR® Depot.

Hypo/Hyperthyroidism:
In Study 2403, the mean change in thyroid stimulating hormone (TSH) from baseline to Month 6 was -0.1 ± 1.61 mU/mL in the SAS-LAR group and -0.3 ± 0.75 mU/mL in the saline control group. The mean change in free thyrxoine (fT4) levels from baseline to Month 6 was 0.32 ± 4.27 pmol/L in the SAS-LAR group and 2.05 ± 8.20 pmol/L in the saline control group. One subject in the SAS-LAR group experienced a decrease in TSH and one subject experienced a decrease in fT4, also in the SAS-LAR group. There were no thyroid related events in the saline-control group.

In clinical trials for the original Sandostatin NDA, in acromegalics treated with Sandostatin LAR® Depot, hypothyroidism was reported as an adverse event in 2% and goiter in 2%.

Vitamin B12:
There was no evidence of decrease vitamin B12 levels with SAS-LAR therapy. In Study 2403 the mean change from baseline in vitamin B12 levels was +39.5 ± 154.50 in the SAS-LAR group and -13.5 ± 92.5 in the saline control group at Month 6. In addition, methylmalonic acid levels were not increased with SAS-LAR therapy. At Month 6, the mean change from baseline in methylmalonic acid levels was -0.004 ± 0.0884 in the SAS-LAR group and 0.064 ± 0.1919 in the saline control group at Month 6.

Table 7.1.7.3.2 shows the patients with clinically notable biochemistry abnormalities.

Table 7.1.7.3.2 Number (%) of patients with clinically notable biochemistry abnormalities newly occurring, post- baseline (Safety population)*

Parameter	Notable Criteria	SAS-LAR N=30 N (%)	Saline control N=30 N (%)
Alkaline phosphatase	>2.5 x ULN	0	0
Bilirubin	>1.5 x ULN	0	1 (3.3)
AST (SGOT)	>3 x ULN	1 (3.3)	1 (3.3)
ALT (SGPT)	>3 x ULN	2 (6.7)	1 (3.3)
HbA_{1c}	>2 x ULN	0	0
Free thyroxine	>2 x ULN	1 (3.3)	0
TSH	>2 x ULN	0	0

*derived from sponsor's Table 10-6

7.1.7.3.3 Urinalysis

Newly occurring, post-baseline glucosuria was not detected in any patient. New or worsening, post-baseline proteinuria (trace or 1+ by dipstick test) was found in 6 (20%) patients in the SAS-LAR group and 2 (7%) in the saline control group. Hematuria was reported as an AE in one patient (RUS/0701/00006) in the SAS-LAR group.

7.1.7.4 Additional analyses and explorations

None

7.1.7.5 Special assessments

None

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs included sitting pulse, sitting systolic and diastolic blood pressures, respiratory rate, height, weight, and hip and waist circumference and were done at screening, baseline, and Months 1, 2, 3,4,5,6 or end of study visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The primary study selected for analysis of laboratory data is Study SMS995B 2403.

Additional safety data were submitted from two previously conducted clinical studies using octreotide subcutaneous injectable formulation. These were provided in this submission as study reports for Studies SMS995B 2408 and SMS995B 2409 (see Sections 7.2.2 and 10.1).

7.1.8.3 Standard analyses and explorations of vital signs data

There were no significant differences between the two treatment groups in the frequency of vital signs abnormalities. Abnormal vital signs were based on below the 10th percentile and above the 90th percentile of the CDC-published NHANES pediatric data as defined by age and sex.

Hypertension was reported as an AE in one patient in the saline control group.

Table 7.1.8.3 Number (%) of patients with newly occurring or worsening vital signs abnormalities post-baseline (Safety Population)
(Sponsor's Table 10-8)

Parameter	Notable criteria †	SAS-LAR N=30 n (%)	Saline control N=30 n (%)
Sitting systolic BP	Low	3 (10.0)	4 (13.3)
	High	11 (36.7)	12 (40.0)
	Low and High	1 (3.3)	0
Sitting diastolic BP	Low	1 (3.3)	1 (3.3)
	High	10 (33.3)	11 (36.7)
	Low and High	2 (6.7)	0

† Criteria are defined as the 10th and 90th percentiles (low and high respectively) of CDC-published NHANES pediatric data

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were performed using a standard 12-lead calibrated machine using a paper speed of 50mm/s and sensitivity at 10mm/mV. The operator was to sign and date all tracings performed. The same reader was to evaluate, sign and date all ECGs on a given patient. Tracings (duplicate original or copy with all signatures and dates) were made available for collection by Novartis.

Any abnormalities were recorded on the ECG eCRF and a comparison to baseline was also to be recorded at month 6. ECGs were done at screening and at 6 months/end of study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The primary study selected for analysis of laboratory data is Study SMS995B 2403.

Additional safety data were submitted from two previously conducted clinical studies using octreotide subcutaneous injectable formulation. These were provided in this submission as study reports for Studies SMS995B 2408 and SMS995B 2409 (see Sections 7.2.2 and 10.1).

7.1.9.3 Standard analyses and explorations of ECG data

There were no clinically significant abnormal ECGs at baseline or at month 6 in either of the two treatment groups. In the SAS-LAR group, 22 patients had normal ECGs at 6 months; 7 had abnormal but clinically insignificant readings; none had abnormal, clinically significant readings; and one patient's ECG was unavailable. In the saline-control group, 19 patients had normal ECGs at 6 months; 7 had abnormal but clinically insignificant readings; none had abnormal, clinically significant readings; and four patients' ECGs were unavailable.

7.1.9.4 Additional analyses and explorations

7.1.9.4.1 Echocardiograms

Echocardiograms were conducted during the screening period to rule out any valvulopathy and to assure a normal systolic ejection fraction. Echocardiograms were also performed at Months 3 and 6 or end of study.

No patient had an abnormal echocardiogram at baseline and only one patient was found to have an abnormality post-baseline. Patient USA/0510/00001, a 15 year old, black girl in the SAS-LAR group, had small, localized pericardial effusion along the diaphragmatic surface classified as a new or worsened abnormality at Month 6 compared to baseline

7.1.9.4.2 Tanner Staging

Tanner staging was done to assess puberty at screening and end of study. Tanner stages of development included assessment of both genital stage and pubic hair stage.

The same changes from baseline in Tanner staging were observed in both treatment groups, i.e. 4 patients in each group had changed by 1-2 Tanner stages at Month 6 compared to baseline.

7.1.9.4.3 Gallbladder Ultrasound

Patients with a history of gallstones were excluded from the study. Ultrasound examination of the gallbladder and biliary tree were to be performed at screening and Month 6 or at the final visit. Information on the number and location of gallstones, and whether there was any gallbladder sludge or biliary dilatation, was recorded in the appropriate eCRF page. At Month 6, a comparison to baseline was to be made.

Eleven (37%) patients in the SAS-LAR group were found to have new or worsened abnormalities of the gallbladder at the end of the study. These abnormalities were reported as AEs, which are described in Section 7.1.2.

Table 7.1.9.4.3 Change from baseline in gallbladder ultrasound (Safety population)
(Sponsor's Table 10-9)

	SAS-LAR N=30 n (%)	Saline control N=30 n (%)
Gallbladder ultrasound compared to baseline:		
unchanged	18 (60.0)	28 (93.3)
new or worsened	2 (6.7)	0
new	5 (16.7)	0
worsened	4 (13.3)	0
not compared	0	1 (3.3)
missing	1 (3.3)	1 (3.3)

7.1.9.4.4 Spot Stool Fat Analysis

A spot stool fat to detect the presence (microscopic or macroscopic) or absence of fecal fat was done at Months 0, 3 and 6 or at the final visit.

There were no clinically relevant changes from baseline in the spot stool fat analysis or differences between SAS-LAR and saline control at Month 3 and Month 6.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not applicable.

7.1.12 Special Safety Studies

No pregnancies or overdoses of study drug occurred during the treatment period.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no indication that octreotide has potential for drug abuse or dependence. Octreotide levels in the central nervous system are negligible, even after doses up to 30,000 mcg. No abuse potential is known or expected with SAS-LAR, therefore no abuse studies have been performed in any indications. The drug has no effect on mental concentration and does not impair the ability to drive or operate heavy machinery.

Withdrawal of SAS-LAR may result in the return of symptoms of the disease being treated. In the case of hypothalamic obesity, no claim for this indication is being made, so no estimate of symptom return is necessary.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancy occurred during the clinical trial 2403.

7.1.15 Assessment of Effect on Growth

Tanner staging assessments were used to monitor for pubertal development in pre-pubertal patients. As described in Section 7.1.9.4.2, there was no difference in progression of Tanner stage between the two groups over the course of this six-month study. Additionally, there were similar mean and median increases in standing height in both groups.

7.1.16 Overdose Experience

As the study drug was administered under the care of a physician, no cases of overdose were reported in the 2403 study. Capacity for overdose is low, and not considered a hazard in normal clinical usage.

7.1.17 Postmarketing Experience

See Section 7.2.2.2.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety population consisted of all randomized patients who were administered at least one dose of study medication.

7.2.1.1 Study type and design/patient enumeration

Sixty-two (62) subjects were randomized in approximately equal numbers to Sandostatin LAR and saline. The study enrolled similar numbers of males and females:

Table 7.2.1.1. Patient Distribution

	Sandostatin LAR	Saline control	Total
# patients randomized	32 (100%)	30 (100%)	62 (100%)
ITT population	30 (94%)	30 (100%)	60 (97%)
# females/ITT	16/30 (53%)	17/30 (57%)	33/60 (55%)

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.

7.2.1.2 Demographics

See Section 6.1.4.4

The mean age in this study was 13.6 years with a range of 6 to 17 years, inclusive. Twenty-five percent were < 12 years and 75% were ≥ 12 years of age. Within the < 12 year group: 9 were on SAS-LAR and 6 were on saline-control. Within the ≥ 12-year group: 21 were on SAS LAR and 24 were on saline-control.

7.2.1.3 Extent of exposure (dose/duration)

The study dose was fixed at 40mg/month. Exposure to study medication was similar in the two treatment groups. The majority of patients (SAS-LAR 93%, in both groups) received study medication for at least 120 days (4 months) and all these patients also completed the full course of injections administered at Months 0, 1, 2, 3, 4 and 5 in the double-blind treatment period.

Overall, 43% of SAS-LAR-treated patients and 60% of control-treated patients received study medication for >150 days.

Table 7.2.1.3 Exposure (days) to study medication by treatment (Safety population)
(Sponsor's Table 8-2)

Duration of treatment ‡	SAS-LAR N=30	Saline control N=30
Exposure (days):		
Mean	146.3	147.8
SD	17.99	25.12
Median	149.5	152.0
Range	85 – 183	61 – 216
Exposure intervals † - n (%):		
≤ 60 days	0	0
61 – 90 days	1 (3.3)	2 (6.7)
91 – 120 days	1 (3.3)	0 (0.0)
121 – 150 days	15 (50.0)	10 (33.3)
151 – 180 days	12 (40.0)	16 (53.3)
≥ 181 days	1 (3.3)	2 (6.7)

‡ Duration of treatment calculated as: last treatment date – first treatment date
† Mutually exclusive exposure intervals

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Additional safety information from two previously conducted pediatric clinical studies using octreotide subcutaneous injections, namely SMS995B2408 and SMS995B2409 were provided as part of this submission. These studies were performed by Dr. Lustig under an investigator initiated IND and the results have been published in the literature.

