CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022074Orig1s017

Trade Name:	SOMATULINE DEPOT
Generic or Proper Name:	(lanreotide)
Sponsor:	Ispen Pharma
Approval Date:	September 15, 2017
Indication:	SOMATULINE DEPOT is a somatostatin analog indicated for: • the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. • the treatment of adult patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival. • the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy. (1.3)

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022074/S-017

SUPPLEMENT APPROVAL

Ipsen Pharma SAS
c/o Ipsen Biopharmaceuticals, Inc.
US Agent for Ipsen Pharma SAS
Attention: Marion Scocca
Director, Global Regulatory Affairs
650 East Kendall Street, 2nd and 4th Floors
Cambridge, MA 02142

Dear Ms. Scocca:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on August 15, 2016 (eCTD SN 0039), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SOMATULINE DEPOT (lanreotide) Injection 60 mg, 90 mg, and 120 mg.

We additionally acknowledge receipt of your major amendment dated and received on May 11, 2017 (eCTD SN 0058), which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed

labeling. Information on submitting SPL files using eLIST may be found in the draft Guidance for Industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft (MS) Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean MS Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Benjamin Vali
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5245
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Benjamin Vali, Regulatory Project Manager, at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Dragos Roman, M.D.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling:
Prescribing Information (PI)
Patient Information (PPI)

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

/s/

DRAGOS G ROMAN
09/15/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOMATULINE DEPOT safely and effectively. See full prescribing information for SOMATULINE DEPOT.

SOMATULINE® DEPOT (lanreotide) injection, for subcutaneous use
Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES----------

Indications and Usage, Carcinoid Syndrome (1.3)	09/2017
Dosage and Administration, Carcinoid Syndrome (2.2)	09/2017

----------INDICATIONS AND USAGE----------

SOMATULINE DEPOT is a somatostatin analog indicated for:

- the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. (1.1)
- the treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival. (1.2)
- the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy. (1.3)

----------DOSAGE AND ADMINISTRATION----------

Administration (2.1):

- For deep subcutaneous injection only.
- Intended for administration by a healthcare provider.
- Administer in the superior external quadrant of the buttock.
- Alternate injection sites.

Recommended Dosage (2.1)

- Acromegaly: 90 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels. See full prescribing information for titration regimen.
- GEP-NETs: 120 mg every 4 weeks.
- Carcinoid Syndrome: 120 mg every 4 weeks. If patients are already being treated with SOMATULINE DEPOT for GEP-NET, do not administer an additional dose for carcinoid syndrome.

Dosage Adjustment:

- See full prescribing information for dosage adjustment in patients with acromegaly and renal or hepatic impairment. (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL single-dose prefilled syringes (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to lanreotide. (4)

----------WARNINGS AND PRECAUTIONS----------

- Cholelithiasis and Gallbladder Sludge: Gallstones may occur; consider periodic monitoring. (5.1)
- Hyperglycemia and Hypoglycemia: Glucose monitoring is recommended and antidiabetic treatment adjusted accordingly. (5.2, 7.1)
- Cardiovascular Abnormalities: Decrease in heart rate may occur. Use with caution in at-risk patients. (5.3)
- Thyroid Function Abnormalities: Decreases in thyroid function may occur; perform tests where clinically indicated. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Acromegaly (>5%): diarrhea, cholelithiasis, abdominal pain, nausea and injection site reactions. (6.1)
- GEP-NET (>10%): abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, and cholelithiasis. (6.1)
- Carcinoid Syndrome: (≥5% and at least 5% greater than placebo): headache, dizziness and muscle spasm. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Cyclosporine: SOMATULINE DEPOT may decrease the absorption of cyclosporine. Dosage adjustment of cyclosporine may needed. (7.2)
- Bromocriptine: SOMATULINE DEPOT may increase the absorption of bromocriptine. (7.3)
- Bradycardia-Inducing Drugs (e.g., beta-blockers): SOMATULINE DEPOT may decrease heart rate. Dosage adjustment of the coadministered drug may be necessary. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed during treatment and for 6 months after the last dose. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acromegaly

SOMATULINE DEPOT is indicated for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.

The goal of treatment in acromegaly is to reduce growth hormone (GH) and insulin growth factor-1 (IGF-1) levels to normal.

1.2 Gastroenteropancreatic Neuroendocrine Tumors

SOMATULINE DEPOT is indicated for the treatment of adult patients with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

1.3 Carcinoid Syndrome

SOMATULINE DEPOT is indicated for the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- *For deep subcutaneous injection only.*
- SOMATULINE DEPOT is intended for administration by a healthcare provider.

Preparation

1. Remove SOMATULINE DEPOT from the refrigerator 30 minutes prior to administration and allow to come to room temperature.
2. Keep pouch sealed until just prior to injection.
3. Prior to administration, inspect the SOMATULINE DEPOT syringe visually for particulate matter and discoloration. Do not administer if particulate matter or discoloration is observed. The content of the prefilled syringe is a semi-solid phase having a gel-like appearance, with viscous characteristics and a color varying from white to pale yellow. The supersaturated solution can also contain micro bubbles that can clear up during injection. These differences are normal and do not interfere with the quality of the product.

Administration

1. Administer as a deep subcutaneous injection in the superior external quadrant of the buttock.
2. Alternate the injection site between the right and left sides from one injection to the next.

2.2 Recommended Dosage

Acromegaly

The recommended starting dosage of SOMATULINE DEPOT is 90 mg given via the deep subcutaneous route, at 4-week intervals for 3 months.

After 3 months, the dosage may be adjusted as follows:

- GH greater than 1 ng/mL to less than or equal to 2.5 ng/mL, IGF-1 normal, and clinical symptoms controlled: maintain SOMATULINE DEPOT dosage at 90 mg every 4 weeks.
- GH greater than 2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled: increase SOMATULINE DEPOT dosage to 120 mg every 4 weeks.
- GH less than or equal to 1 ng/mL, IGF-1 normal, and clinical symptoms controlled: reduce SOMATULINE DEPOT dosage to 60 mg every 4 weeks.

Thereafter, the dosage should be adjusted according to the response of the patient as judged by a reduction in serum GH and/or IGF-1 levels; and/or changes in symptoms of acromegaly.

Patients who are controlled on SOMATULINE DEPOT 60 or 90 mg may be considered for an extended dosing interval of SOMATULINE DEPOT 120 mg every 6 or 8 weeks. GH and IGF-1 levels should be obtained 6 weeks after this change in dosing regimen to evaluate persistence of patient response.

Continued monitoring of patient response with dosage adjustments for biochemical and clinical symptom control, as necessary, is recommended.

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The recommended dosage of SOMATULINE DEPOT is 120 mg administered every 4 weeks by deep subcutaneous injection.

Carcinoid Syndrome

The recommended dosage of SOMATULINE DEPOT is 120 mg administered every 4 weeks by deep subcutaneous injection.

If patients are already being treated with SOMATULINE DEPOT for GEP-NETs, do not administer an additional dose for the treatment of carcinoid syndrome.

2.3 Dosage Adjustment in Renal Impairment

Acromegaly

The recommended starting dosage of SOMATULINE DEPOT in acromegalic patients with moderate or severe renal impairment (creatinine clearance less than 60 mL/min) is 60 mg via the deep subcutaneous route at 4-week intervals for 3 months followed by dosage adjustment *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

2.4 Dosage Adjustment in Hepatic Impairment

Acromegaly
The recommended starting dosage of SOMAUTLINE DEPOT in acromegalic patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) is 60 mg via the deep subcutaneous route at 4-week intervals for 3 months followed by dosage adjustment *[see Dosage and Administration (2.2), Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL sterile, single-dose, prefilled syringes fitted with an automatic needle guard. The prefilled syringes contain a white to pale yellow, semi-solid formulation.

4 CONTRAINDICATIONS

SOMATULINE DEPOT is contraindicated in patients with history of a hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration of lanreotide *[see Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

SOMATULINE DEPOT may reduce gallbladder motility and lead to gallstone formation; therefore, patients may need to be monitored periodically *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

5.2 Hyperglycemia and Hypoglycemia

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Hence, patients treated with SOMATULINE DEPOT may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly *[see Adverse Reactions (6.1)]*.

5.3 Cardiovascular Abnormalities

The most common overall cardiac adverse reactions observed in three pooled SOMATULINE DEPOT cardiac studies in patients with acromegaly were sinus bradycardia (12/217, 5.5%), bradycardia (6/217, 2.8%), and hypertension (12/217, 5.5%) *[see Adverse Reactions (6.1)]*.

In 81 patients with baseline heart rates of 60 beats per minute (bpm) or greater treated with SOMATULINE DEPOT in Study 3, the incidence of heart rate less than 60 bpm was 23% (19/81) as compared to 16% (15/94) of placebo treated patients; 10 patients (12%) had documented heart rates less than 60 bpm on more than one visit. The incidence of documented episodes of heart rate less than 50 bpm as well as the incidence of bradycardia

reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia.

In patients without underlying cardiac disease, SOMATULINE DEPOT may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to SOMATULINE DEPOT treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with SOMATULINE DEPOT in patients with bradycardia.

5.4 Thyroid Function Abnormalities

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare (less than 1%). Thyroid function tests are recommended where clinically indicated.

5.5 Monitoring: Laboratory Tests

Acromegaly: Serum GH and IGF-1 levels are useful markers of the disease and the effectiveness of treatment *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The following adverse reactions to SOMATULINE DEPOT are discussed in greater detail in other sections of the labeling:

- Cholelithiasis and Gallbladder Sludge *[see Warnings and Precautions (5.1)]*
- Hyperglycemia and Hypoglycemia *[see Warnings and Precautions (5.2)]*
- Cardiovascular Abnormalities *[see Warnings and Precautions (5.3)]*
- Thyroid Function Abnormalities *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Acromegaly

The data described below reflect exposure to SOMATULINE DEPOT in 416 acromegalic patients in seven studies. One study was a fixed-dose pharmacokinetic study. The other six studies were open-label or extension studies, one had a placebo-controlled, run-in period, and another had an active control. The population was mainly Caucasian (329/353, 93%) with a median age of 53 years of age (range 19 to 84 years). Fifty-four subjects (13%) were age 66 to 74 and 18 subjects (4.3%) were 75 years of age and older.

Patients were evenly matched for sex (205 males and 211 females). The median average monthly dose was 91.2 mg (e.g., 90 mg injected via the deep subcutaneous route every 4 weeks) over 385 days with a median cumulative dose of 1290 mg. Of the patients reporting acromegaly, severity at baseline (N=265), serum GH levels were less than 10 ng/mL for 69% (183/265) of the patients and 10 ng/mL or greater for 31% (82/265) of the patients.

The most commonly reported adverse reactions reported by greater than 5% of patients who received SOMATULINE DEPOT (N=416) in the overall pooled safety studies in acromegaly patients were gastrointestinal disorders (diarrhea, abdominal pain, nausea, constipation, flatulence, vomiting, loose stools), cholelithiasis, and injection site reactions.

Tables 1 and 2 present adverse reaction data from clinical studies with SOMATULINE DEPOT in acromegalic patients. The tables include data from a single clinical study and pooled data from seven clinical studies.

Adverse Reactions in Parallel Fixed-Dose Phase of Study 1

The incidence of treatment-emergent adverse reactions for SOMATULINE DEPOT 60, 90, and 120 mg by dose as reported during the first 4 months (fixed-dose phase) of Study 1 *[see Clinical Studies (14.1)]* are provided in Table 1.

Table 1: Adverse Reactions at an Incidence of Greater than 5% with SOMATULINE DEPOT Overall and Occurring at Higher Rate than Placebo: Placebo-Controlled and Fixed-Dose Phase of Study 1 By Dose

	Placebo-Controlled Double-Blind Phase Weeks 0 to 4			**Fixed-Dose Phase Double-Blind + Single-Blind** Weeks 0 to 20		
Body System Preferred Term	**Placebo (N=25)**	**SOMATU-LINE DEPOT Overall (N=83)**	**SOMATU-LINE DEPOT 60 mg (N=34)**	**SOMATU-LINE DEPOT 90 mg (N=36)**	**SOMATU-LINE DEPOT 120 mg (N=37)**	**SOMATU-LINE DEPOT Overall (N=107)**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gastrointestinal System Disorders	1 (4%)	30 (36%)	12 (35%)	21 (58%)	27 (73%)	60 (56%)
Diarrhea	0	26 (31%)	9 (26%)	15 (42%)	24 (65%)	48 (45%)
Abdominal pain	1 (4%)	6 (7%)	3 (9%)	6 (17%)	7 (19%)	16 (15%)
Flatulence	0	5 (6%)	0 (0%)	3 (8%)	5 (14%)	8 (7%)
Application Site Disorders (Injection site mass/ pain/ reaction/ inflammation)	0 (0%)	5 (6%)	3 (9%)	4 (11%)	8 (22%)	15 (14%)
Liver and Biliary System Disorders	1 (4%)	3 (4%)	9 (26%)	7 (19%)	4 (11%)	20 (19%)
Cholelithiasis	0	2 (2%)	5 (15%)	6 (17%)	3 (8%)	14 (13%)
Heart Rate & Rhythm Disorders	0	8 (10%)	7 (21%)	2 (6%)	5 (14%)	14 (13%)
Bradycardia	0	7 (8%)	6 (18%)	2 (6%)	2 (5%)	10 (9%)
Red Blood Cell Disorders	0	6 (7%)	2 (6%)	5 (14%)	2 (5%)	9 (8%)
Anemia	0	6 (7%)	2 (6%)	5 (14%)	2 (5%)	9 (8%)
Metabolic & Nutritional Disorders	3 (12%)	13 (16%)	8 (24%)	9 (25%)	4 (11%)	21 (20%)
Weight decrease	0	7 (8%)	3 (9%)	4 (11%)	2 (5%)	9 (8%)

A patient is counted only once for each body system and preferred term.
Dictionary = WHOART.

In Study 1, the adverse reactions of diarrhea, abdominal pain, and flatulence increased in incidence with increasing dose of SOMATULINE DEPOT.

Adverse Reactions in Long-Term Clinical Trials

Table 2 provides the most common adverse reactions (greater than 5%) that occurred in 416 acromegalic patients treated with SOMATULINE DEPOT pooled from 7 studies compared to those patients from the 2 efficacy studies (Studies 1 and 2). Patients with elevated GH and IGF-1 levels were either naive to somatostatin analog therapy or had undergone a 3-month washout *[see Clinical Studies (14.1)]*.

Table 2: Adverse Reactions in SOMATULINE DEPOT-Treated Patients at an Incidence Greater than 5% in Overall Group Versus Adverse Reactions Reported in Studies 1 and 2

System Organ Class	Number and Percentage of Patients			
	Studies 1 & 2 (N=170)		Overall Pooled Data (N=416)	
	N	%	N	%
Patients with any Adverse Reactions	**157**	**92**	**356**	**86**
Gastrointestinal disorders	**121**	**71**	**235**	**57**
Diarrhea	81	48	155	37
Abdominal pain	34	20	79	19
Nausea	15	9	46	11
Constipation	9	5	33	8
Flatulence	12	7	30	7
Vomiting	8	5	28	7
Loose stools	16	9	23	6
Hepatobiliary disorders	**53**	**31**	**99**	**24**
Cholelithiasis	45	27	85	20
General disorders and administration site conditions	**51**	**30**	**91**	**22**
(Injection site pain /mass /induration/ nodule/pruritus)	28	17	37	9
Musculoskeletal and connective tissue disorders	**44**	**26**	**70**	**17**
Arthralgia	17	10	30	7
Nervous system disorders	**34**	**20**	**80**	**19**
Headache	9	5	30	7

Dictionary = MedDRA 7.1

In addition to the adverse reactions listed in Table 2, the following reactions were also seen:

- Sinus bradycardia occurred in 7% (12) of patients in the pooled Study 1 and 2 and in 3% (13) of patients in the overall pooled studies.
- Hypertension occurred in 7% (11) of patients in the pooled Study 1 and 2 and in 5% (20) of patients in the overall pooled studies.
- Anemia occurred in 7% (12) of patients in the pooled Study 1 and 2 and in 3% (14) of patients in the overall pooled studies.

Gastrointestinal Adverse Reactions

In the pooled clinical studies of SOMATULINE DEPOT therapy, a variety of gastrointestinal (GI) reactions occurred, the majority of which were mild to moderate in severity. One percent of acromegalic patients treated with SOMATULINE DEPOT in the pooled clinical studies discontinued treatment because of gastrointestinal reactions.

Pancreatitis was reported in less than 1% of patients.

Gallbladder Adverse Reactions

In clinical studies involving 416 acromegalic patients treated with SOMATULINE DEPOT, cholelithiasis and gallbladder sludge were reported in 20% of the patients. Among 167 acromegalic patients treated with SOMATULINE DEPOT who underwent routine evaluation with gallbladder ultrasound, 17% had gallstones at baseline. New cholelithiasis was reported in 12% of patients. Cholelithiasis may be related to dose or duration of exposure *[see Warnings and Precautions (5.1)]*.

Injection Site Reactions

In the pooled clinical studies, injection site pain (4%) and injection site mass (2%) were the most frequently reported local adverse drug reactions that occurred with the administration of SOMATULINE DEPOT. In a specific analysis, 20 of 413 patients (5%) presented indurations at the injection site. Injection site adverse reactions were more commonly reported soon after the start of treatment and were less commonly reported as treatment continued. Such adverse reactions were usually mild or moderate but did lead to withdrawal from clinical studies in two subjects.

Glucose Metabolism Adverse Reactions

In the clinical studies in acromegalic patients treated with SOMATULINE DEPOT, adverse reactions of dysglycemia (hypoglycemia, hyperglycemia, diabetes) were reported by 14% (47/332) of patients and were considered related to study drug in 7% (24/332) of patients *[see Warnings and Precautions (5.2)]*.

Cardiac Adverse Reactions

In the pooled clinical studies, sinus bradycardia (3%) was the most frequently observed heart rate and rhythm disorder. All other cardiac adverse drug reactions were observed in less than 1% of patients. The relationship of these events to SOMATULINE DEPOT could not be established because many of these patients had underlying cardiac disease *[see Warnings and Precautions (5.3)]*.

A comparative echocardiography study of lanreotide and another somatostatin analog demonstrated no difference in the development of new or worsening valvular regurgitation between the 2 treatments over 1 year. The occurrence of clinically significant mitral regurgitation (i.e., moderate or severe in intensity) or of clinically significant aortic regurgitation (i.e., at least mild in intensity) was low in both groups of patients throughout the study.