7.2.2.1 Study SMS995B2408: A pilot study of the use of octreotide in reducing weight gain in hypothalamic obesity associated with brain tumors, cranial irradiation, or chemotherapy

This study was an open-label, non-randomized pilot study, in which all patients received study drug after a pre-study evaluation period. The objectives of this study were as follows:

1. to evaluate fasting and stimulated glucose and insulin levels in pediatric patients with obesity associated with brain tumors, cranial irradiation or chemotherapy
2. to evaluate the possible efficacy of octreotide in reducing basal and glucose-stimulated insulin secretion in these patients
3. to evaluate the possible efficacy of octreotide in reducing dietary intake and the rate of weight gain in these patients.

Subjects were male and female outpatients greater than 4 years of age diagnosed with either a brain tumor in any intracranial location or with acute lymphoblastic leukemia (ALL). The main criterion for inclusion into this study was an abnormal increase in the patient's body weight.

Patients who had an age-dependent increase in weight of greater than two standard deviations per year, based on a table adapted from the National Center of Health Statistics, for at least one year after brain tumor or ALL treatment were considered to have hypothalamic obesity. Patients had to have a normal weight-for-height ratio at the time of tumor diagnosis. At the time of recruitment, patients diagnosed with a brain tumor were to be in clinical remission or without evidence of disease progression for at least one year and off all therapy for two years. Patients received cranial surgery, 24-70 Gy cranial irradiation to the hypothalamic area or systemic or intrathecal chemotherapy as part of their overall tumor therapy.

Patients received a 3-month supply of octreotide 200 µg/ml for subcutaneous injection. Dosage was started at 5 µg/kg/d SQ divided every 8 hours. At the 3-month evaluation, patients received an additional 3 month supply of octreotide. If the pretreatment rate of weight gain continued after initiation of therapy, the dose of octreotide could be increased, up to a maximum of 15 µg/kg/d divided every 8 hours.

The primary efficacy parameter was the attenuation of the rate of weight gain.

Patients were monitored for adverse events throughout the study. Physical examinations, thyroid evaluations and fasting glucose determinations were performed monthly. Hematologic and biochemistry evaluations and gallbladder ultrasounds were also preformed.

Nine patients were studied at Month 0 but data from the first 8 patients was used for statistical analyses. Patient 9 developed severe peripheral edema and a 6.2 kg weight gain within the first month of therapy. Octreotide therapy was discontinued and the edema resolved. Patient 7 admitted noncompliance with the injection regimen. Patient 6 withdrew after 5 months of therapy because of lack of weight loss. Seven patients experienced abdominal discomfort, flatulence, and loose stools within the first month. Six patients required small increases in their levothyroxine dosage to maintain their pre-study free thyroxine levels of 1.0 ng/mL[2]. There were no patient deaths. Four patients (50%) had gallbladder gravel or gallstones as determined by the Month 6 ultrasound. All four patients had a gallbladder ultrasound that was negative or within normal limits at baseline. Liver function test results remained unaffected and cholelithiasis resolved, as determined by ultrasonography, six months after cessation of octreotide therapy in all four patients.

Octreotide treatment in pediatric patients with hypothalamic obesity at a dose of 5 µg/kg/day to 15 µg/kg/day showed a safety profile similar to that shown in adult patients. Gallstone formation occurred in half the patients treated with octreotide, but resolved after termination of therapy.

7.2.2.2 Study SMS995B2409: Analysis of vagal dysfunction and the effects of insulin normalization in patients with hypothalamic obesity after cranial insult[11]

This was a double-blinded, placebo-controlled study in pediatric patients with clinically documented hypothalamic obesity. Twenty patients were randomized to received octreotide or placebo for 6 months and were stratified by tumor category. The primary objective was to assess

the efficacy of octreotide in inducing weight loss, versus a placebo-control group over a 6-month period. Secondary objectives were (1) to assess the correlation between the suppression of insulin secretion by octreotide and the degree of weight loss; (2) to assess alterations in insulin dynamics in patients with hypothalamic obesity; (3) to assess the magnitude of such weight loss over one year of treatment; (4) to assess changes in the resting and stimulated vagal tone in patients with hypothalamic obesity; and (5) to assess the effects of octreotide and/or weight loss on quality of life in patients with hypothalamic obesity.

Patients were male or female, 8 to 21 years of age and experienced cranial insult related to a tumor or its surgery, radiation or chemotherapy. Patients had normal weight for their height at the time of tumor diagnosis, but at study entry were greater than 150% of their ideal body weight for height. Patients were at least one year past all tumor therapy and gained weight faster than two standard deviations above the mean for their age for at least one year after tumor therapy. Patients also showed some other form of endocrinopathy, to insure the diagnosis of hypothalamic dysfunction.

Patients randomized to octreotide were on an escalating dosage schedule starting with an injection volume to deliver 5 µg/kg/day (divided into 3 daily doses) with bimonthly increments of 5 µg/kg/day to a maximum dosage of 15 µg/kg/day (divided into 3 daily doses) by the beginning of Month 5. At Month 6, the treatment code was broken after all evaluations were performed so the proper dose of octreotide could be administered during Month 6 -12 to patients who had received placebo during the first 6 months. After the 12 month treatment period, all patients were followed and evaluated for an additional 12 months.

The primary efficacy variable was weight gain or loss with octreotide versus placebo.

Patients were monitored for adverse events during the 12-month treatment period and during the 12-month follow-up period. Hematologic and biochemistry laboratory evaluations were performed at baseline and at 2 month intervals during the treatment period. Gallbladder ultrasounds were performed at baseline, Month 6, Month 12 and at Months 18 and 24 if necessary.

There were no patient deaths during the study. One patient randomized to octreotide, developed a slipped femoral epiphysis and was discontinued from the study at Month 8. One patient randomized to placebo developed diabetic hyperosmolar coma after 4 months on study. All nine subjects receiving octreotide noted abdominal discomfort and diarrhea, which resolved by the second month of therapy. Three placebo-treated subjects also complained of diarrhea.[9] Stool fat measurements at Month 6 showed no positive results of fat malabsorption due to octreotide therapy. Two subjects on octreotide developed mild glucose intolerance at Month 6. Four subjects on octreotide required an increase in their L-thyroxine dosage to maintain their free T_4 at its pretreatment level. Of the nine subjects who received octreotide during the double blind phase, four had gallstone or sludge formation at the time of the Month 6 ultrasound. Three of these patients had a gallbladder ultrasound that was within normal limits at baseline; data for the fourth patient at baseline was not available.

Octreotide treatment in pediatric patients with hypothalamic obesity at a dose of 5 µg/kg/day to 15 µg/kg/day showed a safety profile similar to that shown in adult patients. Gallstone or sludge formation occurred in four out of nine patients treated with octreotide. Adverse events were consistent with the safety profile of octreotide seen in other indications.

7.2.2.3 Postmarketing experience

Post-marketing experience is available from other labeled indications, but not for the indication of hypothalamic obesity in children. The sponsor submitted pharmacovigilence reports for patients under the age of 18 who had received SAS-LAR and experienced a safety event.

There were 197 events described in the 73 reported cases. Primary System Organ Class categories where adverse events were reported 20 or more times include general disorders and administration site disorders (29), nervous system disorders (25) and skin and subcutaneous tissue disorders (21). Under general administration site disorders, disease progression, fatigue and injection site pain were the most frequent. Headache was most common in the nervous system disorders category, and alopecia, erythema and rash were most frequent in the skin and subcutaneous disorders category.

There were seven deaths reported for the pediatric population in association with injectable sandostatin use. Most cases involved patients whose fatalities were related to their underlying disease states. None of the post-marketing safety information appear to change the known safety profile of SAS-LAR.

7.2.2.4 Literature

A review of the scientific literature by the sponsor and this reviewer for publications reporting experience with injectable sandostatin in pediatric patients revealed no new safety information in this population.

7.2.3 Adequacy of Overall Clinical Experience

In this study, duration of exposure and drug dosage was limited, but adequate, to assess most safety issues.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal or *in vitro* data was submitted with this sNDA.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing is described in Section 6.1.3 and was adequate for this trial.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information in this area was submitted for this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This efficacy supplement did not involve a new drug.

7.2.8 Assessment of Quality and Completeness of Data

The majority of patients (93% in both groups) received study medication for at least 121 days (4 months). Overall, 43% of SAS-LAR-treated patients and 60% of control-treated patients received study medication for >150 days in Study 2403.

An adequate number of subjects with pertinent risk factors were exposed to the drug. The duration of exposure was adequate to assess safety for the intended use. Study drug dose was limited to one dose (40 mg/month) of Sandostatin LAR® Depot. There were limited demographic subsets as 93% of subjects were White.

7.2.9 Additional Submissions, Including Safety Update

120-Day Safety Update for study SMS995B 2403 (see Section 10.1 for in-depth review)

Study Title: A 6 month open-label extension to study CSMS995B2403: A randomized, multicenter, double-blind trial of Sandostatin LAR® Depot (40mg) versus saline control in the treatment of pediatric hypothalamic obesity

The study was terminated early after review of the data by the Data Safety Monitoring Board for lack of efficacy in a letter dated 14 September 2005.

This extension study failed to meet the primary efficacy outcome and most of the secondary efficacy objectives.

There were mean and median increases in weight at Month 13 for patients treated with SAS-LAR during the core and extension phase.

There was limited long-term drug exposure in these studies. Only 3 patients received 12 months of treatment. Only six patients out of 19 (32%) in the SAS-LAR OLE cohort received study drug for 6 months.

There were serious adverse events reported for nine patients during this extension study (9/32, 28%); 3 patients (23.1%) in the SAS-LAR C+E group and 6 patients (31.6%) in the SAS-LAR OLE group. Four of the nine (44.4%) SAEs were related to cholelithiasis, three (33.3%) were for biliary tract abnormalities, and two (22.2%) were for gastrointestinal disorders. Eleven patients (34%) were found to have new or worsened abnormalities of the gallbladder by the end of the extension study.

Thus, the incidence of new cholelithiasis and new or worsened abnormalities of the gallbladder in this pediatric population in the extension study was comparable to the rates seen in Study 2403 but higher than that seen in other adult indications such as acromegaly or malignant carcinoid syndrome.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety profile for pediatric patients treated with 40mg SAS-LAR administered monthly was consistent with the known safety profile of Sandostatin seen in adult patients in other indications. However, the incidence of new cholelithiasis in this pediatric population was higher than that seen in adults for other indications. In study 2403, the most frequent AEs reported in patients treated with SAS-LAR were diarrhea, cholelithiasis, nasopharyngitis and abdominal pain. The incidence of nasopharyngitis was similar to that seen with saline-control. Nine cases of cholelithiasis in the SAS-LAR group were reported when the gallbladder ultrasound results were obtained at the end of the study. One patient reported “biliary sludge” at the end of study, and subsequently developed gallstones one month later. The tenth patient developed gallstone pancreatitis 3 months after the last dose of study medication.