Other Adverse Reactions

For the most commonly occurring adverse reactions in the pooled analysis, diarrhea, abdominal pain, and cholelithiasis, there was no apparent trend for increasing incidence with age. GI disorders and renal and urinary disorders were more common in patients with documented hepatic impairment; however, the incidence of cholelithiasis was similar between groups.

Gastroenteropancreatic Neuroendocrine Tumors

The safety of SOMATULINE DEPOT 120 mg for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was evaluated in Study 3, a double-blind, placebo-controlled trial. Patients in Study 3 were randomized to receive SOMATULINE DEPOT (N=101) or placebo (N=103) administered by deep subcutaneous injection once every 4 weeks. The data below reflect exposure to SOMATULINE DEPOT in 101 patients with GEP-NETs, including 87 patients exposed for at least 6 months and 72 patients exposed for at least 1 year (median duration of exposure 22 months). Patients treated with SOMATULINE DEPOT had a median age of 64 years (range 30 to 83 years), 53% were men and 96% were Caucasian. Eighty-one percent of patients (83/101) in the SOMATULINE DEPOT arm and 82% of patients (82/103) in the placebo arm did not have disease progression within 6 months of enrollment and had not received prior therapy for GEP-NETs. The rates of discontinuation due to treatment-emergent adverse reactions were 5% (5/101 patients) in the SOMATULINE DEPOT arm and 3% (3/103 patients) in the placebo arm.

Table 3 compares the adverse reactions reported with an incidence of 5% and greater in patients receiving SOMATULINE DEPOT 120 mg administered every 4 weeks and reported more commonly than placebo.

Table 3: Adverse Reactions Occurring in 5% and Greater of SOMATULINE DEPOT-Treated Patients and at a Higher Rate Than in Placebo-Treated Patients in Study 3

Adverse Reaction	SOMATULINE DEPOT 120 mg N=101		Placebo N=103	
	Any (%)	Severe** (%)	Any (%)	Severe** (%)
Any Adverse Reactions	**88**	**26**	**90**	**31**
Abdominal pain[1]	34*	6*	24*	4
Musculoskeletal pain[2]	19*	2*	13	2
Vomiting	19*	2*	9*	2*
Headache	16	0	11	1
Injection site reaction[3]	15	0	7	0
Hyperglycemia[4]	14*	0	5	0
Hypertension[5]	14*	1*	5	0
Cholelithiasis	14*	1*	7	0
Dizziness	9	0	2*	0
Depression[6]	7	0	1	0
Dyspnea	6	0	1	0

[1] Includes preferred terms of abdominal pain, abdominal pain upper/lower, abdominal discomfort
[2] Includes preferred terms of myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain
[3] Includes preferred terms of infusion site extravasation, injection site discomfort, injection site granuloma, injections site hematoma, injection site hemorrhage, injection site induration, injection site mass, injections site nodule, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling
[4] Includes preferred terms of diabetes mellitus, glucose tolerance impaired, hyperglycemia, type 2 diabetes mellitus
[5] Includes preferred terms of hypertension, hypertensive crisis
[6] Includes preferred terms of depression, depressed mood
* Includes one or more serious adverse events (SAEs) defined as any event that results in death, is life threatening, results in hospitalization or prolongation of hospitalization, results in persistent or significant disability, results in congenital anomaly/birth defect, or may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed.** Defined as hazardous to well-being, significant impairment of function or incapacitation

Carcinoid Syndrome

The safety of SOMATULINE DEPOT 120 mg in patients with histopathologically confirmed neuroendocrine tumors and a history of carcinoid syndrome (flushing and/or diarrhea) was evaluated in Study 4, a double-blind, placebo-controlled trial. Patients were randomized to receive SOMATULINE DEPOT (N=59) or placebo (N=56) administered by deep subcutaneous injection once every 4 weeks. Patients in both arms of Study 4 had access to subcutaneous octreotide as rescue medication for symptom control.

Adverse reactions reported in Study 4 were generally similar to those reported in Study 3 for the GEP-NETs population shown in Table 3 above. Adverse reactions occurring in Study 4 in 5% and greater of SOMATULINE DEPOT-treated patients and occurring at least 5% more than in placebo-treated patients were headache (12% vs 5%, respectively), dizziness (7% vs 0%, respectively), and muscle spasm (5% vs 0%, respectively) by week 16.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay

may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to lanreotide in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Laboratory investigations of acromegalic patients treated with SOMATULINE DEPOT in clinical studies show that the percentage of patients with putative antibodies at any time point after treatment is low (less than 1% to 4% of patients in specific studies whose antibodies were tested). The antibodies did not appear to affect the efficacy or safety of SOMATULINE DEPOT.

In Study 3, development of anti-lanreotide antibodies was assessed using a radioimmunoprecipitation assay. In patients with GEP NETs receiving SOMATULINE DEPOT, the incidence of anti-lanreotide antibodies was 4% (3 of 82) at 24 weeks, 10% (7 of 67) at 48 weeks, 11% (6 of 57) at 72 weeks, and 10% (8 of 84) at 96 weeks. Assessment for neutralizing antibodies was not conducted. In Study 4, less than 2% (2 of 108) of the patients treated with SOMATULINE DEPOT developed anti-lanreotide antibodies.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SOMATULINE DEPOT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary: Steatorrhea, cholecystitis, pancreatitis
Body as a Whole: angioedema and anaphylaxis

7 DRUG INTERACTIONS

7.1 Insulin and Oral Hypoglycemic Drugs

Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when SOMATULINE DEPOT treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly *[see Warnings and Precautions (5.2)]*.

7.2 Cyclosporine

Concomitant administration of cyclosporine with SOMATULINE DEPOT may decrease the absorption of cyclosporine, and therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic drug concentrations. *[see Clinical Pharmacology (12.3)]*

7.3 Bromocriptine

Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the absorption of bromocriptine *[see Clinical Pharmacology (12.3)]*.

7.4 Bradycardia-Inducing Drugs

Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dosage adjustments of concomitant drugs may be necessary.

7.5 Drug Metabolism Interactions

The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that SOMATULINE DEPOT may have this effect, avoid other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine). Drugs metabolized by the liver may be metabolized more slowly during SOMAGULINE DEPOT treatment and dose reductions of the concomitantly administered medications should be considered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Limited available data based on postmarketing case reports with SOMATULINE DEPOT use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, decreased embryo/fetal survival was observed in pregnant rats and rabbits at subcutaneous doses 5- and 2-times the maximum recommended human dose (MRHD) of 120 mg, respectively *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
A reproductive study in pregnant rats given 30 mg/kg of lanreotide by subcutaneous injection every 2 weeks (5 times the human dose, based on body surface area comparisons) resulted in decreased embryo/fetal survival. A study in pregnant rabbits given subcutaneous injections of 0.45 mg/kg/day (2 times the human therapeutic exposures at the maximum recommended dose of 120 mg, based on comparisons of relative body surface area) shows decreased fetal survival and increased fetal skeletal/soft tissue abnormalities.

8.2 Lactation

Risk Summary
There is no information available on the presence of lanreotide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Studies show that lanreotide acetate administered subcutaneously passes into the milk of lactating rats; however, due to specifies-specific differences in lactation physiology, animal data may not

reliably predict drug levels in human milk. Because of the potential for serious adverse reactions in breastfed infants from SOMATULINE DEPOT, including effects on glucose metabolism and bradycardia, advise women not to breastfeed during treatment with SOMATULINE DEPOT and for 6 months (6 half-lives) following the last dose.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on results from animal studies conducted in female rats, SOMATULINE DEPOT may reduce fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of SOMATULINE DEPOT in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly patients with acromegaly compared with younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Studies 3 and 4, conducted in patients with neuroendocrine tumors, did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

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.

8.6 Renal Impairment

Acromegaly

Lanreotide has been studied in patients with end-stage renal function on dialysis, but has not been studied in patients with mild, moderate, or severe renal impairment. It is recommended that patients with moderate or severe renal impairment receive a starting dose of lanreotide of 60 mg. Caution should be exercised when considering patients with moderate or severe renal impairment for an extended dosing interval of SOMATULINE DEPOT 120 mg every 6 or 8 weeks *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

Neuroendocrine Tumors (NET) – Gastroenteropancreatic Neuroendocrine Tumors

No effect was observed in total clearance of lanreotide in patients with mild to moderate renal impairment receiving SOMATULINE DEPOT 120 mg. Patients with severe renal impairment were not studied *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Acromegaly

It is recommended that patients with moderate or severe hepatic impairment receive a starting dose of lanreotide of 60 mg. Caution should be exercised when considering patients with moderate or severe hepatic impairment for an extended dosing interval of SOMATULINE DEPOT 120 mg every 6 or 8 weeks *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

Neuroendocrine Tumors (NET) – Gastroenteropancreatic Neuroendocrine Tumors

SOMATULINE DEPOT has not been studied in patients with hepatic impairment.

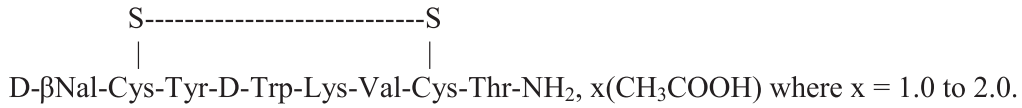
11 DESCRIPTION

SOMATULINE DEPOT (lanreotide) Injection 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL is a prolonged-release formulation for deep subcutaneous injection. It contains the drug substance lanreotide acetate, a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin, water for injection and acetic acid (for pH adjustment).

SOMATULINE DEPOT is available as sterile, ready-to-use, single-dose prefilled syringes containing lanreotide acetate supersaturated bulk solution of 24.6% w/w lanreotide base.

Each syringe contains:	**SOMATULINE DEPOT 60 mg/0.2 mL**	**SOMATULINE DEPOT 90 mg/0.3 mL**	**SOMATULINE DEPOT 120 mg/0.5 mL**
Lanreotide acetate	77.9 mg	113.6 mg	149.4 mg
Acetic Acid	q.s.	q.s.	q.s.
Water for injection	186.6 mg	272.3 mg	357.8 mg
Total Weight	266 mg	388 mg	510 mg

Lanreotide acetate is a synthetic cyclical octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate is chemically known as [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate salt. Its molecular weight is 1096.34 (base) and its amino acid sequence is:



The SOMATULINE DEPOT in the prefilled syringe is a white to pale yellow, semi-solid formulation.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lanreotide, the active component of SOMATULINE DEPOT is an octapeptide analog of natural somatostatin. The mechanism of action of lanreotide is believed to be similar to that of natural somatostatin.

12.2 Pharmacodynamics

Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3, and 4. Activity at human SSTR2 and 5 is the primary mechanism believed responsible for GH inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions.

The primary pharmacodynamic effect of lanreotide is a reduction of GH and/or IGF-1 levels enabling normalization of levels in acromegalic patients *[see Clinical Studies (14.1)]*. In acromegalic patients, lanreotide reduces GH levels in a dose-dependent way. After a single injection of SOMATULINE DEPOT, plasma GH levels fall rapidly and are maintained for at least 28 days.

In Study 4, patients with carcinoid syndrome treated with SOMATULINE DEPOT 120 mg every 4 weeks had reduced levels of urinary 5-hydroxyindoleacetic acid (5-HIAA) compared with placebo *[see Clinical Studies (14.3)]*.

Lanreotide inhibits the basal secretion of motilin, gastric inhibitory peptide, and pancreatic polypeptide, but has no significant effect on the secretion of secretin. Lanreotide inhibits postprandial secretion of pancreatic polypeptide, gastrin, and cholecystokinin (CCK). In healthy subjects, lanreotide produces a reduction and a delay in postprandial insulin secretion, resulting in transient, mild glucose intolerance.

Lanreotide inhibits meal-stimulated pancreatic secretions, and reduces duodenal bicarbonate and amylase concentrations, and produces a transient reduction in gastric acidity.

Lanreotide has been shown to inhibit gallbladder contractility and bile secretion in healthy subjects *[see Warnings and Precautions (5.1)]*.

In healthy subjects, lanreotide inhibits meal-induced increases in superior mesenteric artery and portal venous blood flow, but has no effect on basal or meal-stimulated renal blood flow. Lanreotide has no effect on renal plasma flow or renal vascular resistance. However, a transient decrease in glomerular filtration rate (GFR) and filtration fraction has been observed after a single injection of lanreotide.

In healthy subjects, non-significant reductions in glucagon levels were seen after lanreotide administration. In diabetic non-acromegalic subjects receiving a continuous infusion (21-day) of lanreotide, serum glucose concentrations were temporarily decreased by 20% to 30% after the start and end of the infusion. Serum glucose concentrations returned to normal levels within 24 hours. A significant decrease in insulin concentrations was recorded between baseline and Day 1 only *[see Warnings and Precautions (5.2)]*.

Lanreotide inhibits the nocturnal increase in thyroid-stimulating hormone (TSH) seen in healthy subjects. Lanreotide reduces prolactin levels in acromegalic patients treated on a long-term basis *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

SOMATULINE DEPOT is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption to the bloodstream.

After a single, deep subcutaneous administration, the mean absolute bioavailability of SOMATULINE DEPOT in healthy subjects was 73.4, 69.0, and 78.4% for the 60 mg, 90 mg, and 120 mg doses, respectively. Mean C_{max} values ranged from 4.3 to 8.4 ng/mL during the first day. Single-dose linearity was demonstrated with respect to AUC and C_{max}, and showed high inter-subject variability. SOMATULINE DEPOT showed sustained release of lanreotide with a half-life of 23 to 30 days. Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL at 60 mg.

In studies evaluating excretion, <5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in feces, indicative of some biliary excretion.

Acromegaly

In a repeat-dose administration pharmacokinetics (PK) study in acromegalic patients, rapid initial release was seen giving peak levels during the first day after administration. At doses of SOMATULINE DEPOT between 60 and 120 mg, linear pharmacokinetics were observed in acromegalic patients. At steady state, mean C_{max} values were 3.8 ± 0.5, 5.7 ± 1.7, and 7.7 ± 2.5 ng/mL, increasing linearly with dose. The mean accumulation ratio index was 2.7, which is in line with the range of values for the half-life of SOMATULINE DEPOT. The steady-state trough serum lanreotide concentrations in patients receiving SOMATULINE DEPOT every 28 days were 1.8 ± 0.3; 2.5 ± 0.9 and 3.8 ± 1.0 ng/mL at 60 mg, 90 mg, and 120 mg doses, respectively. A limited initial burst effect and a low peak-to-trough fluctuation (81% to 108%) of the serum concentration at the plateau were observed.

For the same doses, similar values were obtained in clinical studies after at least four administrations (2.3 ± 0.9, 3.2 ± 1.1, and 4.0 ± 1.4 ng/mL, respectively).

Pharmacokinetic data from studies evaluating extended dosing use of SOMATULINE DEPOT 120 mg demonstrated mean steady-state, C_{min} values between 1.6 and 2.3 ng/mL for the 8- and 6-week treatment interval, respectively.

Gastroenteropancreatic Neuroendocrine Tumors

In patients with GEP-NETs treated with SOMATULINE DEPOT 120 mg every 4 weeks, steady state concentrations were reached after 4 to 5 injections and the mean trough serum lanreotide concentrations at steady state ranged from 5.3 to 8.6 ng/mL.

Specific Populations

SOMATULINE DEPOT has not been studied in specific populations. However, the pharmacokinetics of lanreotide in renal impaired, hepatic impaired, and geriatric subjects were evaluated after IV administration of lanreotide immediate release formulation (IRF) at 7 mcg/kg dose.

Geriatric

Studies in healthy elderly subjects showed an 85% increase in half-life and a 65% increase in mean residence time (MRT) of lanreotide compared to those seen in healthy young subjects; however, there was no change in either AUC or C_{max} of lanreotide in elderly as compared to healthy young subjects. Age has no effect on clearance of lanreotide based on population PK analysis in patients with GEP-NET which included 122 patients aged 65 to 85 years with neuroendocrine tumors.

Renal Impairment

An approximate 2-fold decrease in total serum clearance of lanreotide, with a consequent 2-fold increase in half-life and AUC was observed. Patients with acromegaly and with moderate to severe renal impairment should begin treatment with SOMATULINE DEPOT 60 mg. Caution should be exercised when considering patients with moderate or severe renal impairment for an extended dosing interval of SOMATULINE DEPOT 120 mg every 6 or 8 weeks.

Mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment has no effect on clearance of lanreotide in patients with GEP-NET based on population PK analysis which included 106 patients with mild and 59 patients with moderate renal impairment treated with SOMATULINE DEPOT. GEP-NET patients with severe renal impairment (CLcr < 30 mL/min) were not studied.

Hepatic Impairment

In subjects with moderate to severe hepatic impairment, a 30% reduction in clearance of lanreotide was observed. Patients with acromegaly and with moderate to severe hepatic impairment should begin treatment with SOMATULINE DEPOT 60 mg. Caution should be exercised when considering patients with moderate or severe hepatic impairment for an extended dosing interval of SOMATULINE DEPOT 120 mg every 6 or 8 weeks.

The effect of hepatic impairment on clearance of lanreotide has not been studied in patients with GEP-NET.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily subcutaneous doses of lanreotide at 0.5, 1.5, 5, 10, and 30 mg/kg for 104 weeks. Cutaneous and subcutaneous tumors of fibrous connective tissues at the injection sites were observed at the high dose of 30 mg/kg/day. Fibrosarcomas in both genders and malignant fibrous histiocytomas were observed in males at 30 mg/kg/day resulting in exposures 3 times higher than the clinical therapeutic exposure at the maximum therapeutic dose of 120 mg given by monthly subcutaneous injection based on the AUC values. Rats were given daily subcutaneous doses of lanreotide at 0.1, 0.2, and 0.5 mg/kg for 104 weeks. Increased cutaneous and subcutaneous tumors of fibrous connective tissues at the injection sites were observed at the dose of 0.5 mg/kg/day resulting in exposures less than the clinical therapeutic exposure at 120 mg given by monthly subcutaneous injection. The increased incidence of injection site tumors in rodents is likely related to the increased dosing frequency (daily) in animals compared to monthly dosing in humans and therefore may not be clinically relevant.

Lanreotide was not genotoxic in tests for gene mutations in a bacterial mutagenicity (Ames) assay, or mouse lymphoma cell assay with or without metabolic activation. Lanreotide was

not genotoxic in tests for the detection of chromosomal aberrations in a human lymphocyte and *in vivo* mouse micronucleus assay.

In a fertility study conducted with lanreotide in rats, reduced female fecundity was observed at estimated exposure corresponding to approximately 10-fold the plasma exposure at the MRHD of 120 mg. The fertility of male rats was unaffected by the treatment up to an estimated exposure corresponding to approximately 11-fold the plasma exposure at the MRHD of 120 mg.

14 CLINICAL STUDIES

14.1 Acromegaly

The effect of SOMATULINE DEPOT on reducing GH and IGF-levels and control of symptoms in patients with acromegaly was studied in 2 long-term, multiple-dose, randomized, multicenter studies.

Study 1

This 1-year study included a 4-week, double-blind, placebo-controlled phase; a 16-week single-blind, fixed-dose phase; and a 32-week, open-label, dose-titration phase. Patients with active acromegaly, based on biochemical tests and medical history, entered a 12-week washout period if there was previous treatment with a somatostatin analog or a dopaminergic agonist.

Upon entry, patients were randomly allocated to receive a single, deep subcutaneous injection of SOMATULINE DEPOT 60, 90, or 120 mg or placebo. Four weeks later, patients entered a fixed-dose phase where they received 4 injections of SOMATULINE DEPOT followed by a dose-titration phase of 8 injections for a total of 13 injections over 52 weeks (including the placebo phase). Injections were given at 4-week intervals. During the dose-titration phase of the study, the dose was titrated twice (every fourth injection), as needed, according to individual GH and IGF-1 levels.

A total of 108 patients (51 males, 57 females) were enrolled in the initial placebo-controlled phase of the study. Half (54/108) of the patients had never been treated with a somatostatin analog or dopamine agonist, or had stopped treatment for at least 3 months prior to their participation in the study and were required to have a mean GH level greater than 5 ng/mL at their first visit. The other half of the patients had received prior treatment with a somatostatin analog or a dopamine agonist before study entry and at study entry were required to have a mean GH concentration greater than 3 ng/mL and at least a 100% increase in mean GH concentration after washout of medication.

One hundred and seven (107) patients completed the placebo-controlled phase, 105 patients completed the fixed-dose phase, and 99 patients completed the dose-titration phase. Patients not completing withdrew due to adverse events (5) or lack of efficacy (4).

In the double-blind phase of Study 1, a total of 52 (63%) of the 83 lanreotide-treated patients had a greater than 50% decrease in mean GH from baseline to Week 4, including 52%, 44%, and 90% of patients in the 60, 90, and 120 mg groups, respectively, compared to placebo (0%, 0/25). In the fixed-dose phase at Week 16, 72% of all 107 lanreotide-treated patients

had a decrease from baseline in mean GH of greater than 50%, including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60, 90, and 120 mg lanreotide treatment groups, respectively. Efficacy achieved in the first 16 weeks was maintained for the duration of the study (see Table 4).

Table 4: Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 1

		Baseline N=107	Before Titration 1 (16 weeks) N=107	Before Titration 2 (32 weeks) N=105	Last Value Available* N=107
GH					
≤5.0 ng/mL	Number of Responders (%)	20 (19%)	72 (67%)	76 (72%)	74 (69%)
≤2.5 ng/mL	Number of Responders (%)	0 (0%)	52 (49%)	59 (56%)	55 (51%)
≤1.0 ng/mL	Number of Responders (%)	0 (0%)	15 (14%)	18 (17%)	17 (16%)
Median GH	ng/mL	10.27	2.53	2.20	2.43
GH Reduction	Median % Reduction	--	75.5	78.2	75.5
IGF-1					
Normal[3]	Number of Responders (%)	9 (8%)	58 (54%)	57 (54%)	62 (58%)
Median IGF-1	ng/mL	775.0	332.0[1]	316.5[2]	326.0
IGF-1 Reduction	Median % Reduction	--	52.3[1]	54.5[2]	55.4
IGF-1 Normal[3] + GH ≤2.5 ng/mL	Number of Responders (%)	0 (0%)	41 (38%)	46 (44%)	44 (41%)

[1] n=105, [2]n=102, [3]Age-adjusted
*Last Observation Carried Forward

Study 2

This was a 48-week, open-label, uncontrolled, multicenter study that enrolled patients who had an IGF-1 concentration 1.3 times or greater than the upper limit of the normal age-adjusted range. Patients receiving treatment with a somatostatin analog (other than SOMATULINE DEPOT) or a dopaminergic agonist had to attain this IGF-1 concentration after a washout period of up to 3 months.

Patients were initially enrolled in a 4-month, fixed-dose phase where they received 4 deep subcutaneous injections of SOMATULINE DEPOT 90 mg, at 4-week intervals. Patients then entered a dose-titration phase where the dose of SOMATULINE DEPOT was adjusted based on GH and IGF-1 levels at the beginning of the dose-titration phase and, if necessary, again after another 4 injections. Patients titrated up to the maximum dose (120 mg) were not allowed to titrate down again.

A total of 63 patients (38 males, 25 females) entered the fixed-dose phase of the trial and 57 patients completed 48 weeks of treatment. Six patients withdrew due to adverse reactions (3), other reasons (2), or lack of efficacy (1).

After 48 weeks of treatment with SOMATULINE DEPOT at 4-week intervals, 43% (27/63) of the acromegalic patients in this study achieved normal age-adjusted IGF-1 concentrations. Mean IGF-1 concentrations after treatment completion were 1.3 ± 0.7 times the upper limit of normal compared to 2.5 ± 1.1 times the upper limit of normal at baseline.

The reduction in IGF-1 concentrations over time correlated with a corresponding marked decrease in mean GH concentrations. The proportion of patients with mean GH concentrations less than 2.5 ng/mL increased significantly from 35% to 77% after the fixed-dose phase and 85% at the end of the study. At the end of treatment, 24/63 (38%) of patients had both normal IGF-1 concentrations and a GH concentration of less than or equal to 2.5 ng/mL (see Table 5) and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of less than 1 ng/mL.

Table 5: Overall Efficacy Results Based on GH and IGF-1 Levels by Treatment Phase in Study 2

		Baseline N=63	Before Titration 1 (12 wks) N=63	Before Titration 2 (28 wks) N=59	Last Value Available* N=63
IGF-1					
Normal[1]	Number of Responders (%)	0 (0%)	17 (27%)	22 (37%)	27 (43%)
Median IGF-1	ng/mL	689.0	382.0	334.0	317.0
IGF-1 Reduction	Median % Reduction	--	41.0	51.0	50.3
GH					
≤5.0 ng/mL	Number of Responders (%)	40 (64%)	59 (94%)	57 (97%)	62 (98%)
≤2.5 ng/mL	Number of Responders (%)	21 (33%)	47 (75%)	47 (80%)	54 (86 %)
≤1.0 ng/mL	Number of Responders (%)	8 (13%)	19 (30%)	18 (31%)	28 (44%)
Median GH	ng/Ml	3.71	1.65	1.48	1.13
GH Reduction	Median % Reduction	--	63.2	66.7	78.6[2]
IGF-1 normal[1] **+ GH ≤2.5 ng/mL**	Number of Responders (%)	0 (0%)	14 (22%)	20 (34%)	24 (38%)

[1] Age-adjusted, [2]N= 62,
* Last Observation Carried Forward

Examination of age and gender subgroups did not identify differences in response to SOMATULINE DEPOT among these subgroups. The limited number of patients in the different racial subgroups did not raise any concerns regarding efficacy of SOMATULINE DEPOT in these subgroups.

14.2 Gastroenteropancreatic Neuroendocrine Tumors

The efficacy of SOMATULINE DEPOT was established in a multicenter, randomized, double-blind, placebo-controlled trial of 204 patients with unresectable, well or moderately differentiated, metastatic or locally advanced, gastroenteropancreatic neuroendocrine tumors. Patients were required to have non-functioning tumors without hormone-related symptoms.

Patients were randomized 1:1 to receive SOMATULINE DEPOT 120 mg (n=101) or placebo (n=103) every 4 weeks until disease progression, unacceptable toxicity, or a maximum of 96 weeks of treatment. Randomization was stratified by the presence or absence of prior therapy and by the presence or absence of disease progression within 6 months of enrollment. The major efficacy outcome measure was progression-free survival (PFS), defined as time to disease progression as assessed by central independent radiological review using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) or death.

The median patient age was 63 years (range 30 to 92 years) and 95% were Caucasian. Disease progression was present in nine of 204 patients (4.4%) in the 6 months prior to enrollment and 29 patients (14%) received prior chemotherapy. Ninety-one patients (45%) had primary sites of disease in the pancreas, with the remainder originating in the midgut (35%), hindgut (7%), or unknown primary location (13%). The majority (69%) of the study population had grade 1 tumors. Baseline prognostic characteristics were similar between arms with one exception; there were 39% of patients in the SOMATULINE DEPOT arm and 27% of patients in the placebo arm who had hepatic involvement by tumor of greater than 25%.

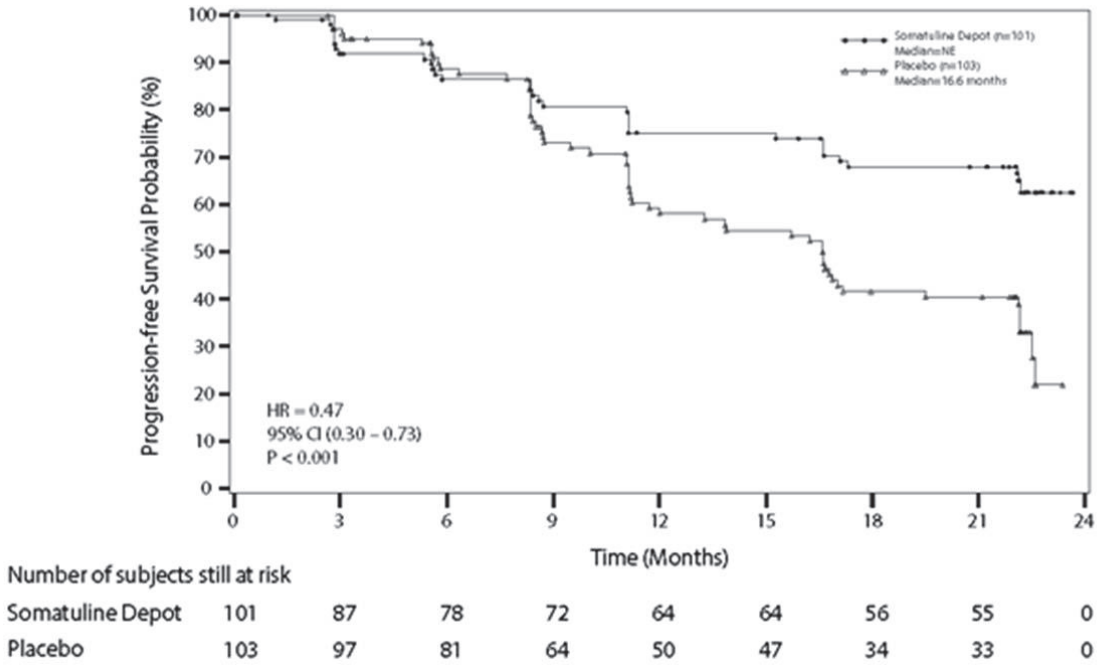
Patients on the SOMATULINE DEPOT arm had a statistically significant improvement in PFS compared to patients receiving placebo (see Table 6 and Figure 1).

Table 6: Efficacy Results in Study 3

	SOMATULINE DEPOT	Placebo
	n=101	n=103
Number of Events (%)	32 (31.7%)	60 (58.3%)
Median PFS (months)(95% CI)	NE[1] (NE, NE)	16.6 (11.2, 22.1)
HR (95% CI)	0.47 (0.30, 0.73)[2]	
Log-rank p-value	<0.001	

[1] NE = not reached at 22 months
[2] Hazard Ratio is derived from a Cox stratified proportional hazards model

Figure 1: Kaplan-Meier Curves of Progression-Free Survival



Number of subjects still at risk									
Somatuline Depot	101	87	78	72	64	64	56	55	0
Placebo	103	97	81	64	50	47	34	33	0

14.3 Carcinoid Syndrome

Study 4 was a multicenter, randomized, 16-week, double-blind, placebo-controlled trial in 115 patients with histopathologically-confirmed neuroendocrine tumors and a history of carcinoid syndrome (flushing and/or diarrhea) who were treatment naïve or stable on another somatostatin analog and who were randomized 1:1 to receive SOMATULINE DEPOT 120 mg (n=59) or placebo (n=56) by deep subcutaneous injection every 4 weeks. Patients were instructed to self-administer a short-acting somatostatin analog (octreotide) as rescue medication as needed for symptom control. The use of rescue therapy and the severity and frequency of diarrhea and flushing symptoms were reported daily in electronic patient diaries. During the 16 week double-blind phase, the primary efficacy outcome measure was the percentage of days in which patients administered at least one injection of rescue medication for symptom control. Average daily frequencies of diarrhea and flushing events were assessed secondarily.

The patient population had a mean age of 59 years (range 27 to 85 years), 58% were female and 77% were Caucasian. Patients in the SOMATULINE DEPOT arm experienced 15% fewer days on rescue medication compared to patients in the placebo arm (34% vs. 49% of days, respectively; p=0.02). The average daily frequencies of diarrhea and flushing events in patients treated with SOMATULINE DEPOT (and rescue medication) were numerically lower relative to patients treated with placebo (and rescue medication), but were not statistically significantly different via hierarchical testing.

16 HOW SUPPLIED/STORAGE AND HANDLING

SOMATULINE DEPOT is supplied in strengths of 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL as a white to pale yellow, semi-solid formulation in a single, sterile, prefilled, ready-to-use, polypropylene syringe (fitted with an automatic needle guard) fitted with a 20 mm needle covered by a low density polythylene sheath.

Each prefilled syringe is sealed in a laminated pouch and packed in a carton.

NDC 15054-1060-3	60 mg/0.2 mL, sterile, prefilled syringe
NDC 15054-1090-3	90 mg/0.3 mL, sterile, prefilled syringe
NDC 15054-1120-3	120 mg/0.5 mL, sterile, prefilled syringe

Storage and Handling

Store SOMATULINE DEPOT in the refrigerator at 2°C to 8°C (36°F to 46°F).

Protect from light.

Store in the original package.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions
Advise patients to immediately contact their healthcare provider if they experience serious hypersensitivity reactions, such as angioedema or anaphylaxis *[see Contraindications (4)]*.

Cholelithiasis and Gallbladder Sludge
Advise patients to contact their healthcare provider if they experience signs or symptoms of gallstones *[see Warnings and Precautions (5.1)]*.

Hyperglycemia and Hypoglycemia
Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of hyper- or hypoglycemia *[see Warnings and Precautions (5.2)]*.

Cardiovascular Abnormalities
Advise patients to immediately contact their healthcare provider if they experience bradycardia *[see Warnings and Precautions (5.3)]*.

Thyroid Function Abnormalities
Advise patients to contact their healthcare provider if they experience signs or symptoms of hypothyroidism *[see Warnings and Precautions (5.4)]*.

Laboratory Tests
Advise patients with acromegaly that response to SOMATULINE DEPOT should be monitored by periodic measurements of GH and IGF-1 levels, with a goal of decreasing these levels to the normal range *[see Dosage and Administration (2.2)]*.

Lactation
Advise women not to breastfeed during treatment with SOMATULINE DEPOT and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females of reproductive potential of the potential for reduced fertility from SOMATULINE DEPOT *[see Use in Specific Populations (8.3)]*.

Manufactured by:
Ipsen Pharma Biotech
83870 Signes, France

Distributed by:
Ipsen Biopharmaceuticals, Inc.
Basking Ridge, NJ 07920 USA

Patient Information
SOMATULINE® DEPOT (So-mah-tu-leen Dee-Poh)
(lanreotide) injection

Read this Patient Information before you receive your first SOMATULINE DEPOT injection and before each injection. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is SOMATULINE DEPOT?

SOMATULINE DEPOT is a prescription medicine used for:

- the long-term treatment of people with acromegaly when:
  - surgery or radiotherapy have not worked well enough or
  - they are not able to have surgery or radiotherapy
- the treatment of adults with a type of cancer known as neuroendocrine tumors, from the gastrointestinal tract or the pancreas (GEP-NETs) that has spread or cannot be removed by surgery
- the treatment of adults with carcinoid syndrome to reduce the need for the use of short-acting somatostatin medicine

It is not known if SOMATULINE DEPOT is safe and effective in children.

Who should not receive SOMATULINE DEPOT?

Do not receive SOMATULINE DEPOT if you are allergic to lanreotide.

What should I tell my healthcare provider before receiving SOMATULINE DEPOT?

Before you receive SOMATULINE DEPOT, tell your healthcare provider about all of your medical conditions, including if you:

- have gallbladder problems
- have diabetes
- have heart problems
- have thyroid problems
- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if SOMATULINE DEPOT will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOMATULINE DEPOT passes into your breast milk. You should not breastfeed if you receive SOMATULINE DEPOT and for 6 months after your last dose of SOMATULINE DEPOT.
- are a female who can become pregnant. SOMATULINE DEPOT may affect fertility in females and may affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SOMATULINE DEPOT and other medicines may affect each other, causing side effects. SOMATULINE DEPOT may affect the way other medicines work, and other medicines may affect how SOMATULINE DEPOT works. Your dose of SOMATULINE DEPOT or your other medicines may need to be changed.

Especially tell your healthcare provider if you take:

- insulin or other diabetes medicines
- cyclosporine (Gengraf, Neoral, or Sandimmune)
- medicines that lower your heart rate such as beta blockers

How will I receive SOMATULINE DEPOT?

- You will receive a SOMATULINE DEPOT injection every 4 weeks in your healthcare provider's office.
- Your healthcare provider may change your dose of SOMATULINE DEPOT or the length of time between your injections. Your healthcare provider will tell you how long you need to receive SOMATULINE DEPOT.
- SOMATULINE DEPOT is injected deep under the skin of the upper outer area of your buttock. Your injection site should change (alternate) between your right and left buttock from one injection of SOMATULINE DEPOT to the next.
- During your treatment with SOMATULINE DEPOT for acromegaly, your healthcare provider may do certain blood tests to see if SOMATULINE DEPOT is working.

What should I avoid while receiving SOMATULINE DEPOT?
SOMATULINE DEPOT can cause dizziness. If you have dizziness, do not drive a car or operate machinery.