A few more patients in the SAS-LAR group versus saline control shifted from normal transaminase values at baseline to high values post-baseline. No adverse events were reported that were related to hematological parameters. There were no relevant differences between the two treatments in vital signs abnormalities based on notable criteria defined by age and sex. Thus, the safety profile of SMS-LAR in pediatric patients was consistent with the known safety profile of sandostatin as seen in adults in other indications with the caveat that gallbladder abnormalities occurred more frequently in the pediatric population. The incidence of diarrhea in clinical trials of adult patients with acromegaly is 36%, which is similar to the incidence of 37% seen in this trial. The incidence of abdominal pain or discomfort in clinical trials of adult patients with acromegaly is 29%, which is higher than the incidence of 17% for abdominal pain and upper abdominal pain seen in this trial. However, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%).

In the two supportive studies, 2408 and 2409, the safety profile was similar to that observed in 2403. The more frequent events were associated with gastrointestinal disturbance, abdominal discomfort, and gallbladder disorders.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The data was not pooled as Study 2403 used Sandostatin LAR® Depot and Study 2408 and 2409 used the subcutaneous formulation of Sandostatin.

7.4.1.1 Pooled data vs. individual study data

Not applicable

7.4.1.2 Combining data

Not applicable

7.4.2 Explorations for Predictive Factors

No new information was revealed regarding factors that could be predictive of risk for adverse events related to Sandostatin LAR® Depot administration.

7.4.3 Causality Determination

Causality related to the administration of Sandostatin LAR® Depot is likely for the ten cases of cholelithiasis. Nine patients in the SAS-LAR group developed cholelithiasis reported as SAEs, suspected to be related to study drug and detected by ultrasound scan of the gallbladder performed at the end of the study. Two of the cases of gallstones were graded as severe or life threatening and the others were mild or moderate in severity. A tenth SAS-LAR patient had a non-serious AE at the end of the study reported as gallbladder "sludge" but gallstones developed after the study and were reported as an SAE.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Doses were fixed at 40 mg/month of Sandostatin LAR® Depot given IM.

8.2 Drug-Drug Interactions

No new drug-drug interactions were submitted with this efficacy supplement.

8.3 Special Populations

This study was performed in a pediatric population with hypothalamic obesity between the ages of 6 and 17, inclusive. Given the limited sample size of study 2403, any formal study of efficacy sub-groups within this population was not possible.

8.4 Pediatrics

The mean age in this study was 13.6 years with a range of 6 to 17 years, inclusive. Twenty-five percent were < 12 years and 75% were ≥ 12 years of age. Within the < 12 year group: 9 were on SAS-LAR and 6 were on saline-control. Within the ≥ 12-year group: 21 were on SAS-LAR and 24 were on saline-control.

8.5 Advisory Committee Meeting

No Advisory Committee meeting occurred for this efficacy supplement.

8.6 Literature Review

Relevant portions of the literature review conducted for this application appear in appropriate sections of the review.

8.7 Postmarketing Risk Management Plan

None

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Study 2403 did not meet the primary or most of the secondary efficacy objectives with the exception of a slight improvement in physical activity for children treated with SAS-LAR.

The study SMS995B2403 failed to provide evidence for the efficacy of SAS-LAR in pediatric patients with hypothalamic obesity after 6 months of treatment. Therefore the data do not support the use of SAS-LAR in patients aged 6 to <18 years with hypothalamic obesity.

The safety profile for pediatric patients treated with 40mg SAS-LAR administered monthly was consistent with the known safety profile of Sandostatin seen in adult patients in other indications. However, the incidence of new cholelithiasis in this pediatric population was higher than that seen in adults for other indications.

9.2 Recommendation on Regulatory Action

The sponsor has fairly responded to the terms of the Written Request. Therefore, Pediatric Exclusivity should be granted for this submission.

9.3 Recommendation on Postmarketing Actions

None

9.4 Labeling Review

The sponsor's proposed changes and the Medical Officer's suggested revisions are organized by the sections of the label in which proposed changes appear. The medical officer's revisions are in red, deletions marked by strike-out, and comments are in *italics*. A telephone conference was held with Novartis to negotiate the final label. At the time of finalization of this review, labeling negotiations were essentially complete; however, minor changes may occur, and one should refer to the final label attached to the approval letter.

A. Changes to CLINICAL PHARMACOLOGY Section:
Current Sandostatin Label:

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot administered by IM injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 mg and 30 mg and after three injections of 10 mg.
Sandostatin LAR® Depot has not been studied in patients with renal impairment.
Sandostatin LAR® Depot has not been studied in patients with hepatic impairment.

Proposed Sandostatin Label:

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot administered by IM injection every four weeks

were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 mg and 30 mg and after three injections of 10 mg.

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR® Depot administered by IM injection every four weeks was approximately 3.0 ng/mL. Steady-state concentration was achieved after 3 injections of 40 mg dose.

Sandostatin LAR® Depot has not been studied in patients with renal impairment.

Sandostatin LAR® Depot has not been studied in patients with hepatic impairment.

~~Sandostatin LAR® Depot has been studied in pediatric patients with hypothalamic obesity. See **Pediatric Use** under **PRECAUTIONS.**~~

Medical Officer comment: The sponsor proposed inserting PK data in the Precautions section. We have placed it in the Pharmacokinetic section.

B. Changes to the PRECAUTIONS Section:
Pediatric Use Subsection

Current Sandostatin Label:

Pediatric Use

Sandostatin LAR® Depot has not been studied in pediatric patients.
Experience with Sandostatin® Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal- steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

Proposed Sandostatin Label:

1.1 Pediatric Use

~~The effectiveness of Sandostatin LAR® Depot pediatric patients with hypothalamic obesity has not been established. Results from a randomized, parallel arm, double-blind, placebo controlled clinical trial in patients 6-17 years of age with hypothalamic obesity resulting from cranial insult were evaluated. Sixty patients were treated in this study in which 30 received 40 mg of Sandostatin LAR Depot and 30 received placebo administered once a month for up to 6 months. The adverse event profile was comparable to that observed in adults. Diarrhea was observed in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. The incidence of biliary tract abnormalities was 33%; 9 of 30 (30%) had asymptomatic gallstones and 1 of 30 (3%) developed acute symptoms requiring cholecystectomy.~~

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo-controlled six-month study in 60 pediatric patients aged 6 – 17 years with hypothalamic obesity resulting from cranial insult. Mean BMI increased 0.1 kg/m^2 in Sandostatin LAR Depot–treated subjects compared to 0.0 kg/m^2 in saline control-treated subjects. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot dosing is 10 to 30 mg once a month. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot.

~~In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR® Depot administered by IM injection every four weeks was approximately 3.0 ng/mL. Steady-state concentration was achieved after 3 injections of 40 mg dose.~~

~~Two studies have been performed using Sandostatin Injection in patients with hypothalamic obesity. Twenty patients were treated for 12 months in a double-blind, placebo-controlled study, where patients on placebo were crossed over to octreotide after six months. Eight patients were treated in an open-label single arm study. Gallstones developed in 3/20 (15%) and 4/8 (50%) of patients in these studies respectively.~~

~~In addition, Sandostatin LAR® Depot has been used in patients with congenital hyperinsulinism (also called nesidioblastosis).~~ Experience with Sandostatin® Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis).The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal- steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

Medical Officer Comment:

Recommend removal of the entire paragraph regarding the pilot sandostatin sc pilot study. The safety data is limited, no efficacy data was submitted for our review, no indication was achieved, and it provides no new information on side effects of this drug in children.

The original Sandostatin injection paragraph regarding nesidioblastosis should remain unchanged. Sponsor insertion implies that Sandostatin LAR was used for these studies.

C. Changes to the PRECAUTIONS Section:

Current Sandostatin Label:
No Geriatric Use section in current label

Proposed Sandostatin Label:

Geriatric Use Subsection

1.3 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Medical Officer Comment:
Approve, pending approval of supplement 019

9.5 Comments to Applicant

No additional comments.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study No: SMS995B 2408

Study Title: A pilot study of the use of octreotide in reducing weight gain in hypothalamic obesity associated with brain tumors, cranial irradiation, or chemotherapy

Investigators: Robert H. Lustig, M.D.

Study center(s): Department of Pediatrics, University of Tennessee, Memphis and St Jude Children's Hospital, Memphis, Tennessee

Publication(s): Lustig RH, Rose SR, Burghen GA, et al (1999) Hypothalamic obesity caused by cranial insult in children: Altered glucose and insulin dynamics and reversal by a somatostatin agonist. J Pediatr; 135(2) (Pt 1): 162—8

Objectives:
1. To evaluate fasting and stimulated glucose and insulin levels in patients with obesity associated with brain tumors, cranial irradiation, or chemotherapy.
2. To evaluate the possible efficacy of the drug octreotide in reducing basal and glucose-stimulated insulin secretion in these patients.
3. To evaluate the possible efficacy of octreotide in reducing dietary intake and the rate of weight gain in these patients.

The study was an exploratory, pilot study and was intended to provide data to plan for a larger, randomized study.

Design: This study was an open-label, non-randomized pilot study, in which all patients received study drug after a pre-study evaluation period. Patients served as their own control.

Patient Population: The subject population was derived from both the male and female outpatient populations of LeBonheur Children's Medical Center or St. Jude Children's Research Hospital. Subjects were greater than 4 years of age diagnosed with either a brain tumor in any intracranial location or with acute lymphoblastic leukemia (ALL). Nine patients were recruited and participated in this study.

The main criterion for inclusion into this study was an abnormal increase in the patient's body weight. Patients who had an age-dependent increase in weight of greater than 2 standard deviations per year, based on a table adapted from the National Center of Health Statistics for at least one year after brain tumor or ALL treatment were considered to have hypothalamic obesity. Patients had to have a normal weight-for-height ratio at the time of tumor diagnosis. At the time

of recruitment, patients diagnosed with a brain tumor were to be in clinical remission or without evidence of disease progression for at least one year and off all therapy for two years. Patients received cranial surgery, 24-70 Gy cranial irradiation to the hypothalamic area or systemic or intrathecal chemotherapy as part of their overall tumor therapy.

Treatment Groups: All patients received a 3 month supply of octreotide 200 μg/ml (in 5 mL multidose vials) for subcutaneous injection. Dosage was started at 5 μg/kg/d SQ divided every 8 hours. At the 3 month evaluation patients received an additional 3 month supply of octreotide. If the pretreatment rate of weight gain continued after initiation of therapy, the dose of octreotide could be increased, up to a maximum of 15 μg/kg/d divided every 8 hours.