What are the possible side effects of SOMATULINE DEPOT?
SOMATULINE DEPOT may cause serious side effects, including:

- **Gallstones.** Gallstones can happen in people who receive SOMATULINE DEPOT and are a common side effect in people with acromegaly and GEP-NET. Tell your healthcare provider if you get any symptoms of gallstones, including:
  - sudden pain in your upper right stomach area (abdomen)
  - sudden pain in your right shoulder or between your shoulder blades
  - yellowing of your skin and whites of your eyes
  - fever with chills
  - nausea
- **Changes in your blood sugar** (high blood sugar or low blood sugar). If you have diabetes, test your blood sugar as your healthcare provider tells you to. Your healthcare provider may change your dose of diabetes medicine especially when you first start receiving SOMATULINE DEPOT or if your dose of SOMATULINE DEPOT changes. High blood sugar is a common side effect in people with GEP-NET. Tell your healthcare provider right away if you have any signs or symptoms of high blood sugar or low blood sugar.

  Signs and symptoms of high blood sugar may include:
  - increased thirst
  - increased appetite
  - nausea
  - weakness or tiredness
  - urinating more often than normal
  - your breath smells like fruit

  Signs and symptoms of low blood sugar may include:
  - dizziness or lightheadedness
  - sweating
  - confusion
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - irritability or mood changes
  - hunger
- **Slow heart rate.** Tell your healthcare provider right away if you have slowing of your heart rate or if you have symptoms of a slow heart rate, including:
  - dizziness or lightheadedness
  - fainting or near-fainting
  - chest pain
  - shortness of breath
  - confusion or memory problems
  - weakness, extreme tiredness
- **High blood pressure.** High blood pressure can happen in people who receive SOMATULINE DEPOT and is a common side effect in people with GEP-NET.
- **Changes in thyroid function.** SOMATULINE DEPOT can cause the thyroid gland to not make enough thyroid hormones that the body needs (hypothyroidism) in people who have acromegaly. Tell your healthcare provider if you have signs and symptoms of low thyroid hormones levels, including:
  - fatigue
  - weight gain
  - a puffy face
  - being cold all of the time
  - constipation
  - dry skin
  - thinning, dry hair
  - decreased sweating
  - depression

The most common side effects of SOMATULINE DEPOT in people with acromegaly include:
- diarrhea
- stomach area (abdominal) pain
- nausea
- pain, itching, or a lump at the injection site

The most common side effects of SOMATULINE DEPOT in people with GEP-NET include:
- stomach area (abdominal) pain
- muscle and joint aches
- vomiting
- headache
- pain, itching, or a lump at the injection site

The most common side effects of SOMATULINE DEPOT in people with carcinoid syndrome include:
- headache
- dizziness
- muscle spasm

Tell your healthcare provider right away if you have signs of an allergic reaction after receiving SOMATULINE DEPOT, including:

- swelling of your face, lips, mouth or tongue
- breathing problems
- fainting, dizziness, feeling lightheaded (low blood pressure)
- itching
- flushing or redness of your skin
- rash
- hives

These are not all the possible side effects of SOMATULINE DEPOT. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of SOMATULINE DEPOT.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not receive SOMATULINE DEPOT for a condition for which it was not prescribed. You can ask your healthcare provider for information about SOMATULINE DEPOT that is written for health professionals.

What are the ingredients in SOMATULINE DEPOT?

Active ingredient: lanreotide acetate

Inactive ingredients: water for injection and acetic acid (for pH adjustment)

Manufactured by: Ipsen Pharma Biotech, Parc d'Activities du Plateau de Signes, 83870 Signes, France
Manufactured for: Ipsen Biopharmaceuticals, Inc., 106 Allen Road, Basking Ridge, NJ 07920 USA.

For more information, go to www.somatulinedepot.com or call Ipsen Biopharmaceuticals, Inc. at 1-866 837-2422.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

SUMMARY REVIEW

Joint Clinical Team Leader/Division Director Review

Date	September 15, 2007
From	Victor Baum, M.D. , Acting Team Leader, DGIEP Dragos Roman, M.D., Deputy Director, DGIEP
Subject	Joint Clinical Team Leader and Division Director Review
NDA/BLA # **Supplement#**	NDA 022074 S-017
Applicant	Ipsen Biopharmaceuticals, Inc.
Date of Submission	August 15, 2016
PDUFA Goal Date	Originally June 15, 2017. Revised to September 15, 2017 due to submission of major amendment on May 11, 2017
Proprietary Name / Non-Proprietary Name	Somatuline Depot/ lanreotide acetate
Dosage form(s) / Strength(s)	Injectable (b) (6)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Somatuline Depot (lanreotide acetate) is a long-acting somatostatin analogue, currently approved in the U.S. for the treatment of acromegaly and for improvement of progression-free survival in patients with gastroenteropancreatic neuroendocrine tumors. It has been on the market in the US since 2007. This efficacy supplement proposes a new indication (b) (4) (b) (4). Approximately 80% of patients with carcinoid syndrome have diarrhea and approximately 90% have flushing (b) (4) (b) (4)

The efficacy of Somatuline Depot in patients with carcinoid syndrome has been evaluated in one study (Study 730). This was a multicenter trial that enrolled 115 adult subjects randomized to receive either lanreotide 120 mg or placebo by deep subcutaneous injection every 28 days for a 16 week double-blind period. The primary efficacy endpoint was the percent of days during which rescue octreotide use was required to control carcinoid-related symptoms. Key secondary endpoints were the average daily frequencies of diarrhea and flushing events.

Based on the prespecified statistical analysis, patients receiving lanreotide had a 14.8% reduction in days of rescue octreotide use compared to patients given placebo (p=0.165). The study failed to show efficacy of lanreotide in the first key secondary endpoint, the average daily frequency of diarrhea. The results for the second key secondary endpoint, the average frequency of flushing episodes, reached nominal significance; (b) (4)

Analysis for efficacy was complicated by a high dropout rate during the double-blind treatment phase of the trial. This was attributed to the fact that the protocol allowed for early roll over of subjects from the double-blind phase to an open-label phase after 4 weeks (the study lasted 16 weeks). There was an imbalance in the numbers of placebo and lanreotide patients who rolled over. This resulted in a complicated data analysis and disagreement between the clinical and statistical reviewers regarding the strength of evidence. While fully recognizing the issues generated by missing data, we conclude that the efficacy response to Somatuline was greater than placebo.

We are in full agreement with the statistical reviewers that the Applicant has not provided robust evidenc (b) (4)

(b) (4)

(b) (4)

medication with octreotide (which is supported by evidence (b) (4)

(b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Carcinoid tumors are tumors of neuroendocrine cell origin predominantly arising in the gastrointestinal tract. • Carcinoid tumors produce a variety of bioactive amines and peptides. These are metabolized when circulated through the liver. Hepatic metastases or extra-gastrointestinal location of tumors bypasses this metabolism, allowing these products to reach the systemic circulation. • Exposure via the central circulation results in episodic diarrhea and flushing (carcinoid syndrome). • Carcinoid tumors occur predominantly in adults.	Carcinoid syndrome is a serious condition associated with diminished quality of life.
Current Treatment Options	• Somatostatin analogues are standard of care in the treatment of symptomatic carcinoid syndrome. Approved drugs include: Sandostatin (a short acting form of octreotide), Sandostatin LAR (a long-acting form of octreotide), and recently Xermelo (a tryptophan hydroxylase inhibitor). • The approved indication for Sandostatin/Sandostatin LAR is reduction of diarrhea and flushing associated with carcinoid syndrome. • The approved indication for Xermelo is treatment of carcinoid syndrome associated diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.	• Somatuline is a synthetic depot formulation of the somatostatin analogue lanreotide.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• 80% of carcinoid syndrome patients have diarrhea and 90% have flushing. • In the "pivotal" clinical trial (Study 730), 59 patients received monthly doses of Somatuline (120 mg by deep subcutaneous injection) for 16 weeks and were compared to 56 patients who received placebo. • The primary efficacy endpoint was days (percent of total days) requiring rescue octreotide to control symptoms. • Lanreotide had a statistically significant 14.8% reduction in days of octreotide use compared to patients given placebo. • Patients were allowed to leave the double-blind phase and enter an open-label trial of Somatuline after 4 weeks of drug or placebo. This early removal complicated the statistical analysis of efficacy and required imputation of substantial missing data. • There were differences in the interpretation of the efficacy study results between the statistical and clinical reviewers. • Additional statistical analyses were necessary to investigare the impact of missing data and reach a conclusion of effectiveness for the proposed patient population. The overall response to Somatuline, following multiple additional sensitivity analyses, favored Somatuline over placebo. • Only a single "pivotal" trial was submitted (carcinoid syndrome is a rare disease).	• (b) (4) • Somatuline decreased the number of breakthrough days (i.e. days requiring any injections of octreotide to control symptoms) compared to placebo. • Given that the affinity of somatuline and octreotide for the somatostatin receptors is not identical, approval of somatuline would provide additional option (b) (4) (b) (4)
Risk	• The treatment-emergent adverse events were manageable.	• The safety data submitted are adequate to support this new indication. This conclusion is based on the availability of placebo-controlled safety data from Study 730, the additional safety data from an extension trial, and the relatively well characterized safety profile of somatuline in other indications (acromegaly and neuroendocrine tumors).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• No new risks were identified.
Risk Management	• Since no new risks were identified, a REMS (Risk Evaluation and Mitigation Strategy) is not required.	• The potential safety risks associated with the use of Somatuline can be addressed via routine labeling.

2. Introduction and Background

Somatuline Depot Injection is a long-acting somatostatin analogue approved initially in the U.S. for the long-term treatment of patients with acromegaly (NDA 22074, approved August 30, 2007). On December 16, 2014, Somatuline was also approved for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (NET) to improve progression-free survival. The applicant is submitting this supplement to add to the label a new indication (b) (4) (b) (4) Please note that in this memorandum, for simplicity, Somatuline Depot Injection will be referred to as Somatuline or lanreotide, unless otherwise specified.

The Applicant submitted a single "pivotal" clinical trial in support of this new indication - Study 730 - a multicenter, randomized, double-blind (DB), 16-week, placebo-controlled phase 3 clinical trial. Efficacy for the proposed indication is claimed based on the results of the primary efficacy analysis of Study 730, which was a comparison with placebo of the frequency of octreotide rescue treatment for breakthrough carcinoid symptoms.

Central to the review of this application is the challenge genrerated by the considerable amount of missing data. At the end-of-phase 2 meeting on July 15, 2008, the Applicant discussed incorporating an"early [patient] roll over" into an open-label study extension protocol. The purpose of early roll over was to remove patients from the DB phase if they did not respond the treatment, switch them to active treatment (lanreotide 120 mg monthly) and collect additional safety data. The criteria for early roll over were defined as "after at least 4 weeks in the study, patients will be allowed to roll over into the initial open label phase of the study, if they used subcutaneous octreotide for at least 21 out of 28 days of study participation, and used a dose [of octreotide] ≥300 μg per day for at least 14 out of the 21 days, regardless of the presence or absence of symptoms." As a result, a considerable proportion of patients did not complete the 16-week DB phase of the trial; this created a significant imbalance between treatment groups in the number of patients who provided data for the primary efficacy analysis, which compared Somatuline and placebo after 16 weeks of treatment. In addition, daily diaries were not uniformly maintained by the subjects, resulting in additional missing data. The amount of missing data caused a significant challenge to data analysis and interpretation (refer to the Statistical Review for details). The FDA statisticians analyzed the data using multiple imputation schemes to fully understand the impact of missing data on efficacy assessments. In addition, sensitivity efficacy analyses were conducted for the first month of treatment (a time point that reduced the impact of the early rollover on efficacy comparision).

The primary clinical reviewer concluded that "the Applicant has provided sufficient evidence (b) (4) (b) (4)", and recommended approval of Somatuline (b) (4) (b) (4)

The statistics reviewers concluded:

> *The single pivotal study reported statistically significant reduction in the primary endpoint, % of days on octreotide in lanreotide arm compared to the placebo arm*

during DB phase based on prorated data. However, there were 30 % of patients with missing data during DB phase, and the results on the primary endpoint were not robust based on various sensitivity analyses (b) (4) (b) (4)*. In conclusion, the data of this single phase 3 study cannot be used to* (b) (4) (b) (4)

This memorandum will integrate both the the statistical observations listed above and the clinical recommendation. In final analysis, we are recommending approval of Somatuline for the treatment of carcinoid syndrom (b) (4) (b) (4)

This efficacy supplement did not include any new CMC or non clinical pharmacology/toxicology information. The Clinical Pharmacology reviewer concluded that this supplemental NDA was acceptable from a clinical pharmacology perspective.

Of note, Somatuline has received orphan drug designation in 2011, and is therefore exempt from Pediatric Research Equity Act of 2007 (PREA).

3. Clinical/Statistical- Efficacy

As already mentioned, the clinical efficacy data are derived from a single phase 3, multi-institutional, double-blind, placebo-controlled trial (Study 730). In addition, one supportive open-label study (Study 718) and biomarker data from Study 726 were submitted (Table 1).

Table 1. Studies Supporting Clinical Efficacy

Study (CSR Location)	Study Design/Objectives	Number of Subjects by Treatment	Duration (Efficacy Data Presented)	Study Narrative Location
Pivotal Phase III Placebo-controlled Study				
730 (Module 5.3.5.1)	Phase III, randomised, DB, placebo-controlled, multicentre study to evaluate efficacy and safety of Somatuline in subjects with carcinoid syndrome	DB Phase: Somatuline: 59 Placebo: 56 IOL Phase: Somatuline: 101 LTOLE Phase: Somatuline: 57	16 weeks (DB phase) 32 weeks At least 2 years after last subject completed IOL phase[a]	(Section 2.1)
Supportive Phase II/III Uncontrolled Study				
718 (Module 5.3.5.2)	Phase II/III, open-label, multicentre, dose-titration study to evaluate efficacy and safety of Somatuline in subjects with carcinoid syndrome	Somatuline: 71	6 months	(Section 2.2)
Pooled Biomarker Analysis Only (Phase III Study)				
726 (Module 5.3.5.1)	Phase III, randomised, DB, placebo-controlled, multicentre study to evaluate efficacy and safety of Somatuline in subjects with non-functioning entero pancreatic endocrine tumour	Somatuline: 101 Placebo: 103	96 weeks	(Section 2.3)

CSR=Clinical Study Report; DB=double-blind; IOL=initial open-label phase; LTOLE: long-term, open-label extension

From Summary of Clinical Efficacy, Table 1, page 10 of 62

Trial 730

The main source of efficacy information in this supplement is Study 730, a 16-week, double blind, randomized, placebo-controlled clinical trial that investigated the efficacy and safety of Somatuline administered deep subcutaneously at a dose of 120 mg once a month to adult carcinoid syndrome patients. The prespecified primary efficacy compared the percentage of days with breakthrough symptoms that required rescue octreotide injections (Somatuline vs. placebo) at week 16. Of note , the protocol did not codify the criteria for the use of octreotide. Under conditions of actual clinical practice patients could use rescue medication (i.e. octreotide s.c.) whenever they felt that symptoms such as diarrhea and flusing were imminent or present. The use of octreotide was based on subject responses via interactive voice response system or web response system ("diary").

Patient population

The study enrolled adult patient with 1) a histopathologically confirmed diagnosis of carcinoid tumor or a carcinoid tumor of unknown location with liver metastases documented biopsy, AND 2) a history of carcinoid syndrome (flushing and/or diarrhea). Patients had to be stable, without evidence of tumor progression documented by two sequential CT scans or two sequential MRIs ≥3 months apart; the last CT or MRI scan had to have been performed within 6 months of study entry. Patients could be either naïve to treatment or, if previously treated, they had to have been shown to be responsive to conventional doses of long acting octreotide (Sandostatin LAR at ≤30 mg every 4 weeks) or to daily doses of ≤600 µg of short-acting octreotide (Sandostatin). For subjects previously treated with Sandostatin LAR, the last dose

must have been at least 4 weeks prior to first somatuline dose. In essence, this was a relatively stable patient population with carcinoid syndrome; the inclusion/exclusion criteria specifically prohibited enrollment of subjects with a history of carcinoid syndrome refractory to treatment with conventional doses of somatostatin analogues.

Trial design

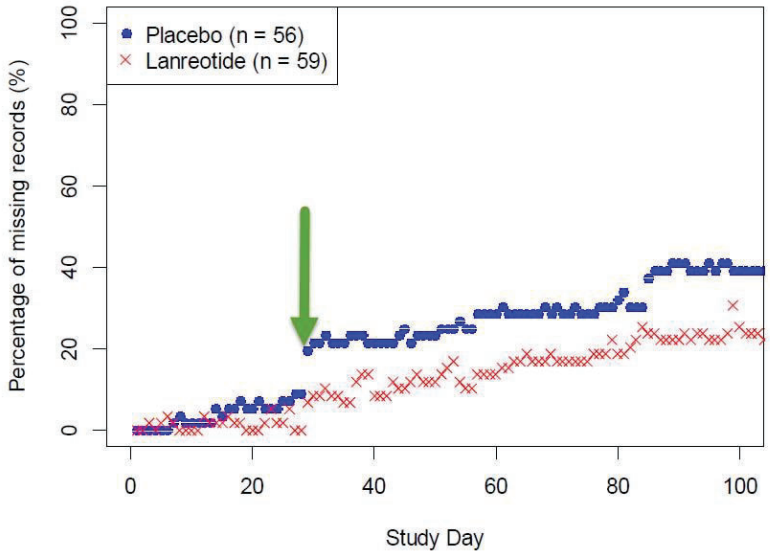
A minimum 4-week screening period was followed by a 16-week DB placebo-controlled phase. Subjects were randomized 1:1 to receive Somatuline 120 mg or placebo every 4 weeks by deep s.c. injection. The DB phase was followed by a 32 week open-label phase followed by a long-term, open-label, extension phase (for ≥2 years). Because patients assigned to placebo might develop intolerable symptoms, patients were allowed to roll over from the DB to the open-label phase. Criteria for roll-over were:

- completed at least 4 weeks of DB study,
- used subcutaneous octreotide rescue for at least 21 out of 28 days of study participation,
- and used an octreotide rescue dose ≥300 μg per day for at least 14 out of the 21 days,

"regardless of the presence or absence of symptoms."

The "roll-over" protocol provision resulted in an unanticipated number of subjects who exited the DB phase of the trial at the end of the first month (see Figure 1, below, modified from the statistical review; green arrow indicates the sudden increase in number of missing diary days coinciding with the time of subject early roll-over at around day 28). As a consequence as many as 24% of patients in the placebo arm and 39% in the Somatuline arm were counted as dropouts for the DB phase of the trial.

Figure 1 Percentage of missing daily diary data by study day during the double-blind phase (Day 1- Day100)



This unanticipated high dropout rate has posed challenges to the data interpretation and required several imputation strategies to assess the impact of dropouts on the primary efficacy analyses (discussed in detail in the Efficacy Results Section).

Baseline Patient Characteristics

Patients' characteristics appeared relatively well balanced at baseline with respect to age (mean age 58 years) and prior somatostatin therapy use (about 55% of patients in each arm used a somatostatin analog prior to enrollment). Of note, the use of rescue octreotide during the screening period (one month in duration) was 47.5% in patients later randomized to the lanreotide arm and 50% in those later randomized to placebo, suggesting comparable severity of disease in the two arms. Baseline octreotide use was calculated as the percentage of days of octreotide use during the 4 weeks of the screening period. The baseline average frequency of diarrhea plus flushing events per day was calculated as the average number of such events per day during the 4 weeks of the screening period.

The daily frequency of symptoms of flushing and diarrhea was low, consistent with the fact that this was a relatively stable patient population (i.e. patients were clinically stable on Sandostatin or immediate release octreotide, as the protocol indicated). A low number of flushing and diarrheal events at baseline provided additional challenges to efficacy analyses (of note, both flushing and diarrhea were evaluated as part of a pre-specified hierarchical efficacy analysis scheme). There were also small imbalances between the two treatment groups with respect to baseline diarrhea and flushing. (Table 2).

Table 2. Average Daily Frequency of Diarrhea and Flushing Events during Screening (ITT Population)

	Lanreotide (N=59)	**Placebo (N=56)**
Average Daily Frequency of Flushing Events		
n	59	56
Median	0.57	1.09
Mean (SD)	1.53 (1.98)	2.20 (3.27)
95% CI	(1.01, 2.04)	(1.32, 3.08)
Min, max	0.0, 8.6	0.0, 15.5
Average Daily Frequency of Diarrhea		
DiarrheaDiarrhea Events		
n	59	56
Median	1.57	0.86
Mean (SD)	2.13 (1.85)	1.57 (1.67)
95% CI	(1.65, 2.61)	(1.12, 2.02)
Min, max	0.0, 8.0	0.0, 6.7

Only the observed data are used in the calculation. Missing data are excluded from the analysis.
ITT=intent-to-treat.
Data Source: Final Study Report, Study 730, Tables 14.2.2.2.1 and 14.2.2.1.1

Efficacy Results

The analysis populations are shown in Table 3.

Table 3. Analysis Populations

Analysis Populations	Lanreotide (N=59)	Placebo (N=56)	Total (N=115)
	n (%)		
ITT	59 (100)	56 (100)	115 (100)
Safety	58 (98.3)	57 (101.8)[a]	115 (100)
PP	54 (91.5)	46 (82.1)	100 (87)

ITT, Intention to Treat; Safety; All randomized patients who received at least one injection; PP, Per protocol. [a], One patient in the placebo group inadvertently received placebo although assigned to Somatuline.
Source: Data from Final Study Report, Study 730, Table 14.1.1.1

As already mentioned, as a result of early rollover, 14/59 (23.7%) subjects in the Somatuline group and 22/56 (39.3%) in the placebo group did not complete the DB phase of the trial. The issue of potential missing data was discussed early in the clinical program. At the End-of-Phase 2 meeting, the Division advised the sponsor to not apply "100% usage to subjects who drop early, because it would lead to bias in favor of the study drug, especially if placebo subjects had more tendency to move to the open-label phase." The Division asked the sponsor to propose "an alternative imputation strategy." The sponsor accepted the recommendation and did not impute 100% usage. Instead, they applyed 0% octreotide rescue therapy usage to subjects who dropped early. An argument has been made (see the primary clinical review) that such an imputation may minimize drug-to-placebo treatment differences and therefore biases against a drug effect; consequently, this single imputation method can be viewed to support a conclusion of efficacy. While this argument is reasonable, it should also be recognized that it is based on a single assumption and as such it should not be regarded as a replacement for an analysis that uses a variety of multiple imputation approaches. The statistical review proposes multiple imputations that will be further discussed.

Primary Endpoint

The applicant based the primary efficacy analysis on the observed diary days for each patient (i.e. no imputation, or more specifically, "an imputation of '0' for missing data was applied). This analysis resulted in a difference of 14.7% (95% CI :-26.75, -2.78; p=0.165) supporting a lanreotide effect in the reduction of octreotide rescue. Concerned about the amount of missing data, the FDA statistical reviewer conducted several sensitivity analyses using different imputation methods, including extreme imputations such as "worst" and "best" case scenarios. All were conducted for the ITT population for a minimum duration of 100 days as a cutoff (16 weeks represent about 120 days) (see Table 7 of the statistical review, reproduced below). The point estimate for the difference in octreotide use between lanreotide and placebo varied between -30.53% to 3.23%. Such apparent instability of the point estimate is a reflection of the amount of missing data; therefore imputations favoring the drug dramatically move the point estimate in the direction of a drug benefit (an almost doubling

from -14.76% to -30.53%), while imputations favoring placebo erase the entire observed drug effect and favor the placebo arm by 3.23%.

Table 7 Primary and sensitivity analyses on the primary endpoint and the best/worst case imputation data (ITT population)

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Primary endpoint (percent of octreotide usage calculated using available diary days)					
ANCOVA: LS Means	33.72 (4.39)	48.49 (4.50)	-14.76	(-26.75, -2.78)	0.0165
Exploratory rank analysis: rank ANCOVA					0.0164
Exploratory rank analysis: Stratified Wilcoxon Rank Sum test					0.0463
Hodges-Lehmann est. of treatment difference			-7.24	(-28.6, 0.0)	
Worst case imputations					
Placebo "No" & LAN "Yes"					
ANCOVA: LS means	35.46 (4.38)	32.23 (4.48)	3.23	(-8.75, 15.21)	0.594
Rank ANCOVA					0.88
Stratified Wilcoxon Rank Sum test					0.98
"Yes" for both arms					
ANCOVA: LS means	35.70 (4.72)	54.81 (4.84)	-19.11	(-32.03, -6.18)	0.004
Rank ANCOVA					0.0063
Stratified Wilcoxon Rank Sum test					0.0189
Best case imputations					
"No" for both arms					
ANCOVA: LS means	24.53 (3.69)	32.72 (3.77)	-8.19	(-18.28, 1.90)	0.110
Rank ANCOVA					0.076
Stratified Wilcoxon Rank Sum test					0.22
Placebo "Yes" & LAN "No"					
ANCOVA: LS means	24.77 (4.11)	55.30 (4.20)	-30.53	(-41.76, -19.3)	< 0.0001
Rank ANCOVA					< 0.0001
Stratified Wilcoxon Rank Sum test					0.0001

Source: reviewer's analyses and Table 16 on page 62 of CSR

A more clinically informative sensitivity analysis is provided in Table 9 of the statistical review, reproduced below. It focuses on the treatment effect for the first month of the trial and it covers approximately 28 days of treatment or up to the time of the second injection (lanreotide is administered monthly). While this analysis has the disadvantage that it assesses efficacy prior to lanreotide reaching steady state, it is not affected by the significant number of dropouts since most patients were rolled into the extension phase at the end of the first month. The point estimate for this analysis (-11.2%; CI -23.1,0.8) almost reached statistical significance (p=0.066). As indicated, and importantly, this analysis reflects treatment effect at suboptimal drug concerntations, prior to lanreotide reaching steady state (expected at 4 months).

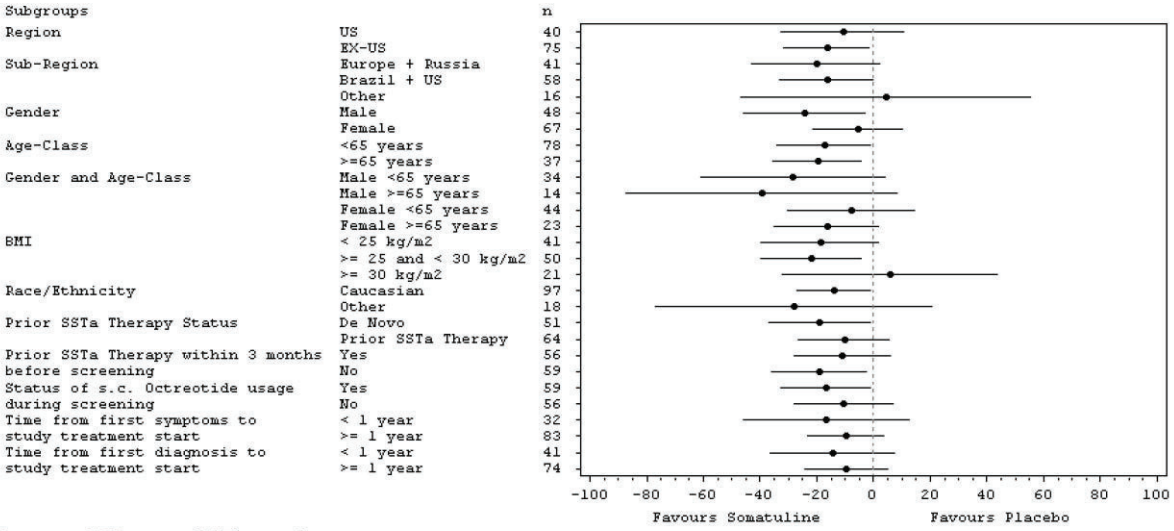
Table 9 Analyses of the octreotide usage using available diary data prior to the second injection

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Based on available days until the second injection					
ANCOVA: LS-means (SE)	33.2 (4.4)	44.4 (4.5)	-11.2	(-23.1, 0.8)	0.066

Source: Reviewer's analyses

Results favoring Somatuline over placebo (observed data) were seen consistently across a variety of demographic subgroups (Figure 5 of the statistical review). All but 2 point estimates favored Somatuline.

Figure 5 Forest plot of the subgroup analyses for the percentage of days with octreotide use during the double-blind phase (ITT Population)



Source: CSR page 65 Figure 4

Analyses of symptoms related to carcinoid disease (flushing and diarrhea)

Analyses of symptom improvement (flushing and diarrhea) did not reach statistical significance in a formal testing (Table 12 and 13 of the statistical review, reproduced below). According to the Statistical Analysis Plan, average daily frequency of diarrhea was to be tested after the primary efficacy endpoint testing; although the primary endpoint reached statistical significance, the changes in frequency of diarrhea did not (p=0.2544). Because of this, according to the prespecified hierarchical testing, daily frequency of flushing could not be tested (although it reach nominal statistical significance with a p value of 0.023). Regardless of the statistical aspects of these comparisons, it should be noted that patients had few diarrhea and flushing events at baseline and the treatment differences we small for the point estimates: mean difference of -0.21 episodes per day for diarrhea and –0.42 episodes per day for flushing.

(b) (4)

Table 12 Primary and best/worst case sensitivity analyses for average daily frequency of diarrhea

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Baseline Mean (SD)	2.13 (1.85)	1.57 (1.67)	-	-	-
Sponsor's analysis using available # of days as denominator					
DB Phase LS Mean (SE)	1.34 (0.13)	1.55 (0.14)	-0.21	(-0.58, 0.15)	0.254
Worst case imputations (for both arms)					
DB Phase LS Mean (SE)	1.77 (0.21)	2.26 (0.22)	-0.49	(-1.06, 0.09)	0.0954
Best case imputations (for both arms)					
DB Phase LS Mean (SE)	1.28 (0.13)	1.41 (0.14)	-0.13	(-0.49, 0.23)	0.489

Source: Table 4 on page 20 of clinical overview; Sponsor's response to statistical IR request dated April 23, 2017

Table 13 Primary and best/worst case sensitivity analyses for average daily frequency of flushing events

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Baseline Mean (SD)	1.53 (1.98)	2.20 (3.27)	-	-	-
Sponsor's analysis using available # of days as denominator					
DB Phase LS Mean (SE)	1.04 (0.13)	1.46 (0.14)	-0.42	(-0.79, -0.06)	0.023
Worst case imputations (for both arms)					
DB Phase LS Mean (SE)	1.52 (0.22)	2.01 (0.23)	-0.49	(-1.11, 0.12)	0.115
Best case imputations (for both arms)					
DB Phase LS Mean (SE)	0.93 (0.13)	1.36 (0.14)	-0.43	(-0.78, -0.07)	0.019

Source: Table 4 on page 20 of clinical overview; Sponsor's response to statistical IR request dated April 23, 2017.

Finally, biochemical changes from baseline in 5-HIAA , a known biomarker of symptomatic carcinoid syndrome, showed median reductions from baseline in the Somatuline arm, while the placebo showed increases from baseline in median values.

Efficacy Conclusions

As previously described, the applicant claimed a statistically significant treatment effect for Somatuline based on a reduction of 14.8% of octreotide usage (95% confidence interval: -26.8, -2.8; p-value of 0.0165 from the pre-specified ANCOVA model). FDA statistical reviewers tested this assertion under a a variety of imputations but in the final analysis could not arrive at a conclusion that Study 730 provides "solid and strong evidence (b) (4) (b) (4)

While we agree with this position on pure statistical grounds, we believe that on clinical grounds there is enough evidence to support approva (b) (4). We believe that the clinical data for the first month of treatment are consistent with a somatuline treatment effect on the reduction of rescue therapy usage because 1) nominal statistical significance was almost reached in this analysis that minimized the amount of missing data; 2) this analysis

was conducted under conditions when a carryover effect was not expected; 3) at the time of this analysis lanreotide exposure was below the target concentration (i.e. before drug steady state could be reached). This observation, which integrates clinical, clinical pharmacology, and statistical information, is evidence of a treatment effect.

We are in full agreement with the statistical reviewers that the Applicant has not provided convincing evidence (b) (4) and we recommend that the actual indication should reflect this. To this end we recommend that the indication should be changed to reflect the drug effect on the use of rescue medication with octreotide (which is supported by evidence) (b) (4) (b) (4)

Specifically, the proposed indication:

(b) (4)

should be changed to:

> *Treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.*

and thus reflect the actual observations made in Study 730.

4. Safety

Comparative safety data for this new indication are derived primarily from Study 730 in which 58 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for 16 weeks in the DB phase. Additionally, 101 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for 32 weeks in the initial open-label phase, and 57 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for at least 2 years in the long-term, open-label phase. We agree with the clinical reviewer's conclusion of safety (reproduced below) and we do not recommend a REMS or any postmarketing studies for the current indication,

> *"In summary, the safety profile of Somatuline Depot 120 mg administered to subjects with NETs and symptoms of CS diarrhea and flushing, is consistent with the profile previously reported in other indications. No new emerging safety concerns have been identified that change the benefit-risk balance of Somatuline Depot."*

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

/s/

VICTOR C BAUM
09/15/2017

DRAGOS G ROMAN
09/15/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 12, 2017

TO: NDA 022074 File

THROUGH:

FROM: Benjamin Vali, M.S., Regulatory Project Manager

SUBJECT: Officer/Employee List

APPLICATION/DRUG: NDA 022074 (S-017)/SOMATULINE DEPOT (lanreotide) Injection 60 mg, 90 mg, and 120 mg

The following officers or employees of FDA participated in the decision to approve this supplemental application and consented to be identified on this list:

Baum, Victor
Beitz, Julie G
Chakder, Sushanta K
Chen, Wen-Hung
Chen, Yeh-Fong
Dinatale, Miriam
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Ishihara, Richard
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	NDA 022,074 (S-017)
Priority or Standard	Standard
Submit Date(s)	August 15, 2016
Received Date(s)	August 15, 2016
PDUFA Goal Date	June 15, 2017
Division/Office	Division of Gastroenterology and Inborn Errors Products/ODE3/CDER
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Acting Team Leader	Victor Baum, M.D.
Review Completion Date	May 30, 2017
Established Name	Lanreotide acetate
(Proposed) Trade Name	Somatuline Depot
Applicant	Ipsen Biopharmaceuticals, Inc.
Formulation(s)	Deep subcutaneous injection
Dosing Regimen	120 mg every 4 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BM	bowel movement
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CgA	Chromogranin A
CI	Confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	Creatine phosphokinase
CRF	case report form
CRO	contract research organization
CS	Carcinoid syndrome
CSR	clinical study report
DB	Double-blind phase
DBT	Double-blind Treatment
DMC	data monitoring committee
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCTD	electronic common technical document
eDiary	electronic case report form
EORTC-QLQ	Europpean Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GEP NETs	Gastroenteropancreatic neuroendocrine tumors
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GRMP	good review management practice
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin (5-hydroxytryptamine)
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOL	Initial open-label phase
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LANREOTIDE	lanreotide Autogel, Somatuline Depot
LAR	Sandostatin LAR® Depot; LAR: Long-acting release
LTOLE	Long-term open-label extension phase
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NET	neuroendocrine tumor
NME	new molecular entity
OLE	Open-label Entension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	Proton pump inhibitor
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	prothrombin time
REMS	risk evaluation and mitigation strategy
SOC	system organ class
SSA	Somatostatin analog
SSTR	Somatostatin receptor
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Somatuline Depot (lanreotide acetate) is a synthetic cyclical octapeptide that has biological activity similar to the naturally occurring analog, somatostatin. In 2007, the product was approved for the long-term treatment of patients with unresectable gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival. In this efficacy supplement, Applicant Ipsen Biopharmaceuticals proposes to extend the indicatio (b) (4) (b) (4) The primary efficacy endpoint was comparison with placebo in using the active drug octreotide as rescue treatment for breakthrough carcinoid diarrhea and flushing. Carcinoid diarrhea and flushing occur in patients who have primarily hepatic metastatic carcinoid tumors that produce sufficient bioactive mediators to overcome the hepatic "first pass" effect and to generate carcinoid diarrhea and flushing. Orphan-drug designation was approved in 2011, and no pediatric study was submitted.