Duration of Treatment: Patients were to receive study drug daily for a minimum of 6 months unless side effects became unmanageable or the patient discontinued participation in the study. Patients who had a clinical response to study drug would be offered an additional 6 months of study drug treatment. All patients were followed and evaluated for 6 months after the last dose of study drug was administered.

Endpoints:
Efficacy: The primary efficacy parameter was the attenuation of the rate of weight gain.
Safety: Patients were monitored for adverse events throughout the study. Physical examinations, thyroid evaluations and fasting glucose determinations were performed monthly. Hematologic and biochemistry evaluations and gallbladder ultrasounds were also preformed.
Pharmacology: Study drug blood levels were not measured in this study.

Statistical Analyses: This study was a pilot investigation. Patient data was summarized for safety and efficacy endpoints using a single analysis population (all patients). Only summary assessments were performed. Summary statistics include n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables. Changes from baseline results are also presented.

Protocol Amendments: None reported

Results:
Patient Demographics: Nine patients (four boys and five girls; seven White and two African-American; ages 10 to 18 years). Seven were survivors of brain tumors of the posterior fossa; four underwent resection, two received chemotherapy, and six received cranial irradiation. Two patients had acute lymphocytic leukemia and received chemotherapy and cranial irradiation.

Patient Disposition:

- Patient 9 developed severe peripheral edema and a 6.2-kg weight gain within the first month of therapy. Octreotide therapy was discontinued and the edema resolved. Patient 9 is not included in the statistical analyses.
- Patient 7 admitted to noncompliance with the injection regimen
- Patient 6 withdrew after 5 months of therapy because of lack of weight loss

- Patient 5 continued octreotide therapy for 1 full year and lost 16.2 kg (9.8% of initial body weight)
- Patient 1 continued octreotide therapy for 1 full year and lost 21.7 kg (21.7% of initial body weight)

Concomitant Medication Use: According to the published protocol, patients may not be receiving any antineoplastic agents. Patients on other medications, such as anticonvulsants, H2-blockers, or vitamin or mineral supplementation, would be maintained on their current therapies. Patients on other endocrine medications (except for growth hormone) would be maintained on their therapies throughout the study. Every attempt would be made to keep patients receiving hydrocortisone replacement (< 15 mg/m2/d) on the same dose throughout the study, to minimize the possibility that glucocorticoid dose would play a role in the patient's weight gain or loss. However, in the sponsor's submitted report, no concomitant medications were identified for this study.

Efficacy:
According to the published article, octreotide promoted weight loss in five of eight patients and weight stabilization in three. The pattern was notable for the lack of effect during the first two months, but with weight loss occurring between months 2 and 6 of therapy. In comparison with a 6-month pre-study observation period, patients exhibited weight loss (+6.0±0.7 kg vs. -4.8±1.8 kg; P=0.04) and decrease in body mass index (+2.1±0.3 kg/m^2 vs. -2.0±0.7 kg/m^2; P=0.0001). Recall calorie count decreased during the 6 months of treatment (P=0.015). OGTT demonstrated biochemical glucose intolerance in six of eight patients initially and in two of seven at study end, whereas insulin response was decreased (281±47 μU/mL vs. 114±35 μU/mL; P=0.04). Percent weight change correlated with changes in insulin response (P=0.012) and changes in plasma leptin (P=0.0004).

Safety:
Deaths: There were no patient deaths.

Adverse Events that Led to study Withdrawal:
Patient 9 developed severe peripheral edema and a 6.2-kg weight gain within the first month of therapy. Octreotide therapy was discontinued and the edema resolved.

Adverse Events: Adverse events were reported in the sponsor's report for one patient (12.5%) who reported nausea at the Month 1 study visit and moderate flatulence at the Month 2 study visit according to the sponsor's report.

The investigator's published report states there were seven patients who experienced abdominal discomfort, flatulence, and loose stools within the first month, which resolved spontaneously.

Laboratory Parameters:
Six patients required small increases in their levothyroxine dosage to maintain their pre-study free thyroxine of 1.0 ng/mL.

HbA_{1c} levels remained constant (5.6%±0.1% at 0 months vs. 5.3%±0.1% at 6 months; p=ns).

Special Safety Studies:

- Gallbladder Evaluations: Four patients (50%) had asymptomatic gallbladder sludging/gravel or gallstones as determined by the Month 6 ultrasound. All four patients had a gallbladder ultrasound that was negative or within normal limits at baseline. According to the published report, liver function tests remained unaffected, and all four patients' gallbladder abnormalities resolved, as determined by ultrasonography, six months after cessation of octreotide therapy in all four patients.

Investigator's Conclusion: Patients with hypothalamic obesity demonstrate excessive insulin secretion. Octreotide administration promoted weight loss, which correlated with reduction in insulin secretion on OGTT and with reduction in leptin levels. Pre-study biochemical glucose tolerance improved in several patients while they were receiving octreotide. These results suggest that normalization of insulin secretion may be an effective therapeutic strategy in this syndrome.

Company's Conclusions: Octreotide treatment in pediatric patients with hypothalamic obesity at a dose of 5 µg/kg/day to 15 µg/kg/day showed a safety profile similar to that shown in adult patients. Gallstone formation occurred in half the patients treated with octreotide, but resolved after termination of therapy. Additional adverse events were few. Nausea and flatulence, reported for one patient, are not unexpected.

Medical Officer's Conclusions: Octreotide treatment in pediatric patients with hypothalamic obesity at a SQ dose of 5 µg/kg/day to 15 µg/kg/day appeared to promote weight loss. The significant reduction in body weight and body mass index was more notable at the maximum dose investigated, 15µg/kg/day sc octreotide, compared to the starting dose of 5µg/kg/day. Gallstone formation occurred in 50% of the patients treated with octreotide, but resolved after termination of therapy.

10.1.2 Study No: SMS995B 2409

Study Title: Analysis of vagal dysfunction and the effects of insulin normalization in patients with hypothalamic obesity after cranial insult

Investigators: Robert H. Lustig, M.D.

Study center(s): University of Tennessee Pediatric Clinical Research Center at LeBonheur Children's Medical Center, Memphis, Tennessee

Publication(s): Lustig RH, Hinds PS, Ringwald-Smith K, et al (2003) Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab, 88(6):2586-92

Objectives:
The primary objective was to assess the efficacy of octreotide in inducing weight loss, versus a placebo-control group over a 6-month period.

Secondary objectives were (1) to assess the correlation between the suppression of insulin secretion by octreotide and the degree of weight loss;
(2) to assess alterations in insulin dynamics in patients with hypothalamic obesity;
(3) to assess the magnitude of such weight loss over one year of treatment;
(4) to assess changes in the resting and stimulated vagal tone in patients with hypothalamic obesity;
(5) to assess the effects of octreotide and/or weight loss on quality of life in patients with hypothalamic obesity.

Design: This was a double-blinded, placebo-controlled study in pediatric patients with clinically documented hypothalamic obesity. Patients were randomized to received octreotide or placebo for 6 months and were stratified by tumor category.

Patient Population: Twenty patients were recruited; 10 were randomized to receive octreotide and 10 to receive placebo during the 6 month double-blind phase of the study.

Patients included were male or female, 8 to 21 years of age and experienced cranial insult related to a tumor or its surgery, radiation or chemotherapy. Patients had normal weight for their height at the time of tumor diagnosis, but at study entry were greater than 150% of their ideal body weight for height. Patients were at least one year past all tumor therapy and gained weight faster than 2 standard deviations above the mean for their age for at least one year after tumor therapy. Patients also showed some other form of endocrinopathy, to insure the diagnosis of hypothalamic dysfunction.

Treatment Groups:
Active therapy: Sandostatin® Injection (octreotide acetate) was provided for subcutaneous injection. Patients randomized to octreotide were on an escalating dosage schedule starting with an injection volume to deliver 5 μg/kg/day (divided into 3 daily doses) with bimonthly increments of 5 μg/kg/day to a maximum dosage of 15 μg/kg/day (divided into 3 daily doses) by the beginning of Month 5.

Reference therapy: Placebo was saline only, and was given by subcutaneous injection 3 times daily, with a monthly increment of volume to match the volume of study drug.

At Month 6, the treatment code was broken after all evaluations were performed so the proper dose of octreotide could be administered during Month 6 -12 to patients who had received placebo during the first 6 months.

Duration of Treatment: Patients received treatment for 12 months; 6 months of double-blind octreotide or placebo (saline) followed by 6 months of octreotide for all patients. After the 12 month treatment period, all patients were followed and evaluated for an additional 12 months.

Endpoints:
Efficacy: The primary efficacy variable was weight gain or loss with octreotide versus placebo.
Safety: Patients were monitored for adverse events during the 12 month treatment period and during the 12 month follow-up period. Patients were seen by their pediatric endocrinologist bimonthly during the treatment period and for the first six months of the follow-up period, and finally at 24 months after study initiation. Hematologic and biochemistry laboratory evaluations were performed at baseline and at 2 month intervals during the treatment period. Gallbladder ultrasounds were performed at baseline, month 6, month 12 and at months 18 and 24 if necessary.
Pharmacology: Pharmacokinetic evaluations were not performed in this study.

Statistical Analyses: This study was a preliminary comparative investigation. Patient data was summarized for safety and efficacy endpoints using a single analysis population (all patients). Only summary assessments were performed. Data for the 12 month treatment period were received and summarized. Summary statistics include n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables. Changes from baseline results are also presented. Patient-specific listings support all summarized results.

Protocol Amendments:
None noted.

Results:
Patient Demographics:
Twenty patients (11 male, 9 female), age 14.2±0.7 years, were recruited. Thirteen subjects had craniopharyngioma, 4 subjects had hypothalamic astrocytoma, 1 had pineal germinoma, and 2 subjects had ALL and received 24 Gy of cranial irradiation at diagnosis.

Table 10.1.2.1 Demographics of the hypothalamic obesity cohort, stratified by treatment group

	Octreotide (n = 10)	Placebo (n = 10)
Age (yr)	13.8 ± 1.2	14.2 ± 0.9
Sex	6 M, 4 F	5 M, 5 F
Diagnoses	Craniopharyngioma, 6 Hypothalamic astrocytoma, 2 ALL, 2	Craniopharyngioma, 7 Hypothalamic astrocytoma, 1 Germinoma, 1 Optic pathway glioma, 1
Race	10 Caucasians	7 Caucasians 2 African-Americans 1 Cuban-American
Initial height (cm)	160.7 ± 3.9	163.2 ± 5.1
Initial weight (kg)	95.4 ± 8.8	98.1 ± 7.7
Initial BMI (kg/m^2)	36.4 ± 2.4	36.2 ± 1.3
Annualized weight gain (kg/yr)	15.0 ± 3.9	20.3 ± 4.5
History of surgery	8	8
History of cranial irradiation	10	10
History of chemotherapy	2	2
Receiving GH therapy	2	5

Patient Disposition:
Two subjects were discontinued from the study before the month 6 visit. One subject, randomized to octreotide, at month 2 exhibited a recurrence of her craniopharyngioma and another developed diabetic hyperosmolar nonketotic coma after 4 months of placebo treatment; their data are not included. Eighteen subjects completed the 6 months of study. However, only seven patients out of ten completed the full six months of octreotide therapy and only 8 out of 10 were studied for the efficacy and safety effects of octreotide therapy.

Protocol Violations:
Patient #7 admitted to non-compliance with the injection regimen, particularly in the last three months of the study.
Patient #6 withdrew after five months of therapy due to lack of weight loss.

Concomitant Medication Use: According to the published protocol, patients may not be receiving any antineoplastic agents. Patients on other medications, such as anticonvulsants, H2-blockers, or vitamin or mineral supplementation, would be maintained on their current therapies. Patients on other endocrine medications (including growth hormone) would be maintained on their therapies throughout the study. Every attempt would be made to keep patients receiving hydrocortisone replacement (< 15 $mg/m^2/d$) on the same dose throughout the study, to minimize the possibility that glucocorticoid dose would play a role in the patient's weight gain or loss.

Efficacy:
The nine subjects treated with octreotide exhibited Δ weight of +1.6±0.6 kg, and ΔBMI of -0.2±0.2 kg/m^2, whereas the nine subjects treated with placebo exhibited Δ weight of +9.2±1.7 kg, and ΔBMI of +2.2±0.5 kg/m^2, respectively. A more beneficial effect of octreotide was noted upon reaching the maximum dose of 15μg/kg•d. Change in caloric intake between Months 0 and 6 was -200±103 vs. +103±513 kcal/d (P=NS), and Δ leptin was -12.4±6.9 vs. -5.5±4.6 ng/ml (P=NS) on octreotide vs. placebo, respectively. OGTT documented Δ insulin response (peak-basal) of -417±304 pm after octreotide vs. +216±215 pm after placebo (P=0.034). Improvement in physical activity by parent report was noted with octreotide, but not placebo (P=0.03). For the octreotide group, changes in quality of life positively correlated with changes in insulin response (P=0.041). Table 10.1.2.2, below, summarizes the efficacy results.

Table 10.1.2.2 Initial, final, and changes in weight, BMI, and laboratory data in Study 2409

Parameter	Month 0		Month 6		Change		P
	Octreotide	Placebo	Octreotide	Placebo	Octreotide	Placebo	
Weight (kg)	98.5 ± 9.2	102.7 ± 6.8	100.0 ± 9.5	111.9 ± 7.5	+1.6 ± 0.6	+9.1 ± 1.7	<0.001 t test
BMI (kg/m^2)	37.4 ± 2.5	36.8 ± 1.2	37.2 ± 2.5	39.0 ± 1.4	−0.2 ± 0.2	+2.2 ± 0.5	<0.001 t test
Caloric intake (kcal/d)	1994 ± 226	2342 ± 959	1818 ± 277	2325 ± 451	−200 ± 103	+102 ± 513	NS
Leptin (ng/ml)	45.3 ± 8.2	34.7 ± 4.7	32.8 ± 5.1	29.1 ± 4.4	−12.4 ± 6.9	−5.5 ± 4.6	NS
Fasting glucose (mM)	4.37 ± 0.25	3.91 ± 0.43	5.22 ± 0.37	3.98 ± 0.23	+0.85 ± 0.29	+0.07 ± 0.28	0.076 t test 0.022 median test
Peak glucose (mM)	8.36 ± 0.61	6.87 ± 0.38	9.65 ± 1.06	6.99 ± 1.86	+1.29 ± 0.64	+0.12 ± 0.42	NS
Glucose response (mM)	3.98 ± 0.48	3.04 ± 0.44	4.43 ± 0.73	3.00 ± 0.44	+0.45 ± 0.55	−0.06 ± 0.21	NS
Fasting insulin (pM)	209.6 ± 35.4	264.6 ± 48.5	198.5 ± 84.8	200.1 ± 33.3	−11.2 ± 66.2	−64.6 ± 52.6	NS
Peak insulin (pM)	1472 ± 159	2215 ± 354	966 ± 277	2322 ± 468	−506 ± 369	+147 ± 238	NS
Insulin response (pM)	1181 ± 155	1905 ± 352	764 ± 250	2122 ± 451	−417 ± 304	+216 ± 215	0.110 t test 0.034 median test

P values are in reference to the change from months 0–6 between octreotide and placebo groups. To convert glucose concentrations from mM to mg/dl, multiply by 18; to convert insulin concentrations from pM to μU/ml, multiply by 0.1394.

Safety:
Deaths: There were no patient deaths.

Adverse Events:
According to the published report, all nine subjects receiving octreotide noted abdominal discomfort and diarrhea, which resolved by the second month of therapy. Three placebo-treated subjects also complained of diarrhea.

One patient randomized to octreotide, developed a slipped femoral epiphysis and was discontinued from the study at Month 8.

According to the sponsor, diarrhea was reported for 2 patients (20%) treated with octreotide and 1 patient (10%) on placebo treatment.

Laboratory Parameters:
Two subjects receiving octreotide developed mild glucose intolerance at Month 6; however, none of the nine subjects developed overt diabetes mellitus. One African-American subject with acanthosis nigricans, originally assigned to the placebo group, and who exhibited impaired glucose tolerance at both Month 0 and Month 6, developed diabetes (fasting glucose=386, HbA_{1c} =9.3%) during the open-label extension at Month 8, (2 months on octreotide), and octreotide was discontinued. Another subject developed diabetic hyperosmolar nonketotic coma after 4 months of placebo treatment. On average, HbA_{1c} levels increased from 5.4±0.1% to 5.8±0.1% with octreotide treatment, and from 5.6± 0.1% to 5.7±0.1% with placebo. All others with normal glucose tolerance at baseline maintained normal glucose tolerance.

Four subjects required an increase in their L-thyroxine dosage to maintain their free T_4 at its pretreatment level.

Special Safety Studies:
Gallbladder Assessment: Of the nine subjects who received octreotide, four exhibited gallstone or sludge formation at the time of the Month 6 ultrasound. Three of these patients had a gallbladder ultrasound that was within normal limits at baseline; data for the fourth patient at

baseline was not available. These four subjects were treated during the 6-month open-label extension period with ursodiol 300 mg orally twice daily while remaining on octreotide therapy and their gallbladder anomalies resolved by the Month 12 ultrasound.

Stool Fat Assessment: Stool fat measurements at Month 6 showed no positive results due to octreotide therapy. All subjects had measurements of fecal fat performed at Month 0 and Month 6. In each instance, measurements were negative, arguing against the possibility of fat malabsorption due to octreotide therapy.

Investigator's Conclusion: Octreotide suppressed insulin, and stabilized weight and BMI. Improved quality of life correlated with the degree of insulin suppression. Octreotide was safe and well tolerated.

Company's Conclusions:
Octreotide treatment in pediatric patients with hypothalamic obesity at a dose of 5 µg/kg/day to 15 µg/kg/day showed a safety profile similar to that shown in adult patients. Gallstone formation occurred in four patients treated with octreotide. Additional adverse events were few and were consistent with the safety profile of octreotide seen in other indications.

Medical Officer's Conclusions:
Octreotide treatment in pediatric patients with hypothalamic obesity at a SQ dose of 5 µg/kg/day to 15 µg/kg/day appeared to promote weight loss. The significant reduction in body weight and body mass index was more notable at the maximum dose investigated, 15µg/kg/day sc octreotide, compared to the starting dose of 5µg/kg/day. Four patients, out of a total of nine, treated with octreotide during the double blind phase had gallstone or sludge formation at the time of the Month 6 ultrasound. Three of these patients had a gallbladder ultrasound that was within normal limits at baseline; data for the fourth patient at baseline was not available.

10.1.3 120-Day Safety Update for study SMS995B 2403

Study Title: A 6 month open-label extension to study CSMS995B2403: A randomized, multicenter, double-blind trial of Sandostatin LAR® Depot (40mg) versus saline control in the treatment of pediatric hypothalamic obesity

The study was terminated early after review of the data by the Data Safety Monitoring Board for lack of efficacy in a letter dated 14 September 2005.

Study center(s): 14 centers enrolled patients in 5 countries: Belgium (1), Canada (1), Poland (1), Russia (3), USA (8)

Study period:
First patient enrolled: 04-Feb-2005
Last patient completed: 28-Oct-2005

Primary objectives:
1. to evaluate the safety and tolerability of Sandostatin LAR® Depot in pediatric patients with hypothalamic obesity
2. to evaluate changes in body mass index (BMI) with Sandostatin LAR® Depot (40mg) in pediatric patients with hypothalamic obesity

Secondary objectives:
1. to measure changes in weight with Sandostatin LAR® Depot (40mg) in pediatric patients with hypothalamic obesity
2. to evaluate the effect of Sandostatin LAR® Depot on the metabolic and energy balance parameter, leptin
3. to evaluate the effect of Sandostatin LAR® Depot on insulin dynamics (C-peptide, amylin, insulin) and glucose time profiles during the oral glucose tolerance test (OGTT).
4. to evaluate the change from baseline in waist to hip ratio
5. to evaluate changes from baseline in volitional dietary intake, i.e. percent intake of carbohydrates, fats, and protein and physical activity
6. to determine the change from baseline in visceral and subcutaneous fat in the abdomen by Quantitative CT scan and to assess body composition of fat, fat free mass (lean tissue) and bone based on DEXA scans
7. to monitor the plasma concentrations of Sandostatin during the treatment period
8. to determine the proportion of patients who responded to the study medication. A response is defined at stabilization or reduction in BMI from baseline (Δ BMI ≤ 0).

Design:
This was a six-month, open-label extension, multi-center trial in pediatric patients with hypothalamic obesity. Patients participating in the original core protocol were able to continue into the 6-month extension if they re-qualified by meeting the inclusion/ exclusion criteria. Patients who provided written consent and entered the extension study received Sandostatin LAR 40 mg as two intragluteal 20 mg injections, once a month beginning at Month 7 for up to 6 months.

Patient Population:
There were 62 patients randomized into the core study and 56 completed the core. These patients could continue into the extension study if they met the inclusion/ exclusion criteria and provided written consent. There were 32 patients that entered the extension study. Thirteen of the 32 patients (41%) were randomized to SAS-LAR during the core study and continued on into the open label extension phase (OLE). Nineteen patients (59%) received placebo during the core phase and SAS-LAR during the OLE phase of the study.

Patients included in the core study were males or females aged 6 to < 18 years who had experienced a cranial insult related to cranial trauma or to a tumor or its treatment, and were suffering from hypothalamic obesity. They had been normal weight for height within a year of diagnosis of their cranial insult or tumor, but at screening, they were >120% of ideal body weight for height or BMI was >27kg/m2. Their weight gain was >2 standard deviations above the mean for their age for at least one year following all tumor therapy. Patients were to have documented

normal pituitary function tests and stabilized maintenance therapy. Written informed consent was obtained according to the legal requirements of the countries.