This review primarily assesses the efficacy and safety of one multicenter, randomized, double-blind, placebo-controlled phase 3 study, Study 730. At the end of phase 2 (EOP2) meeting on July 15, 2008, the Applicant discussed an "early roll over" into an initial open label (IOL) study protocol with the Division. The purpose was to protect patients from unbearable carcinoid syndrome and also to collecting essential efficacy data. The criteria for early roll over were defined as "After at least 4 weeks in the study, patients will be allowed to roll over into the initial open label phase of the study, if they used subcutaneous octreotide for at least 21 out of 28 days of study participation, and used a dose ≥300 µg per day for at least 14 out of the 21 days, regardless of the presence or absence of symptoms." As a result, 14 (23.7%) subjects in the Somatuline group and 22 (39.3%) in the placebo group were early-rolled-over to the open-label phase. This produced an imbalance in treatment breakthrough event collection between the Somatuline and placebo groups. The placebo group had 8 more subjects (than the Somatuline group) whose breakthrough days were imputed to 0% usage of octreotide, i.e., their breakthrough events during the 12 weeks (12 weeks of the16 weeks study) double-blind (DB) study period were not counted. This breakthrough day calculation is apparently in favor of placebo group.

A total of 115 patients with histopathological-confirmed neuroendocrine tumors and a history of carcinoid syndrome (flushing and/or diarrhea) were enrolled. Fifty-nine patients received Somatuline Depot 120 mg deep subcutaneous (s.c.) injection every 4 weeks, and 56 patients received placebo. Patients were instructed to administer subcutaneous short-acting octreotide [FDA approved product for treating carcinoid syndrome (CS) diarrhea and flushing]. The dose of octreotide was ≤600 mcg subcutaneously daily for breakthrough CS diarrhea or flushing. The

use of short-acting octreotide and the severity and frequency of diarrhea and flushing symptoms were reported daily in electronic patient diaries. The primary efficacy endpoint was the percentage of days in which patients had to use at least one injection of the short-acting octreotide for CS symptom control.

Patients in the Somatuline Depot arm required fewer days of rescue octreotide than placebo [-14.76% (95% Confidence Interval -26.78, -2.75): 33.72% vs. 48.49% of days, respectively; p=0.0165]. Results of the subgroup analyses showed a reduction in mean percentage of days, for all subgroups such as age, sex, race, and time since diagnosis.

Due to the number of subjects whose data were missing from the DB phase due to early roll over, a post hoc responder analysis was conducted. The responder criterion was defined as free of octreotide use during the last 4 weeks of the DB phase. The results showed that 40.7% of subjects in the Somatuline Depot arm did not use rescue octreotide, while 23.4% of the placebo arm had days of octreotide use.

Based on these studies, the Applicant recommends that:

- Somatuline 120 mg deep s.c. injection every 4 week (b) (4) (b) (4)

The benefit-risk evaluations are listed as follows:

- Clinical significance: CS diarrhea is a refractory secretory diarrhea. It is estimated about 80% of patients with CS will have diarrhea.
- Most CS diarrhea occurs in patients with carcinoid tumors metastatic to liver. The 5-year survival rate is 40% (Strosberg, 2012).
- Unmet medical need: CS patients become refractory to the marketed octreotide (short-acting and slow-releasing) with high rates. It is estimated that 60% of CS patients become refractory to slow-releasing octreotide in 3 months (Strosberg, 2014).
- Somatuline Depot reduced the days of using the FDA approved active drug octreotide for treating CS diarrhea and flushing. The responder analysis shows that 40.7% of patients on Somatuline Depot did not need to use the approved active drug octreotide during the last 4 weeks of the 16 weeks of controlled study, compared to 23.4% of placebo patients.

(b) (4)

Safety assessments demonstrated that:

- A total of 219 symptomatic CS patients with diarrhea and flushing were treated. The treatment duration was up to 48 weeks and the highest dose was 120 mg once every 4 weeks. There was no significant safety signal reported.
- The most frequently reported treatment-emergent adverse events (≥ 3 subjects) were headache, dizziness, vomiting, flatulence and muscle spasms.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In summary, the Applicant has provided sufficient evidence to support the effectiveness of Somatuline Depo (b) (4). From the clinical reviewer perspective, the result (b) (4) are clinically meaningful. The reviewer recommends Approval of Somatuline Depo (b) (4) (b) (4)

1.3. Benefit-Risk Assessment

(Next page)

Benefit-Risk Summary and Assessment

The Benefit-Risk assessment shows favorable results for Somatuline Depot therapy [redacted] (b) (4) [redacted] (b) (4) It is reported that 80% of patients with carcinoid syndrome (CS) have diarrhea, and more than 90% have flushing. [redacted] (b) (4) most patients will soon develop refractory diarrhea to octreotide therapy. Study 730 shows that Somatuline Depot reduced the number of days of using octreotide by 14% in a 16-week controlled study phase. Also, Study 730 shows that at the last 4 weeks of the 16-week controlled period, 40.7% of the Somatuline group did not use the approved product octreotide for treating CS diarrhea and flushing as compared with only 23.4% of patients in placebo group.

The most frequently reported treatment-emergent adverse events (≥ 3 subjects) were headache, dizziness, vomiting, flatulence and muscle spasms.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Somatuline Depot 120 mg every 4 weeks • Route of administration: deep s.c. injection • Population: patients with metastatic carcinoid tumor who had diarrhea and flushing ≥3 episodes per day	Treatment naïve patients and experienced patients who are still sensitive to octreotide treatment.
Current Treatment Options	• SSA therapy: Sandostatin Injection (octreotide acetate; Short acting) and Sandostatin LAR Depot (octreotide acetate for injectable suspension; Long-acting release)	Available therapy is effective but the majority of patients with CS diarrhea become refractory to SSA therapy within several months.
Benefit	• 80% of symptomatic carcinoid patients have CS diarrhea and 90% have flushing. • 60% of CS patients develop refractory diarrhea to octreotide therapy in 3 months. • Somatuline Depot reduced the days of using octreotide.	The product reduces the days of breakthrough of CS diarrhea and flushing that requires octreotide therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 40.7% of patients in Somatuline Depot group were free-of-octreotide use during the last 4 weeks of the 16-week study. (b) (4)	
Risk	• The most frequently reported treatment-emergent adverse events (≥ 3 subjects) were headache, dizziness, vomiting, flatulence and muscle spasms.	The risk of developing refractory diarrhea to Somatuline treatment has not been assessed.
Risk Management	• (b) (4) • REMS (Risk Evaluation and Mitigation Strategy) is not required.	A total of 219 symptomatic CS patients with diarrhea and flushing were treated. The mean duration was up to 48 weeks and the highest dose was 120 mg once every 4 weeks. There was no significant safety signal reported.

2 Therapeutic Context

2.1. Analysis of Condition

Disease Background and Scientific Rationale

1) Carcinoid syndrome: multi-mediator diarrhea and flushing

Carcinoid tumors are common neuroendocrine tumors of the gastrointestinal tract. The estimated incidence is approximate 50,000 cases per year worldwide (Yao, 2008). Based on embryonic origin, carcinoid tumor can be divided into 3 types:

(1) Foregut carcinoid:
- 30% of patients are symptomatic,
- Intrathoracic, gastric, and duodenal (2/3)
- Some release histamine, instead of serotonin (5-HT)

(2) Midgut carcinoid:
- 70% of patients are symptomatic
- Located at small intestine, appendix, proximal colon

(3) Hindgut carcinoid:
- Symptomatic only when patients have liver metastases
- Located at distal colon and rectum

CS occurs when carcinoid tumor cells secrete large amounts of serotonin and other vasoactive products into the systemic circulation. The secretory products include serotonin, kallikrein/bradykinin, prostaglandin, tachykinins, and histamine. In general, symptoms associated with CS include cutaneous flushing, diarrhea, wheezing, abdominal pain, and valvular heart disease. More than 90% of patients with carcinoid syndrome have hepatic metastases, usually from carcinoids of small bowel origin. When tumors are confined to the intestine, the bioactive substances released are metabolized to inactive forms by the liver, a "first-pass" effect similar to that of oral drugs. However, when tumors invade into hepatic non-portal regions, the bioactive secretory products of tumor cells will be released directly into venous circulation by-passing the first-pass effect. Thus, carcinoid syndrome is strongly associated with metastasis to liver.

It is estimated that 80% of symptomatic carcinoid patients present with diarrhea (Wilson, 2009). There are 2 types of CS diarrhea: (1) Bioactive products released from carcinoid tumors stimulate secretory diarrhea; and (2) Niacin deficiency induced malabsorption diarrhea. Carcinoid tumors have at least 5 types of bioactive secretory products that can be associated with CS diarrhea:

- Serotonin: stimulates intestinal secretion, motility, and decrease of absorption,

causing secretory diarrhea.

- Kallikrein/Bradykinin: dilates blood vessels, causing flushing, palpitations, low blood pressure, and diarrhea.
- Prostaglandin E, and F: cause diarrhea.
- Tachykinins: cause diarrhea and inflammation.
- Histamine: causes flushing and diarrhea.

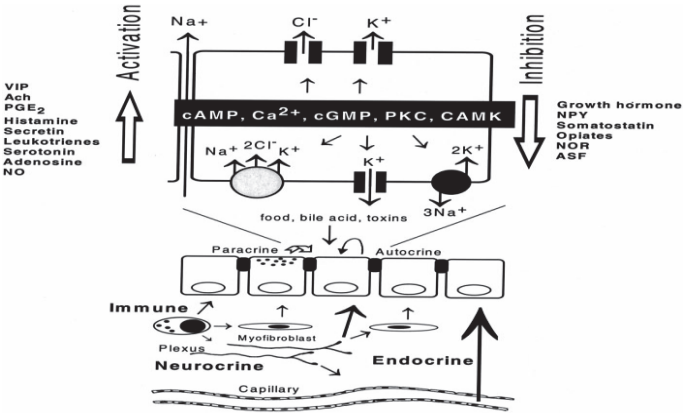
CS patients can also have niacin-deficiency diarrhea. Tryptophan is an essential amino acid for niacin synthesis. Normally, 1% of dietary tryptophan is converted to serotonin. In CS patients, 70% of dietary tryptophan is converted to serotonin, which limits the availability of tryptophan for niacin synthesis. Clinically, niacin deficiency presents as pellagra and includes diarrhea.

2) Mechanisms of CS diarrhea

Mechanisms of CS diarrhea involve activation of electrolyte secretion by colonic epithelial cells. As shown in Figure 1, the diarrhea mediators increase the intracellular concentrations of secondary messengers: cAMP, Ca2+, cGMP, protein kinase C (PKC), and calmodulin-dependent kinase (CAMK). The secondary messengers, in turn, stimulate secretion of KCl and NaCl by activation of transport proteins in luminal (CFTR Cl^- channels, K^+ channels) and basolateral (Na^+ - $2Cl^-$-K^+ co-transporter, K^+ channels, Na^+-K^+-ATPase) membranes.

Some important stimulatory mediators (most are also secreted by CS tumor cells) are shown in the left side of the figure, such as vasoactive intestinal polypeptide (VIP), acetylcholine (Ach), histamine, secretin, leukotrienes, serotonin, adenosine, and nitric oxide (NO). Other bioactive secretory products, kallikrein/bradykinin, prostaglandin E and F, and tachykinins are also involved. These secretory mediators are secreted in paracrine or autocrine fashion by tumor cells or are released from enteric nerves or immune cells (mast cells and lymphocytes) triggered by tumor bioactive products, or are transported by capillaries.

Figure 1: Activation of electrolyte secretion in colon cells



From Kunzelmann, K and Mall, M. Electrolyte transport in the mammalian colon: Mechanisms and implications for

disease. Pysiol. Rev. 82:245-289, 2002.

2.2. Analysis of Current Treatment Options

Patients with carcinoid syndrome are treated with the somatostatin analog octreotide, 150 to 250 µg subcutaneously three times daily or administered as a long-acting intramuscular depot formulation. Treatment relieves CS diarrhea in 90% of patients for 1 year (Cornett, 2015). After that, many patients stop responding to octreotide.

In selected patients with refractory carcinoid syndromes, resection of hepatic metastases can provide improvement. Hepatic artery occlusion, liver-directed debulking procedures, and chemotherapy can also provide symptomatic improvement in patients with hepatic metastases.

Table 1: Summary of Commonly Used Agents for CS diarrhea

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Tolerability
Sandostatin Injection (Short-acting octreotide)	Suppression of severe diarrhea/flushing with metastatic carcinoid tumors	1988	100-600 mcg/day in 2-4 divided doses for 2 weeks	Most patients develop resistance in months
Sandostatin LAR (Long-acting release octreotide)	Suppression of severe diarrhea/flushing associated with metastatic carcinoid tumors	2002	20 mg every 4 weeks for 2 months	Most patients develop resistance in months

From Modlin IM, 2010.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Somatuline Depot (Lanreotide Autogel) was initially approved in U.S. in 2007. It is currently marketed in the U.S. for treatment of (1) acromegalic patients who have had an inadequate response to surgery or radiotherapy, and (2) patients with unresectable metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

3.2 Summary of Presubmission/Submission Regulatory Activity

Development of Somatuline Depot was under NDA 022,074 (IND 63,239):

- The Pre-IND meeting was held on June 27, 2003. The Division of Gastrointestinal and Coagulation Drug Products agreed that "a non-inferiority study design is appropriate as long as the active comparator drug is FDA approved for the proposed indication, is administered at the appropriate dose and the non-inferiority margin is adequately justified." Also, the Division agreed to the study design allowing the use of over the counter medications for diarrhea, stated "Such use of over the counter medications for diarrhea should be analyzed. The use of these agents should be standardized in the protocol."
- The IND was submitted on November 17, 2003.
- The EOP2 meeting was held on July 15, 2008. At the meeting, the Applicant discussed an "early roll over" protocol with the Division. The criteria for early roll-over were defined as "After at least 4 weeks in the study, patients will be allowed to roll over into the initial open label phase of the study, if they used subcutaneous octreotide for at least 21 out of 28 days of study participation, and used a dose ≥300 µg per day for at least 14 out of the 21 days, regardless of the presence or absence of symptoms." The Applicant proposed to (b) (4) The Division disagreed with the method for imputing missing data (b) (4) (b) (4)) is not realistic and would lead to bias in favor of the study drug, especially if placebo subjects had more tendency to move to the open label phase. You should propose an alternative imputation strategy that would not have potential to bias the efficacy assessment of the study drug."

  In the meeting, the Division (DGIEP) requested that carcinoid tumors be diagnosed by histopathology for all patients, and recommended that "If proportion of days with rescue medication (octreotide) is the primary endpoint, we recommend you use an ANCOVA model with covariates for your stratification variables. In addition, frequency and/or severity of diarrhea and flushing at baseline may also be important covariates." The Division recommended that the statistical plan include efficacy comparisons within the subgroup of patients naïve to SSA and within the subgroup of patients responsive to conventional dose of subcutaneous LAR, since these groups of patients (naïve and non-naïve) may respond differently."
- On September 8, 2011, orphan-drug designation was approved of Somatuline Depot for treatment of symptoms associated with carcinoid syndrome.
- On June 7, 2013, the Division sent recommendations to the Applicant: "(1) we do not agree with the proposed stratified ANCOVA model; (2) the primary analysis, observed percentage of days of subcutaneous octreotide usage with available data should be implemented without weighting strategy; and (3) all changes that occurred at the late stage of the clinical trials may be considered exploratory only."
- The pre-NDA meeting was held on September 10, 2015. In the meeting, DGIEP stated

that "We recognize that this drug has already been approved in this population for treatment of neuroendocrine tumors. Therefore it is acceptable from the information you have submitted for you to file a sNDA." The Division also recommended that "you should combine the symptomatic NET populations (from clinical trials 730, 718, 216 and 166) for a safety data base in symptomatic patients."

3.3 Foreign Regulatory Actions and Marketing History

Somatuline Depot is registered in over 70 countries world-wide for the treatment of acromegaly and carcinoid syndrome. It received its first marketing authorization in 2001 in Europe.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

OSI audit was not conducted.

4.2 Product Quality

At submission of the clinical review, the CMC review is not available for review.

4.3 Clinical Microbiology

Clinical microbiology study was not conducted in this submission.

4.4 Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were submitted in the supplemental NDA.

4.5 Clinical Pharmacology

At submission of the clinical review, the Clinical Pharmacology review is not available.

4.5.1 Mechanism of Action

Lanreotide is the active component of Somatuline Depot. It is an octapeptide analog of natural somatostatin. The mechanism of action of lanreotide is believed to be similar to that of natural somatostatin.

4.5.2 Pharmacodynamics

Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR 1, 3, and 4. Activity at human SSTR 2 and 5 is the primary mechanism believed responsible for GH (growth hormone) inhibition. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine, and paracrine functions.

4.5.3 Pharmacokinetics

The label of Somatuline Depot states that the product "is thought to form a drug depot at the injection site due to the interaction of the formulation with physiological fluids. The most likely mechanism of drug release is a passive diffusion of the precipitated drug from the depot towards the surrounding tissues, followed by the absorption to the bloodstream."

"After a single, deep subcutaneous administration, the mean absolute bioavailability of Somatuline Depot in healthy subjects was 73.4%, 69.0%, and 78.4% for the 60 mg, 90 mg, and 120 mg doses, respectively. Mean Cmax values ranged from 4.3 to 8.4 ng/mL during the first day. Single-dose linearity was demonstrated with respect to AUC and Cmax, and showed high inter-subject variability. Somatuline Depot showed sustained release of lanreotide with a half-life of 23 to 30 days. Mean serum concentrations were > 1 ng/mL throughout 28 days at 90 mg and 120 mg and > 0.9 ng/mL at 60 mg."

"In studies evaluating excretion, <5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in feces, indicative of some biliary excretion."

4.6 Devices and Companion Diagnostic Issues

There was no diagnostic device include in this application.

4.7 Consumer Study Reviews

There was no consumer study review for this submission.

5 Sources of Clinical Data and Review Strategy

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5.1 Table of Clinical Studies

The clinical efficacy data were from one pivotal phase 3, DB, placebo-controlled study (Study 730). In addition, one supportive, phase 2 open-label study in subjects with carcinoid syndrome (Study 718) was submitted (Table 2).

The biomarker data (urinary 5-HIAA) were from Study 726, a phase 3, randomized DB, placebo-controlled, multicenter study. The data were pooled with biomarker data from Study 730.

Table 2: Studies Supporting Clinical Efficacy for the Somatuline Depot sNDA

Study (CSR Location)	Study Design/Objectives	Number of Subjects by Treatment	Duration (Efficacy Data Presented)	Study Narrative Location
Pivotal Phase III Placebo-controlled Study				
730 (Module 5.3.5.1)	Phase III, randomised, DB, placebo-controlled, multicentre study to evaluate efficacy and safety of Somatuline in subjects with carcinoid syndrome	DB Phase: Somatuline: 59 Placebo: 56 IOL Phase: Somatuline: 101 LTOLE Phase: Somatuline: 57	16 weeks (DB phase) 32 weeks At least 2 years after last subject completed IOL phase[a]	(Section 2.1)
Supportive Phase II/III Uncontrolled Study				
718 (Module 5.3.5.2)	Phase II/III, open-label, multicentre, dose-titration study to evaluate efficacy and safety of Somatuline in subjects with carcinoid syndrome	Somatuline: 71	6 months	(Section 2.2)
Pooled Biomarker Analysis Only (Phase III Study)				
726 (Module 5.3.5.1)	Phase III, randomised, DB, placebo-controlled, multicentre study to evaluate efficacy and safety of Somatuline in subjects with non-functioning entero pancreatic endocrine tumour	Somatuline: 101 Placebo: 103	96 weeks	(Section 2.3)

CSR=Clinical Study Report; DB=double-blind; IOL=initial open-label phase; LTOLE: long-term, open-label extension

a Or when marketing approval for the treatment of carcinoid syndrome had been obtained in the respective countries (which ever occurred first)

Safety assessment was based on one phase 3 study (Study 730) and five supportive studies (Studies 726, 718, 216, 166, and 729) (Table 3). All of the results in the submission were reviewed. The data supported a substantive clinical review. Literature was not relied upon to support the safety and efficacy.

Table 3: Safety Data Sources

Purpose	General criteria	Safety reporting
Pivotal Study 730		
Pivotal efficacy and safety	DB comparative Autogel study to establish substantial evidence of efficacy and safety. Two open-label phases (the initial open-label phase and the long term open-label extension phase) were also part of this study.	• AEs • Vital signs • Gallbladder • Laboratory data
Supportive Studies 726, 718, 216, 166, and 729		
Supportive efficacy and/or safety	DB comparative and Open Label Autogel studies intended to support efficacy and/or safety conclusions.	• AEs • Vital signs • Gallbladder • Laboratory data
PMS data		
Supportive safety	PMS data in NET observed under Somatuline Depot 120 mg (e.g. spontaneous reports, externally sponsored studies, literature reports, registries, etc. excluding IPSEN sponsored clinical trials).	• AEs • SAEs • Deaths • Pregnancy data

AE=adverse event; DB=double-blind; ISS=Integrated Summary of Safety; NET= neuroendocrine tumour; PMS=postmarketing surveillance; SAE=serious adverse event; SAP=statistical analysis plan.
Data Source: Module 5.3.5.3 ISS SAP Table 1.
Note: 'Category 1' and 'Category 2' are used in the SAP to denote pivotal and supportive studies, respectively.

5.2 Review Strategy

The efficacy review was based on Study 730. Serious concerns of the effectiveness of Somatuline Depot were raised by the Statistic Reviewers during the review meetings. The clinical reviewer disagrees with the following Statistics Reviewers' comments.

1) "Because of 30% of diary data missing, the effectiveness of Somatuline cannot be approved."
   The "Missing Data" was caused by the pre-specified "Early roll-over" agreement at the EOP2 meeting between the Applicant and the previous Statistical team as well as the Division. The purpose of roll-over was to provide potential relief for protecting patients with unbearable carcinoid diarrhea, and for preserving essential efficacy data (4 weeks DB phase) for analyses.

   There were 14 (23.7%) subjects in the Somatuline group and 22 (39.3%) in the placebo group, who were early-rolled over to the open-label phase (Figure 2). This generated an imbalance in collecting breakthrough data between Somatuline and placebo groups in the DB phase. The placebo group had 8 more subjects (than the Somatuline group) whose breakthrough events during the 12 weeks of the 16 weeks DB study were not counted (Figures 2 and 3). Despite the advantage to the placebo group, Somatuline group had significant reduction of breakthrough days as compared with the placebo ($p=0.0165$).

   Furthermore, the Statistics Reviewer disqualifies the 28 day (4 weeks) DB data of patients who had early roll over later (Figure 3). Accordingly, there will be 8 more subjects (than for the Somatuline group) whose breakthrough events were not counted during the initial 4 weeks of the 16 weeks DB study on top of the advantage of 12 weeks not counted for the placebo group.

   The fact is that Somatuline Depot met the primary efficacy endpoint with $p=0.0165$, even though there are 8 more subjects in placebo group whose breakthrough events not counted during the 12 weeks of the 16 weeks DB study.

   Figure 2: Despite removal of more unsuccessful patients by early roll over (ERO) giving an advantage to the placebo (due to imputation), the Somatuline group met the primary efficacy endpoint

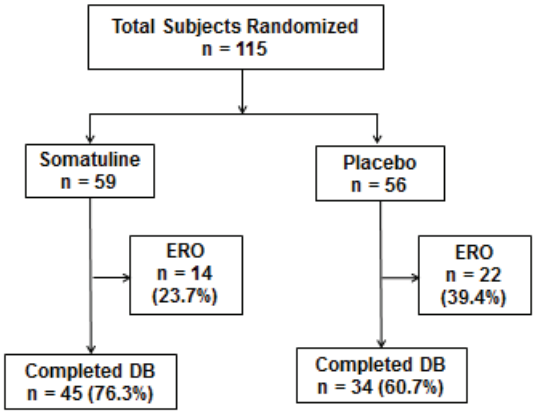
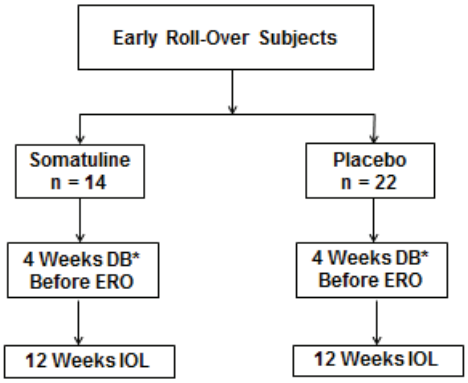


Figure 3: The Statistics Reviewer deleted existing data of the initial 4 weeks of the DB phase before early roll over, which resulted in the assessment that the primary endpoint was not met



Reviewer Notes: In the Statistics Reviewer analysis, the data from the initial 4 weeks of the DB phase were deleted. This deletion leads to 8 more placebo subjects (comparing to Somatuline group) whose breakthrough events during the initial 4 weeks of DB phase were not counted in the efficacy analysis. The advantage to the placebo group causes Somatuline group not met the primary efficacy endpoint.
*Dentote the initial 4 weeks double-blind phase before early roll over.

Medical Officer Comments:
Disproportionate removal of unsuccessful placebo subjects generates artifact such that the change of the primary endpoint is not proportional to the activity of product, but rather related to the disproportionate removal of placebo subjects. Given the method of imputation of missing data, the larger removal of placebo subjects, results in the apparent less inadequate activity of the product. In the Somatuline review, the disproportionate removal of placebo subjects occurred at two times. The first removal (b) (4) (b) (4) the Statistics Reviewer removed 8 additional placebo subjects from breakthrough events for 4 weeks in the DB phase. Based on these facts, the clinical reviewer believes that it is the artifact generated by the disproportionate removal of unsuccessful placebo subjects that resulted in Somatuline not meeting the primary endpoint, rather than ineffectiveness of the drug.

2) "Because Frequency of Diarrhea does not correlate with Breakthrough Days, effectiveness of Somatuline is not true."
In Study 730, "Frequency of diarrhea" is confounded by octreotide injections. "Frequency of diarrhea" does not qualify to serve as the primary endpoint. Also, it does not qualify to be used as an untreated anchor of diarrhea to adjudge the effectiveness of Somatuline.

Octreotide injection is driven by the urgency of bowel movement that is triggered by releasing mediators such as 5-HT, histamine, kallikrein, prostaglandins E and F, and tachykinins from metastatic carcinoid tumor cells. The diarrhea mediators then stimulate sensory neurons at intestinal wall, and trigger rescue octreotide injection. Once the injection takes place, it suppresses the frequency of diarrhea and symptoms. Thus, an increase of increase of octreotide injections may not associate with an increase of diarrhea episodes.

On the other hand, "Breakthrough day" is proportional to the capability of carcinoid tumors to generate carcinoid diarrhea and flushing. Therefore, it qualifies to serve as the primary efficacy endpoint.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Study 730

6.1.1 Study Design

Overview and Objective

Study Title: "Double Blind, Randomised, Placebo Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot (Lanreotide Autogel) Injection in the Treatment of Carcinoid syndrome"

The primary objective of this trial was to evaluate the efficacy of Somatuline Depot injections administered every 4 weeks for the control of symptoms associated with carcinoid syndrome (diarrhea and/or flushing) as compared to placebo, measured by the usage of s.c. octreotide as rescue medication to control symptoms.

Trial Design

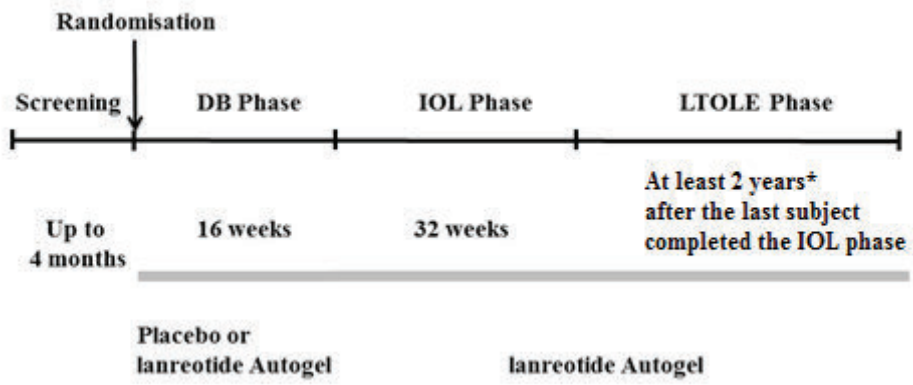
This was a phase 3, placebo-controlled, randomized, multicenter, double-blind study in patients with carcinoid syndrome (diarrhea and/or flushing). The study consisted of a screening period (a minimum of 4 weeks), followed by a 16-week, DB, placebo-controlled phase in which subjects were randomized (1:1) to receive either Somatuline Depot (120 mg) or placebo every 4 weeks by deep s.c. injection. The DB phase was followed by a 32-week, IOL phase and a long-term, open-label extension (LTOLE) phase (at least 2 years after the last subject completed the IOL phase), in which all subjects received Somatuline Depot. The protocol allowed early roll-over from the DB to the IOL. The criteria for early roll over were:

- Completed at least 4 weeks of DB study
- Used subcutaneous octreotide for at least 21 out of 28 days of study participation
- And used a dose ≥300 µg per day for at least 14 out of the 21 days, regardless of the presence or absence of symptoms."

The Applicant applied 0% of rescue octreotide usage during the 12 weeks of the 16 weeks DB study to subjects who rolled over early from the DB phase.

Following instruction, the daily frequency and severity of symptoms (diarrhea and flushing) and octreotide use were recorded by the subject at the end of each day using an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) (during screening, DB, and IOL phases).

Figure 4: Study Design



Note: DB=double-blind; IOL=initial open-label; LTOLE=long-term open-label extension; lanreotide Autogel=lanreotide Autogel 120 mg.
*or when marketing approval for the treatment of symptoms of carcinoid syndrome is obtained (whichever occurs first).

Inclusion Criteria (Study 730)

Subjects were eligible for participation in the study if they met the following criteria:

1. At least 18 years of age at the time of first dosing.
2. Subjects must have given signed informed consent before any study related activities were conducted.
3. Subjects in the U.S. must have given written authorization for the release of protected health information in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations; subjects in other countries must have provided appropriate authorization as needed by regulatory authorities in each country.
4. Subjects must have been willing to receive s.c. octreotide injections as rescue medication, as needed to control their symptoms, if any.
5. If female, the subject must not have been pregnant (confirmed by negative pregnancy test) and must have had the following documented via verbally given history:
    a. At least 1 year postmenopausal (natural cessation of menses), or
    b. Surgically sterile (if by tubal ligation, surgery must have been performed more than 3 months prior to entry into the study), or
    c. If the subject was of childbearing potential and sexually active, she must have been using an acceptable form of contraception (oral, injected, transdermal or implanted contraceptives, diaphragm or barrier method with spermicidal and/or intrauterine device); local methods such as condoms or sponges/vaginal tablets were not acceptable forms of contraception.
6. Subjects with a histopathological confirmed diagnosis of carcinoid tumor or, a carcinoid tumor of unknown location with liver metastases (documented biopsy), and a history of carcinoid syndrome (flushing and/or diarrhea) who were either naïve to treatment with an SSA or responsive (according to the opinion of the principal investigator) to

conventional doses of LAR (≤30 mg every 4 weeks) or to daily doses of ≤600 μg of s.c. octreotide.

7. Confirmation of positive SSTR status by somatostatin receptor scintigraphy (SRS) (up to 6 months prior to study entry at the Screening Visit).
8. Absence of tumor progression documented by two sequential CT scans or two sequential MRIs (≥3 months apart); the last CT or MRI scan must have been performed within 6 months of study entry (Screening Visit).
9. Subjects previously treated with LAR, must have received their last dose of LAR at least 4 weeks prior to first dose of study treatment (no later than at the Screening Visit).
10. Be able to communicate and cooperate with the principal investigator and the staff and willing to comply with the study instructions.

Exclusion Criteria (Study 730)

Subjects were excluded from entering the study for the following reasons:

1. History of known allergy or hypersensitivity to:
    a. Investigational drug or any components of its formulation
    b. Octreotide.
2. History of carcinoid syndrome refractory to treatment with conventional doses of SSA.
3. Treatment with any other investigational drug within 30 days prior to study entry (Screening Visit) and/or at any time during the subject's participation in the study.
4. Treatment with interferon, chemotherapy and/or radiotherapy (a radiolabeled SSA) and/or tumor debulking <3 months prior to study entry (Screening Visit).
5. History of hepatic arterial embolization, hepatic arterial chemoembolization and/or selective internal radiation therapy <6 months prior to study entry (Screening Visit).
6. Short bowel syndrome.
7. Uncontrolled diabetes and/or hypertension.
8. Severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m2) and/or severe liver impairment as evidenced by serum total bilirubin >1.5 mg/dL associated with bile duct blockage or with alkaline phosphatase (ALP), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5.0 times the upper limit of normal (ULN).
9. Diagnosis of cardiac disease New York Heart Association (NYHA) functional classification >Class I.
10. Life expectancy less than 1 year.
11. Any malignancies except:
    a. Carcinoid tumor
    b. Basal cell carcinoma of the skin
    c. In situ carcinoma of the cervix
    d. ≥5 years disease free after curative cancer treatment.
12. Any serious medical condition that could jeopardize the safety of the subject and/or the efficacy assessments of the study.

13. Subject is being treated with a proton pump inhibitor (PPI) and has been at a stable dose (no change in dose or frequency of administration) for less than 4 weeks at study entry (Screening Visit).

Study Endpoints and Analyses

Primary Efficacy Endpoint

The daily use of s.c. octreotide for CS diarrhea and/or flushing was recorded. The percentage of days with breakthrough (any injections of octreotide) was compared between the Somatuline and placebo arms. The average percentage of days that subcutaneous octreotide was used during the 16-week DB phase, based on subject IVRS/IWRS (Interactive Voice Response System/Interactive Web Response system) diary records.

The baseline octreotide use was calculated as the percentage of days of octreotide use during the 4 weeks of the Screening period. The baseline average frequency of diarrhea plus flushing events per day was calculated as the average number of carcinoid syndrome events per day during the 4 weeks of the Screening period. The primary efficacy analysis was based on data obtained during the 16-week DB phase.

Secondary Efficacy Endpoints (Study 730)

Analysis of the secondary efficacy endpoints is listed in the following table:

Table 4: Hierarchical Testing Procedure for Secondary Efficacy Endpoints

Rank	Secondary Criteria
1	Average frequency of diarrhea events per day during the 16-week DB phase of the study based on IVRS/IWRS diary records
2	Average frequency of flushing events per day during the 16-week DB phase of the study based on IVRS/IWRS diary records
3	Usage of other concomitant rescue medications for diarrhea and/or flushing events (e.g. loperamide and/or tincture of opium). Measured as the percentage of days that the other rescue medications were used as rescue medication the 16-week DB phase of the study based on IVRS/IWRS diary records
4	Proportion of subjects who roll over into the IOL phase before completing the DB phase of the study.
5	Changes from baseline in Global Health Status/QoL subscore (item 29 and 30 of the QLQ-C30) during the 16-week DB phase of the study.
6	Changes from baseline in QoL (GI symptoms subscore) during the 16-week DB phase of the study; assessed using EORTC QLQ-G.I.NET.21 questionnaires
7	Changes from baseline in QoL (Endocrine symptoms subscores) during the 16-week DB phase of the study; assessed using EORTC QLQ-G.I.NET.21 questionnaires.
8	Absolute changes from baseline in biochemical marker - plasma CgA during the 16-week DB phase of the study.
9	Absolute changes from baseline in biochemical marker – urinary 5-HIAA during the 16-week DB phase of the study.

Note: DB=double-blind; IVRS= Interactive Voice Response System; IWRS= Interactive Web Response System; IOL=initial open-label; QoL=quality of life; CgA=Chromogranin A; 5-HIAA=5-hydroxyindoleacetic acid

Statistical Analysis (Study 730)

Intent-to-treat (ITT) population was defined as all subjects who were randomized at baseline to receive Somatuline (59 subjects) or placebo (56 subjects). There were 115 subjects who were randomized to receive the treatment and placebo at baseline.

Per protocol (PP) population was defined as all subjects in the ITT population who had no major protocol violations/deviations during the DB phase. There were 100 subjects in the per protocol population. Among them, 79 subjects were completed the DB phase.

Safety population: All randomized subjects who received at least one injection of study treatment. There were 115 subjects in the Safety population.

Table 5: Analysis Populations for the Double-blind Treatment Period

Analysis Populations	Lanreotide (N=59)	Placebo (N=56)	Total (N=115)
	n (%)		
ITT	59 (100)	56 (100)	115 (100)
Safety	58 (98)	57 (102)[a]	115 (100)
PP	54 (91)	46 (82)	100 (87)

Data Source: Table 14.1.1.1.

[a]For the placebo group, n=56 for the ITT population and n=57 for the safety population. This discrepancy can be attributed to the fact that subjec (b) (6) was randomized to lanreotide Autogel, but erroneously received placebo, therefore was included in the safety population as per the actual treatment received.