The patient population for the extension study excluded patients who discontinued from the core study for any reason, experienced unresolved safety complications during the core study, or failed to meet the inclusion /exclusion criteria or sign the informed consent of the extension study.

Treatment Groups:
There was no placebo therapy in this open-label, extension study. All patients received Sandostatin LAR Depot 40 mg intramuscular injection (2 intragluteal injections of 20 mg each) once a month beginning at Study Month 7 for up to 6 months.

Cohort SAS-LAR **C+E**: Those patients randomized to SAS-LAR during the core study who continued into the open label extension phase (OLE)

Cohort SAS-LAR **OLE**: Those patients who received placebo during the core phase and SAS-LAR during the OLE phase of the study

Endpoints:
Efficacy:
Primary:
The primary efficacy analysis was performed on the safety population. The primary efficacy result was the change from baseline to last post-baseline assessment of BMI. BMI was calculated as the patient's weight (in kilograms) divided by the square of the patient's height (units are measured in meters, squared height units are measured in meters squared).

Secondary: Change from baseline in weight, leptin, insulin AUC, C-peptide AUC, amylin AUC, glucose AUC, dietary intake, physical activity, waist-to-hip ratio, visceral and subcutaneous abdominal fat, and proportion of patients responding to study medication (change in BMI ≤ 0). All analyses were conducted within each cohort (C+E or OLE).

Safety: The safety information collected included adverse events, results of physical examinations, data on vital signs, laboratory evaluations, and ECGs. Additional safety evaluations included echocardiograms, gallbladder ultrasound scans, Tanner staging and spot stool fat analysis.

Pharmacology: Serum samples were collected for octreotide concentrations measurements at Month 7 through Month 13 for all patients. For Month 7, a pre-dose blood sample (2 mL) was taken prior to receiving the Sandostatin LAR dose and prior to the OGTT test being performed. Three additional samples were collected from each patient and the time points of these samples were distributed randomly within the 30-day period of the month. To ensure that population samples were uniformly distributed within Month 7, sampling times were assigned into three time intervals between days 1-10, 11-20, 21-30. In addition, trough blood samples were collected

for octreotide measurement prior to each LAR dose at Months 8, 9, 10, 11, and 12. A sample was also collected at Month 13.

Statistical Analyses:
The study followed an open label non-randomized design. Two cohorts were identified: patients randomized to SAS-LAR during the Core Phase who continued into the OLE Phase (the SAS-LAR C+E cohort), and patients who received placebo during the Core Phase and SAS-LAR during the OLE Phase (the SAS-LAR OLE cohort).

T-testing was used to compare within-cohort changes from baseline to final study assessment using last observation carry-forward methodology (LOCF). Data from all centers that participated in the trial were pooled. All enrolled patients completed at least one post-baseline assessment and so were included in primary and secondary efficacy analyses. Summary statistics include n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables. When appropriate, two-sided 95% confidence intervals (95%-CI) for means and/or proportions as well as descriptive p-values were provided. The p-values were used to assess specific clinically-identified hypotheses. Unless otherwise specified, all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

For primary efficacy (change from baseline in BMI) change was calculated such that negative changes represented improvements (reductions). No interim analyses of OLE data were performed. All efficacy analyses were performed in the Safety population. Baseline for the SAS-LAR C+E cohort was defined as Month 0 and for the SAS-LAR OLE cohort as Month 7.

Protocol Amendments:
There were no amendments made to this extension study.

Results:

Patient Demographics:
The majority of patients were Caucasian (97%), aged ≥ 12 years (69%) with a mean age of 13.3 years. In the SAS-LAR C+E cohort, the ages ranged from 6 to 16 years; there were 6 subjects < 12 years of age and 7 subjects ≥ 12 years. In the SAS-LAR OLE cohort, the ages ranged from 11 to 17 years; there were 4 subjects < 12 years of age and 15 subjects ≥ 12 years. At baseline, no gallbladder ultrasound or echocardiogram abnormalities were found in any of the patients.

Table 10.1.3.1 Demographic characteristics by treatment and overall (Safety population)

		SAS-LAR C+E N=13	SAS-LAR OLE N=19	Total N=32
Age (years)	Mean	11.5	14.6	13.3
	SD	3.28	2.46	3.18
	Median	12.0	15.0	13.5
	Range	6 - 16	11 – 17	6 - 17
Age group – n (%)	< 12 years	6 (46.2)	4 (21.1)	10 (31.3)
	≥ 12 years	7 (53.8)	15 (78.9)	22 (68.8)
Sex – n (%)	Male	7 (53.8)	7 (36.8)	14 (43.8)
	Female	6 (46.2)	12 (63.2)	18 (56.3)
Race : Ethnicity n (%)	Caucasian	2 (15.4)	4 (21.1)	6 (18.8)
	Caucasian: Other	11 (84.6)	14 (73.7)	25 (78.1)
	Pacific islander: Other	0 (0.0)	1 (5.3)	1 (3.1)
Country – n (%)	Belgium	2 (15.4)	3 (15.8)	5 (15.6)
	Canada	0 (0.0)	1 (5.3)	1 (3.1)
	Poland	1 (7.7)	2 (10.5)	3 (9.4)
	Russia	4 (30.8)	5 (26.3)	9 (28.1)
	USA	6 (46.2)	8 (42.1)	14 (43.8)
Weight (kg)	Mean	75.31	91.70	85.04
	SD	19.89	27.79	25.85
	Median	72.00	86.00	85.30
	Range	47.4 – 104.0	51.1 – 161.0	47.4 – 161.0
Height (cm)	Mean	148.8	160.8	155.9
	SD	13.20	9.47	12.47
	Median	146.0	161.0	157.5
	Range	123 - 172	140 -182	123 - 182

Patient Disposition:
There were 32 patients entered into this open-label extension study; 13 patients had received SAS-LAR in the core study and 19 patients received saline control in the core. Patients continued into the extension study at 14 centers in 5 countries: Belgium (1 center), Canada (1 center), Poland (1 center), Russia (3 centers), USA (8 centers).

There were 23 patients entered into the extension but who did not complete the extension study. At the recommendation of the DSMB, the extension study was terminated due to lack of efficacy and patients in the extension study were discontinued with the reason listed as “administrative problems”.

One patient discontinued from the study because of an AE. Patient USA/0502/00001

(SAS-LAR OLE group), a 17 year old, female, Caucasian was discontinued from the study due to grade 1 (mild) cholelithiasis suspected to be related to study drug. This patient received 2 months of treatment before discontinued

Table 10.1.3.2 Patient disposition by treatment and overall (All patients)

	SAS-LAR C+E N=13 n (%)	SAS-LAR OLE N=19 n (%)	Total N=32 n (%)
Patients:			
Exposed	13 (100.0)	19 (100.0)	32 (100.0)
Completed extension study	3 (23.1)	6 (31.6)	9 (28.1)
Discontinued	10 (76.9)	13 (68.4)	23 (71.9)
Main reason for discontinuation:			
Adverse event(s)	0 (0.0)	1 (5.3)	1 (5.3)
Patient withdrew consent	1 (7.7)	2 (10.5)	3 (9.4)
Administrative problems	9 (69.2)	10 (52.6)	19 (59.4)

Protocol Violations:
There were 8 subjects (61.5%) in the SAS-LAR C+E cohort with a protocol violation and 18 subjects (94.7%) in the SAS-LAR OLE cohort. The medical reviewer concurs with the sponsor's assessment that there was only one major protocol violation. Patient USA/520/001 administered weight loss medication and was excluded from the per-protocol analysis. He had been receiving active SAS-LAR treatment from the beginning of the core phase.

Concomitant Medication Use:
Concomitant medications and significant non-drug therapies reflected the patients' endocrine disorders and the medications required to treat these [e.g. glucocorticoids (SAS-LAR C+E, OLE: 69%, 79%), somatotropin (SAS-LAR C+E, OLE: 31%, 63%), thyroid hormones (SAS-LAR C+E, OLE: 54%, 95%) and vasopressin (SAS-LAR C+E, OLE: 69%, 79%)].

Patient Exposure to Study Drug:
All patients in the SAS-LAR C+E group received study medication for 6 months in the core study and then continued receiving study drug in the extension study. In the SAS-LAR OLE group, all patients had been receiving placebo in the core study and began treatment with study drug in the open-label extension study.

The mean duration of exposure for the SAS-LAR C+E group was 295 days (9.8 months); the median duration of exposure was 303 days (10 months). Only three patients received 12 months of treatment. Six patients out of 19 (32%) in the SAS-LAR OLE cohort received study drug for 6 months and 19 patients total (C+E plus OLE) received study drug for ≥ 6 months.

Table 10.1.3.3 Number (%) of patients receiving study medication at each visit, by treatment and overall (Safety population)

	SAS-LAR C+E N=13 n (%)	SAS-LAR OLE N=19 n (%)	Total N=32 n (%)
Visit 2 (C+E baseline)	13 (100.0)		
Visit 3 (Month 1)	13 (100.0)		
Visit 4 (Month 2)	13 (100.0)		
Visit 5 (Month 3)	13 (100.0)		
Visit 6 (Month 4)	13 (100.0)		
Visit 7 (Month 5)	13 (100.0)		
Visit 9 (Month 7 or OLE baseline)	13 (100.0)	19 (100.0)	32 (100.0)
Visit 10 (Month 8)	13 (100.0)	18 (94.7)	31 (96.9)
Visit 11 (Month 9)	11 (84.6)	16 (84.2)	27 (84.4)
Visit 12 (Month 10)	8 (61.5)	13 (68.4)	21 (65.6)
Visit 13 (Month 11)	6 (46.2)	8 (42.1)	14 (43.8)
Visit 14 (Month 12)	3 (23.1)	6 (31.6)	9 (28.1)

Primary Efficacy Outcome:

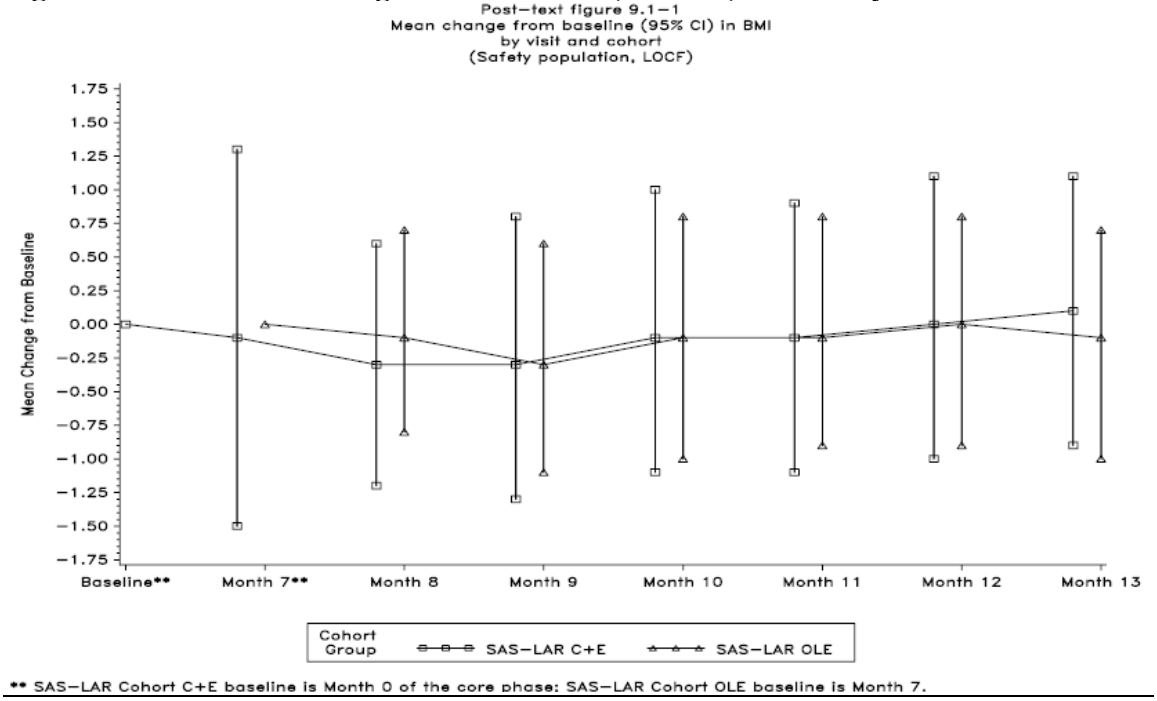
This extension study failed to meet the primary efficacy outcome. There were mean and median increases in weight at Month 13 for patients treated with SAS-LAR during the core and extension phase. Patients treated with SAS-LAR for only 6 months in the OLE phase had a smaller mean weight gain. This is summarized in Table 10.1.4 and Figure 10.1.1.

Table 10.1.3.4 Primary Efficacy Evaluation: Mean Change from Baseline in BMI (kg/m^2) by Cohort** (Safety Population, LOCF)

Cohort Group	N*	BMI baseline Mean**	Actual mean change from baseline†	End of study vs. baseline P-value#
SAS-LAR C+E	13	33.6	0.1	0.922
SAS-LAR OLE	19	34.9	-0.1	0.704

*N is the number of patients with observations at Baseline and at either Month 13 or final OLE study visit
** SAS-LAR Cohort C+E baseline is Month 0 of the core phase; SAS-LAR Cohort OLE baseline is Month 7
# P-value is from t-test of End of Study vs. Baseline BMI
† Change calculated at last non-missing post-baseline assessment

Figure 10.1.3.1 Mean Change from Baseline (95% CI) in BMI by Visit and Cohort



Secondary Efficacy Outcomes:

This extension study did not meet most of the secondary efficacy objectives.

Table 10.1.3.5 Secondary Efficacy Evaluations: (Safety Population)

Cohort Group	N*	BMI baseline Mean**	Actual mean change from baseline	End of study vs. baseline P-value#
Weight (kg)				
SAS-LAR C+E	13	75.31	3.68	0.069
SAS-LAR OLE	19	91.70	0.62	0.460
Waist-to-Hip Ratio				
SAS-LAR C+E	12	1.069	0.012	0.786
SAS-LAR OLE	16	1.045	0.008	0.793
Leptin (µg/L)				
SAS-LAR C+E	12	99.4	0.8	0.921
SAS-LAR OLE	15	132.1	-20.3	0.207
Insulin AUC Post-OGTT (pmol/L)				
SAS-LAR C+E	10	1294.48	-581.15	0.016*
SAS-LAR OLE	13	1353.45	-607.53	0.034*
C-peptide AUC Post-OGTT (nmol/L)				
SAS-LAR C+E	7	4.57	0.01	0.989
SAS-LAR OLE	7	5.69	-2.73	0.036*

Amylin AUC Post-OGTT (pmol/L)				
SAS-LAR C+E	13	95.47	-15.31	0.623
SAS-LAR OLE	12	60.39	-6.31	0.606
Glucose AUC Post-OGTT (mmol/L)				
SAS-LAR C+E	13	125.9	31.6	0.160
SAS-LAR OLE	13	120.5	34.8	0.026*
Visceral fat (cm^2)##				
SAS-LAR C+E	12	58.1	14.0	0.086
SAS-LAR OLE	12	74.2	-0.8	0.905
Subcutaneous fat (cm^2)##				
SAS-LAR C+E	12	395.8	12.6	0.292
SAS-LAR OLE	10	408.4	1.3	0.931
Total fat (kg)##				
SAS-LAR C+E	13	33.8	2.3	0.049*
SAS-LAR OLE	13	34.1	0.4	0.568
Total lean tissue (kg)##				
SAS-LAR C+E	13	38.4	3.0	<0.001*
SAS-LAR OLE	13	43.1	1.5	0.003*
Total bone (kg)##				
SAS-LAR C+E	13	1.7	0.1	0.002*
SAS-LAR OLE	13	1.8	0.0	0.302
24-h total calorie intake				
SAS-LAR C+E	13	1685.2	-123.5	0.407
SAS-LAR OLE	16	1741.0	-23.2	0.839
Physical activity (intensity-minutes)				
SAS-LAR C+E	12	666.5	292.4	0.243
SAS-LAR OLE	17	625.8	223.0	0.279

*N is the number of patients with observations at Baseline and at either Month 13 or final OLE study visit
** SAS-LAR Cohort C+E baseline is Month 0 of the core phase; SAS-LAR Cohort OLE baseline is Month 7
# P-value is from t-test of End of Study vs. Baseline BMI
There are 3 patients whose total body results omit their right or left arm

Safety Data:

Deaths:
No deaths occurred during the OLE phase.

Serious Adverse Events:
There were serious adverse events reported for nine patients during this extension study (9/32, 28%); 3 patients (23.1%) in the SAS-LAR C+E group and 6 patients (31.6%) in the SAS-LAR OLE group. Four of the nine (44.4%) SAEs were related to cholelithiasis, three (33.3%) were for biliary tract abnormalities, and two (22.2%) were for gastrointestinal disorders.

Three patients in the SAS-LAR C+E group had cholelithiasis suspected to be related to study drug (by preferred term: 2 cholelithiasis; 1 ultrasound of biliary tract abnormal). Four patients in the SAS-LAR OLE group had cholelithiasis (by preferred term: 2 cholelithiasis; 2 ultrasound of biliary tract abnormal) suspected to be related to study drug, one patient had abdominal pain related to study drug, and one patient had hypernatremia not related to study drug. All SAEs were mild or moderate in severity with the exception of Patient RUS/0701/00005 (SAS-LAR C+E group), with cholelithiasis suspected to be related to study drug graded as severe (Grade 3) and Patient USA/0503/00001 (SAS-LAR OLE group) with hypernatremia not related to study drug, graded as life-threatening (Grade 4). Neither patient was discontinued from the study. These two patients are discussed below:

Patient SMS995B2403 [701 0005] – – Cholelithiasis
Treatment group: Sandostatin LAR® Depot 40mg
Event(s): 1. SAE (Cholelithiasis)
This 17 year-old Caucasian Female has a medical history of polycystic ovary syndrome and hypothalamic obesity. The patient completed treatment on the core protocol on 18 Mar 2005. This patient was randomized to Sandostatin LAR® Depot 40mg for the core study. She commenced treatment on the extension study on 21 Apr 2005. The patient's last dose of study drug was 22 Aug 2005. On 29 Sep 2005, the patient underwent a scheduled early termination ultrasound of the gallbladder. The ultrasound demonstrated multiple tiny gallstones. The previous ultrasound was negative and the patient was asymptomatic. The patient consulted a gastroenterologist. The gastroenterologist recommended Ursofalk 1000mg per day for 6 months. The investigator suspected a relationship between the event and the study medication.

Patient SMS995B2403 [503 0001] – Hypernatremia, abdominal cramping, diarrhea, increased frequency of stools
Treatment group: Sandostatin LAR® Depot 40mg
Event(s): 1. SAE (Hypernatremia, abdominal cramping, diarrhea, increased frequency of stools)
1. This 13-year-old Caucasian Female has a medical history of diabetes insipidus, hypothyroidism, germinoma and precocious puberty. The patient completed treatment on the core protocol on 20 Jan 2005. This patient was randomized to placebo for the core study. She commenced treatment on the extension study on 17 Mar 2005. On 18 Mar 2005, the patient complained of abdominal cramps and increased frequency of stools leading to diarrhea. The patient was treated with Imodium. The event resolved on 28 March 2005. Due to the patients' medical history of diabetes insipidus, sodium levels were approximately 160-170 mmol/L. The patient's sodium level was 173 mmol/L and 161 mmol/L on 24 Mar and 28 Mar 2005 respectively. The patient was treated with one liter 0.9% saline on 28 Mar 2005 which brought her sodium level up to 164mmol/L. The sodium level was reported to be back within normal limits on 04 Apr 2005. The patient made a complete recovery by 02 April 2005. The investigator suspected the diarrhea to be related to study medication, with the hypernatremia secondary to diarrhea. The patient's last dose of study drug was 11 Aug 2005.

The percentage of patients with a SAE was lower in the group treated with SAS-LAR in both the core plus extension phases of the study (23%) than in the group treated with placebo in the core

and SAS-LAR in the extension (32%). Seven of the 9 patients with a SAE had cholelithiasis that was suspected to be related to study drug. The patients had been asymptomatic and cholelithiasis was found at a scheduled ultrasound scan.

Adverse Events that Led to Study Withdrawal:
One patient (1/32, 3.1%) experienced an adverse event, classified as treatment-emergent, that led to discontinuation in OLE. The adverse event was for cholelithiasis in the SAS-LAR OLE cohort and the patient is described below.

Patient SMS995B2403 [502 0001] – – Cholelithiasis
Treatment group: Sandostatin LAR® Depot 40mg
Event(s): 1. SAE (Cholelithiasis)
This 18 year-old Caucasian Female has a medical history of craniopharyngioma and hypothalamic obesity. The patient completed treatment on the core protocol on 22 Mar 2005. This patient was randomized to placebo for the core study. She commenced treatment on the extension study on 31 May 2005. The patient's last dose of study drug was 01 Aug 2005. On 01 Aug 2005, the patient underwent a scheduled ultrasound of the gallbladder. The ultrasound revealed a new appearance of cholelithiasis. Previous scans were negative and the patient was asymptomatic. The investigator suspected a relationship between the event and the study medication. Follow up report dated 25 August 2005 indicate the patient's condition to be present and unchanged.

Adverse Events that Led to Study Drug Dose Adjustment/Temporary Interruption Withdrawal:
There were two patients who required study drug dose adjustment or temporary interruption. One patient had a varicella infection and the other patient had moderate dyspepsia related to study drug.

Treatment-Emergent Adverse Events:
Twenty-seven of thirty-two (84.4%) patients experienced a treatment-emergent adverse event, 12 of 13 (92.3%) in the SAS-LAR C+E cohort, and 15 of 19 (78.9%) in the SAS-LAR OLE cohort.

The majority of study drug related AEs were mild or moderate in severity. As expected for patients treated with SAS-LAR, gastrointestinal disorders including diarrhea and hepatobiliary disorders including cholelithiasis were the most common AEs reported as related. These were all were mild or moderate in severity, except for one report of severe cholelithiasis in a patient in the SAS-LAR C+E group, (Patient RUS/0701/00005, described earlier).

Adverse Events:
Overall, a higher proportion of patients receiving SAS-LAR in the core plus extension experienced AEs than patients who received SAS-LAR only in the extension. This was due in part to a greater percentage of patients with infections in the SAS-LAR C+E group. Hepatobiliary disorders were reported for a similar percentage of patients both groups, while gastrointestinal disorders were reported for a slightly greater percentage of patients in the SAS-LAR C+E group than for the SAS-LAR OLE group

Table 10.1.3.6 Number (%) of patients with AEs overall and by primary system organ class (Safety population)

	SAS-LAR C+E N=13 n (%)	SAS-LAR OLE N=19 n (%)	Total N=32 n (%)
Number of patients with AE(s)	12 (92.3)	15 (78.9)	27 (84.4)
Primary system organ class affected:			
Blood and lymphatic system disorders	0 (0.0)	1 (5.3)	1 (3.1)
Endocrine disorders	1 (7.7)	1 (5.3)	2 (6.3)
Gastrointestinal disorders	6 (46.2)	7 (36.8)	13 (40.6)
General disorders and administration site conditions	1 (7.7)	1 (5.3)	2 (6.3)
Hepatobiliary disorders	3 (23.1)	5 (26.3)	8 (25.0)
Immune system disorders	1 (7.7)	1 (5.3)	2 (6.3)
Infections and infestations	9 (69.2)	4 (21.1)	13 (40.6)
Injury, poisoning and procedural complications	1 (7.7)	1 (5.3)	2 (6.3)
Investigations	1 (7.7)	2 (10.5)	3 (9.4)
Metabolism and nutrition disorders	2 (15.4)	1 (5.3)	3 (9.4)
Musculoskeletal and connective tissue disorders	1 (7.7)	0 (0.0)	1 (3.1)
Nervous system disorders	0 (0.0)	1 (5.3)	1 (3.1)
Psychiatric disorders	2 (15.4)	0 (0.0)	2 (6.3)
Renal and urinary disorders	2 (15.4)	0 (0.0)	2 (6.3)
Reproductive system and breast disorders	1 (7.7)	0 (0.0)	1 (3.1)
Respiratory, thoracic and mediastinal disorders	3 (23.1)	2 (10.5)	5 (15.6)
Skin and subcutaneous tissue disorders	2 (15.4)	0 (0.0)	2 (6.3)

Nasopharyngitis, diarrhea and cholelithiasis were the most commonly reported AEs. Nasopharyngitis was reported for a greater percentage of patients in the SAS-LAR C+E group than in the SAS-LAR OLE group

Laboratory Parameters:
Laboratory assessments of hematology, biochemistry and urinalysis were performed at Month 7, Month 9 and at Month 13 or end of study. Criteria for clinically notable laboratory abnormalities were defined in the protocol and are below:

Table 10.1.3.7 Clinically Notable Laboratory Abnormalities

Alkaline Phosphatase	> 2.5 x IULN
Bilirubin	> 1.5 x IULN
SGOT (AST)	> 3 x IULN
SGPT (ALT)	> 3 x IULN
HbA_{1C}	> 2 x IULN
FT_4, TSH	> 2.0 x IULN

Hematology:
There were no clinically relevant changes from baseline of any hematology parameter in either treatment group.

Biochemistry:
For most of the biochemistry parameters, post-baseline versus baseline distributions of normal, low and high values did not show any clinically relevant differences in either treatment group.

The following trends were noted:

- Insulin levels showed a shift from high values at baseline to normal values post-baseline in the SAS-LAR C+E group during the first 6 months of the study, but this effect was diminished during the extension phase and was not observed in the SAS-LAR OLE group.
- Oral glucose tolerance test – glucose levels indicated a notably higher number of patients shifting from normal to high values post-baseline in the SAS-LAR C+E group. There was no data for the SAS-LAR OLE group for this parameter.
- Mean HbA1c increased slightly in both groups post-baseline.
- The majority of patients had high leptin levels at baseline and post-baseline in both groups.
- For thyroid stimulating hormone, in both groups, about half the patients had low levels at baseline that remained low post-baseline. Mean FT4 and mean TSH decreased slightly in both groups post-baseline. Hypothyroidism was reported as an AE for one patient in the SAS-LAR OLE group

There was one patient with clinically notable biochemistry abnormalities. Patient BEL/0102/00002 (SAS-LAR OLE) had grade 3 SGOT and SGPT values. At screening SGOT=145 U/L (ULN=60 U/L, 3xULN=180 U/L), 3 months=149 U/L, 6 months=392 U/L, 9 months=81 U/L, and 13 months=64 U/L. SGPT values (ULN=72 U/L, 3xULN=216U/L) were as follows: screening=213 U/L, 3 months=453 U/L, 6 months=185 U/L, and 13 months=127U/L.

Urinalysis:
Newly occurring, post-baseline glucosuria was not detected in any patient. New or worsening, post-baseline proteinuria (trace or 1+ by dipstick test) was found in 3 patients in the SAS LAR C+E group. Hematuria was reported as an AE in one patient in the SAS-LAR C+E group.

Vital Signs:

There were mean and median increases in weight at Month 13 for patients treated with SAS-LAR during the core and extension phase. Patients treated with SAS-LAR for only 6 months in the OLE phase had a smaller mean weight gain.

There was no significant differences between the two groups in terms of systolic and diastolic blood pressure, (see Table below).

There were no relevant differences between the two treatments in the frequency of vital signs abnormalities based on notable criteria defined by height, age and sex.

Table 10.1.3.8 Number (%) of patients with newly occurring or worsening abnormalities of vital signs post-baseline (Safety population)

Parameter	Notable criteria †	SAS-LAR N=13 n (%)	SAS-LAR N=19 n (%)
Sitting systolic BP	Low	2 (15.4)	2 (10.5)
	High	5 (38.5)	11 (57.9)
	Low and High	2 (15.4)	0 (0)
Sitting diastolic BP	Low	0 (0)	2 (10.5)
	High	5 (38.5)	4 (21.1)
	Low and High	2 (15.4)	0 (0)

† Criteria are defined as the 10th and 90th percentiles (low and high respectively) of CDC-published NHANES pediatric data

Special Safety Studies:
Follow-up analyses were performed of ECGs, echocardiograms, Tanner staging, gallbladder ultrasound and spot stool fat analysis to assess patients' status relative to baseline measurements.

ECG evaluations:
There were no clinically significant abnormal ECGs at baseline or at Month 13 in either of the two groups.

Echocardiograms:
An echocardiogram was to be performed at Month 9 and at Month 13 for each patient. Due to the early discontinuation of patients from the extension study, echocardiograms were performed at the early termination visit. There were no clinically significant changes in echocardiogram results post-baseline.

Tanner staging:
There was no change from baseline in Tanner staging for most patients (SAS-LAR C+E 92%, SAS-LAR-OLE 58%). There were 4 patients in the SAS-LAR-OLE group and 1 patient in the SAS-LAR C+E group that changed by 1-2 Tanner stages at Month 13 compared to baseline.

Gallbladder ultrasound:

Gallbladder ultrasounds were performed at baseline, at the end of the core phase, at Month 9 and at the end of the extension study. The incidence of new and/or worsening abnormalities at the end of the study is summarized in Table 10.1.3.9.

Eleven patients (34%) were found to have new or worsened abnormalities of the gallbladder by the end of the extension study. In addition to the patients with cholelithiasis reported as AEs, there were patients with gallbladder sludge that was not present at baseline.

Table 10.1.3.9 Change from baseline at end of study in gallbladder ultrasound (Safety population)

	SAS-LAR C+E N=13 n (%)	SAS-LAR OLE N=19 n (%)
Gallbladder ultrasound compared to baseline:		
unchanged	9 (69.2)	11 (57.9)
new or worsened	4 (30.8)	7 (36.8)
not compared	0 (0)	1 (5.3)

SAS-LAR C+E baseline is month 0 of the core phase; SAS-LAR OLE baseline is month 7

Spot stool fat analysis:
There were no clinically relevant changes from baseline in the spot stool fat analysis or differences between the SAS-LAR C+E and SAS-LAR OLE groups at Month 9 and Month 13.

Company's Conclusions:
The safety and tolerability of Sandostatin LAR® Depot in pediatric patients with hypothalamic obesity was comparable for patients treated for 6 months or for 12 months.

The adverse events reported were similar to those previously reported for this patient population. The percentage of patients with an AE was greater for patients treated with SAS-LAR 40 mg for 12 months (92%) versus patients treated in the extension study for 6 months (79%). There were, however, only 13 patients entered into the extension study who had received SAS-LAR in the core phase of the study.

The nature and severity of AEs reported was similar between the group treated with SAS-LAR for 12 months and the group treated with SAS-LAR for 6 months.

There was a greater frequency of infections in the SAS –LAR C+E group (69%) than in the SAS –LAR OLE group (21%) with the largest difference being the percentage of patients with nasopharyngitis.

SAEs were reported for a smaller percentage of patients in the SAS –LAR C+E group (23%) than in the SAS –LAR OLE group (32%). Gallstone formation was reported for a smaller percentage of patients in the group treated for 12 months with SAS-LAR than in the group treated for only 6 months.

There were no unexpected safety problems found with long-term treatment, and the results were consistent with previous findings.

Medical Officer's Conclusions:

This extension study failed to meet the primary efficacy objective and most of the secondary efficacy objectives.

There were mean and median increases in weight at Month 13 for patients treated with SAS-LAR during the core and extension phase.

There was limited long-term drug exposure in these studies. Only 3 patients received 12 months of treatment. Only six patients out of 19 (32%) in the SAS-LAR OLE cohort received study drug for 6 months.

There were serious adverse events reported for nine patients during this extension study (9/32, 28%); 3 patients (23.1%) in the SAS-LAR C+E group and 6 patients (31.6%) in the SAS-LAR OLE group. Four of the nine (44.4%) SAEs were related to cholelithiasis, three (33.3%) were for biliary tract abnormalities, and two (22.2%) were for gastrointestinal disorders. Eleven patients (34%) were found to have new or worsened abnormalities of the gallbladder by the end of the extension study. Similarly, eleven patients (11/30, 37%) were found to have new or worsened abnormalities of the gallbladder and 33% experienced new cholelithiasis by the end of Study 2403.

Thus, the incidence of new cholelithiasis and new or worsened abnormalities of the gallbladder in this pediatric population in the extension study was comparable to the rates seen in Study 2403 but higher than that seen in other adult indications such as acromegaly or malignant carcinoid syndrome.

10.2 Line-by-Line Labeling Review

See Section 9.4.

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