Demographic and Other Baseline Characteristics

The Applicant stated that the demographic characteristics at baseline were balanced between the treatment and placebo groups. There were 8 subjects who were placed in the wrong treatment group by error (three in the Somatuline group and 5 in the placebo group). These were recorded as major deviations, but were not excluded from the PP population because they adhered to treatment according to the protocol.

Overall, most subjects were female (58.3%) and most were white (76.5%). The mean age of the subjects was 58.6 (27 to 85) years. Most subjects (72.2%) had their symptoms for ≥1 year before treatment start and had been diagnosed ≥1 year prior to treatment start (64.3%, Table 6).

Table 6: Demographic and Baseline Characteristics (ITT Population)

	Lanreotide (N=59)	Placebo (N=56)	Total (N=115)
Age, years[a]			
N	59	56	115

Mean (SD)	57.9 (10.6)	59.3 (11.6)	58.6 (11.1)
Min, max	38, 77	27, 85	27, 85
Sex, n(%)			
Male	27 (45.8)	21 (37.5)	48 (41.7)
Female	32 (54.2)	35 (62.5)	67 (58.3)
Race/ethnicity, n(%)[b]			
Asian	6 (10.2)	3 (5.4)	9 (7.8)
Black / African American	2 (3.4)	3 (5.4)	5 (4.3)
White	44 (74.6)	44 (78.6)	88 (76.5)
Multi race	7 (11.9)	6 (10.7)	13 (11.3)
BMI, kg/m^2[c]			
N	57	55	112
Mean (SD)	26.75 (5.16)	26.93 (4.71)	26.84 (4.92)
Min, max	16.3, 45.2	18.6, 40.4	16.3, 45.2
Time since first symptoms to treatment start, n(%)[d]			
<1 year	14 (23.7)	18 (32.1)	32 (27.8)
≥1 year	45 (76.3)	38 (67.9)	83 (72.2)
Time since first diagnosis to treatment start, n(%)[e]			
<1 year	19 (32.2)	22 (39.3)	41 (35.7)
≥1 year	40 (67.8)	34 (60.7)	74 (64.3)

Data Source: Table 14.1.3.1.1.
ITT=intent-to-treat; N=total number of subjects in group; n=number of subjects with assessment; SD=standard deviation; BMI=body mass index.
Note: Treatment group refers to the group that a subject was randomized to receive during the DB phase.
All subjects received lanreotide during the IOL and/or the LTOLE phases.
a Age was calculated as the difference between date of birth and the first visit date/365.25.
b Subjects were included under the multi race category, if multiple race/ethnicity options were checked.
c BMI was calculated as: (weight in kg)/(square of height in meters).
d Time from first symptoms to study treatment start is derived from the first date of either: date of carcinoid syndrome, date of flushing or date of diarrhea.
e Time from first diagnosis to study treatment start is derived from the diagnosis date of carcinoid tumor.

Other Baseline Information

Diarrhea Events

In general, subjects in the Somatuline group experienced more diarrhea events per day during the Screening period as compared with those in the placebo group [mean (SD): 2.13 (1.85) events versus 1.57 (1.67), respectively] in the following table.

Table 7: Summary of Average Daily Frequency of Diarrhea Events during Screening (ITT Population)

	Lanreotide (N=59)	**Placebo (N=56)**
Average Daily Frequency of Diarrhea Events		
n	59	56
Median	1.57	0.86
Mean (SD)	2.13 (1.85)	1.57 (1.67)
95% CI	(1.65, 2.61)	(1.12, 2.02)
Min, max	0.0, 8.0	0.0, 6.7

Data Source: Table 14.2.2.1.1.
Notes: Only the observed data are used in the calculation. The missing data are excluded from the analysis.

Treatment group refers to the group the subjects were randomized to during the double-blind phase.
ITT=intent-to-treat; n= number of subjects taken into account for the analysis.

Flushing Events

Subjects in the Somatuline group had numerically fewer flushing events per day during the Screening period compared with those in the placebo group [mean (SD): 1.53 (1.98) versus 2.20 (3.27) events, respectively] in the following table.

Table 8: Summary Statistics of Average Daily Frequency of Flushing Events during Screening (ITT Population)

	Lanreotide (N=59)	**Placebo (N=56)**
Average Daily Frequency of Flushing Events		
n	59	56
Median	0.57	1.09
Mean (SD)	1.53 (1.98)	2.20 (3.27)
95% CI	(1.01, 2.04)	(1.32, 3.08)
Min, max	0.0, 8.6	0.0, 15.5

Data Source: Table 14.2.2.2.1
Notes: Only the observed data are used in the calculation. The missing data are excluded from the analysis.
Treatment group refers to the group the subjects were randomized to during the double-blind phase.
ITT=intent-to-treat; n= number of subjects taken into account for the analysis.

Diarrhea and/or Flushing Events

Overall, subjects in the Somatuline group experienced a comparable number of diarrhea and/or flushing events per day during the Screening period with subjects in the placebo group [mean (SD): 3.65 (2.92) versus 3.37 (4.25) events, respectively] in the following table.

Table 9: Summary Statistics of Average Daily Frequency of Diarrhea and/or Flushing Events during Screening (ITT Population)

	Lanreotide (N=59)	**Placebo (N=56)**
Average Daily Frequency of Diarrhea and/or Flushing Events		
n	59	56
Median	2.75	2.41
Mean (SD)	3.65 (2.92)	3.37 (4.25)
95% CI	(2.89, 4.41)	(2.63, 4.91)
Min, max	0.0, 10.9)	0.0, 17.8

Data Source: Post-hoc Table 14.2.5.4.8.1.3
Notes: Only the observed data are used in the calculation. The missing data are excluded from the analysis.
Treatment group refers to the group the subjects were randomized to during the double-blind phase.
ITT=intent-to-treat; n=number of subjects taken into account for the analysis.

Prior SSA Therapy

At baseline, 56 (48.7%) and 24 (20.9%) of subjects were previously being treated with octreotide LAR and octreotide (short acting), respectively. The Applicant stated that there was no differences across the Somatuline and placebo groups for the previous use of octreotide LAR, octreotide (short acting), or short acting octreotide.

However, there was a difference in the prior usage of SSA between the subjects in US and the subjects in countries outside the US (Ex-US). Four subjects (3.5%) in US had no experience of receiving SSA therapy prior to entering the study. While 47 subjects (40.9%) of subjects from Ex-US received SSA therapy prior to the study.

Table 10: Prior SSA Therapy (ITT Population)

	Lanreotide (N=59) n (%)	Placebo (N=56) n (%)	Total (N=115) n (%)
Prior use of LAR[a]			
Yes	28 (47.5%)	28 (50.0%)	56 (48.7%)
No	31 (52.5%)	28 (50.0%)	59 (51.3%)
Prior use of octreotide (short acting)			
Yes	15 (25.4%)	9 (16.1%)	24 (20.9%)
No	44 (74.6%)	47 (83.9%)	91 (79.1%)
Prior use of other SSA			
Yes	0	0	0
No	59 (100.0%)	55 (98.2%)	114 (99.1%)
Missing	0	1 (1.8%)	1 (0.9%)
Region and prior SSA therapy, n (%)			
US	21 (35.6)	19 (33.9)	40 (34.8)
Subjects with no prior SSA therapy	2 (3.4)	2 (3.6)	4 (3.5)
Subjects with prior SSA therapy	19 (32.2)	17 (30.4)	36 (31.3)
EX-US	38 (64.4)	37 (66.1)	75 (65.2)
Subjects with no prior SSA therapy	24 (40.7)	23 (41.1)	47 (40.9)
Subjects with prior SSA therapy	14 (23.7)	14 (25.0)	28 (24.3)
Prior SSA therapy, n (%)			
Prior SSA therapy within 3 months before screening	28 (47.5)	28 (50.0)	56 (48.7)
No Prior SSA therapy within 3 months before screening	31 (52.5)	28 (50.0)	59 (51.3)
s.c. octreotide usage during screening, n (%)			
s.c. Octreotide during screening	30 (50.8)	29 (51.8)	59 (51.3)
No s.c. Octreotide during screening	29 (49.2)	27 (48.2)	56 (48.7)

Data Source: Table 14.1.3.5 and Table 14.1.3.1.1.
a Octreotide LAR
Note: a subject may have been counted in several prior SSA therapy categories. No subjects were using an SSA pump or other SSA drugs at Baseline.

The percentage of subjects who had not previously used octreotide was assessed during screening and stratified by prior use of SSA. The analysis showed similar results for naïve subjects in both treatment groups (26.9% for the Somatuline group compared with

28.0% for the placebo group) and for subjects who had previously used SSA (66.7% for the Somatuline group compared with 64.5% for the placebo group).

Table 11 Octreotide Usage Status During the Screening Period Stratified by Prior Use of SSA

	No Use of Octreotide Stratified by Prior Use of SSA		Lanreotide	Placebo
Screening	Naive[a]	N	26	25
		n (%)	7 (26.9)	7 (28.0)
	Prior SSA	N	33	31
		n (%)	22 (66.7)	20 (64.5)

Data Source: Table 14.2.3.10.2.1 and Table 14.2.3.10.3.1
a De novo octreotide usage

Medical and Surgical History

Significant medical and surgical history reported in more than 10% of subjects in each treatment group, by SOC, is summarized for the ITT population in the following table. The most frequently reported pre-existing conditions were endocrine disorders (reported in 100% of subjects in both treatment groups), followed by gastrointestinal disorders (reported in 89.8% for the Somatuline group compared with 94.6% for the placebo group) and then vascular disorders (reported in 88.1%% for the Somatuline group compared with 89.3% for the placebo group).

Table 12: Significant Medical and Surgical History Reported in ≥10% of Subjects by SOC in Any Treatment Group (ITT Population)

	Lanreotide (N=59) n (%)	Placebo (N=56) n (%)	Total (N=115) n (%)
Any pre-existing conditions or procedures	59 (100.0)	56 (100.0)	115 (100.0)
Endocrine disorders	59 (100.0)	56 (100.0)	115 (100.0)
Gastrointestinal disorders	53 (89.8)	53 (94.6)	106 (92.2)
Vascular disorders	52 (88.1)	50 (89.3)	102 (88.7)
Surgical and medical procedures	48 (81.4)	47 (83.9)	95 (82.6)
Neoplasms benign, malignant and unspecified (include cysts and polyps)	34 (57.6)	32 (57.1)	66 (57.4)
Metabolism and nutrition disorders	19 (32.2)	21 (37.5)	40 (34.8)
Hepatobiliary disorders	19 (32.2)	19 (33.9)	38 (33.0)
Investigations	18 (30.5)	20 (35.7)	38 (33.0)
Reproductive system and breast disorders	15 (25.4)	13 (23.2)	28 (24.3)
Nervous system disorders	15 (25.4)	12 (21.4)	27 (23.5)
Cardiac disorders	14 (23.7)	27 (48.2)	41 (35.7)
Musculoskeletal and connective tissue disorders	14 (23.7)	18 (32.1)	32 (27.8)
Psychiatric disorders	13 (22.0)	16 (28.6)	29 (25.2)
Renal and urinary disorders	13 (22.0)	12 (21.4)	25 (21.7)
Respiratory, thoracic and mediastinal disorders	11 (18.6)	15 (26.8)	26 (22.6)
Skin and subcutaneous tissue disorders	11 (18.6)	9 (16.1)	20 (17.4)

Infections and infestations	10 (16.9)	14 (25.0)	24 (20.9)
Immune system disorders	9 (15.3)	12 (21.4)	21 (18.3)
Blood and lymphatic system disorders	9 (15.3)	10 (17.9)	19 (16.5)
Eye disorders	8 (13.6)	11 (19.6)	19 (16.5)
Injury, poisoning and procedural complications	8 (13.6)	7 (12.5)	15 (13.0)
General disorders and administration site conditions	7 (11.9)	13 (23.2)	20 (17.4)
Social circumstances	7 (11.9)	8 (14.3)	15 (13.0)

Data Source: Table 14.1.3.7.
Note: MedDRA Version: 18.1, was used to map the verbatim terms. Any subject who experienced the same coded event more than once was counted only once for that coded event.
As instructed in the CRF, only clinically significant history as per investigator's judgment was recorded.

The most frequently reported pre-existing events within each of the most frequently reported SOCs were carcinoid syndrome (reported in 100% of subjects in both treatment groups), diarrhea (reported in 79.7% for the Somatuline group compared with 85.7% for the placebo group) and flushing (reported in 62.7% for the Somatuline group compared with 75.0% for the placebo group). Gallbladder disorder was assessed at baseline. Most subjects in both the Somatuline and the placebo groups did not have cholelithiasis or bile sludge present at baseline.

Prior and Concomitant Medications

As shown in the following table, 74.6% of subjects in the Somatuline group and 75.0% of subjects in the placebo group used medications before the start of the study. Agents acting on the renin-angiotensin system were the most frequently used medications (reported in 22.0% for the Somatuline group and 30.4% for the placebo group), followed by beta blocking agents (reported in 25.4% for the Somatuline group and 21.4% for the placebo group).

Overall, 11.9% of subjects in the Somatuline group and 7.1% of subjects in the placebo group used other concomitant rescue medications for diarrhea only (most often loperamide) before the start of the study. No subjects used rescue medications for flushing events.

Table 13: Prior Medications Most Frequently Reported in Subjects by Therapeutic Class (ITT Population)

Therapeutic class	**Lanreotide (N=59) n (%)**	**Placebo (N=56) n (%)**
Any prior medications	44 (74.6)	42 (75.0)
Beta blocking agents	15 (25.4)	12 (21.4)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	14 (23.7)	12 (21.4)
Agents acting on the renin-angiotensin system	13 (22.0)	17 (30.4)
Diuretics	11 (18.6)	12 (21.4)
Analgesics	9 (15.3)	14 (25.0)
Psychoanaleptics	9 (15.3)	8 (14.3)
Lipid modifying agents	9 (15.3)	7 (12.5)
Drugs for acid related disorders	8 (13.6)	12 (21.4)

Drugs used in diabetes	7 (11.9)	6 (10.7)
Vitamins	6 (10.2)	10 (17.9)
Antiinflammatory and antirheumatic products	6 (10.2)	8 (14.3)
Antithrombotic agents	5 (8.5)	13 (23.2)
Calcium channel blockers	5 (8.5)	8 (14.3)
Mineral supplements	5 (8.5)	5 (8.9)
Thyroid therapy	4 (6.8)	8 (14.3)
Drugs for treatment of bone diseases	4 (6.8)	2 (3.6)
Cough and cold preparations	3 (5.1)	2 (3.6)
Sex hormones and modulators of the genital system	3 (5.1)	2 (3.6)
All other therapeutic products	3 (5.1)	1 (1.8)
Antianemic preparations	2 (3.4)	5 (8.9)
Drugs for obstructive airway diseases	2 (3.4)	5 (8.9)
Psycholeptics	2 (3.4)	5 (8.9)
Ophthalmologicals	2 (3.4)	4 (7.1)
Antiemetics and antinauseants	2 (3.4)	2 (3.6)
Corticosteroids for systemic use	2 (3.4)	2 (3.6)
Drugs for functional gastrointestinal disorders	2 (3.4)	1 (1.8)
Anti-parkinson drugs	2 (3.4)	0
Unspecified herbal and traditional medicine	2 (3.4)	0
Antibacterials for systemic use	1 (1.7)	4 (7.1)
Antihistamines for systemic use	1 (1.7)	4 (7.1)
Cardiac therapy	1 (1.7)	3 (5.4)
Antigout preparations	1 (1.7)	2 (3.6)
Urologicals	1 (1.7)	2 (3.6)
Antiepileptics	1 (1.7)	1 (1.8)
Blood substitutes and perfusion solutions	1 (1.7)	1 (1.8)
Corticosteroids, dermatological preparations	1 (1.7)	1 (1.8)
Drugs for constipation	1 (1.7)	1 (1.8)
Antihypertensives	1 (1.7)	0
Bile and liver therapy	1 (1.7)	0
General nutrients	1 (1.7)	0
Immunosuppressants	1 (1.7)	0
Other alimentary tract and metabolism products	1 (1.7)	0
Other gynecologicals	1 (1.7)	0
Other nervous system drugs	1 (1.7)	0
Pancreatic hormones	1 (1.7)	0
Vasoprotectives	1 (1.7)	0
Digestives, incl. enzymes	0	6 (10.7)
Stomatological preparations	0	2 (3.6)
Anesthetics	0	1 (1.8)
Endocrine therapy		(1.8)
Muscle relaxants		(1.8)
Peripheral vasodilators	0	1 (1.8)

Therapeutic class	Lanreotide (N=59) n (%)	Placebo (N=58) n (%)
Any concomitant medications	45 (76.3)	42 (75.0)
Beta blocking agents	16 (27.1)	12 (21.4)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	15 (25.4)	13 (23.2)
Analgesics	14 (23.7)	23 (41.1)
Vitamins	14 (23.7)	18 (32.1)
Agents acting on the renin-angiotensin system	13 (22.0)	20 (35.7)
Diuretics	12 (20.3)	12 (21.4)
Lipid modifying agents	11 (18.6)	7 (12.5)
Drugs for acid related disorders	10 (16.9)	15 (26.8)
Psychoanaleptics	10 (16.9)	11 (19.6)
Antiinflammatory and antirheumatic products	9 (15.3)	13 (23.2)
Antibacterials for systemic use	8 (13.6)	5 (8.9)
Psycholeptics	7 (11.9)	10 (17.9)
Drugs used in diabetes	7 (11.9)	6 (10.7)
Antithrombotic agents	6 (10.2)	14 (25.0)
Calcium channel blockers	6 (10.2)	9 (16.1)
Mineral supplements	6 (10.2)	6 (10.7)

Data Source: Table 14.1.4.1.1.
Note: World Health Organisation (WHO) Drug Dictionary, version June 2015, was used to code the concomi ant medications. Subjects with more than one preferred term within a therapeutic class were only counted once for that therapeutic class.
This table includes medications started prior to the date of the first study injection.

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The percentage of subjects who were using concomitant medications during the DB phase was comparable between both treatment groups (76.3% for the Somatuline group and 75.0% for the placebo group). The concomitant medications most frequently used during the

DB phase were analgesics (23.7% of subjects in the Somatuline group and 41.1% of subjects in the placebo group) and agents acting on the renin-angiotensin system (22.0% of subjects in the Somatuline group and 35.7% of subjects in the placebo group).

Table 14: Concomitant Medications Used during DB Phase in Subjects by Therapeutic Class (ITT Population)

Therapeutic class	Lanreotide (N=59) n (%)	Placebo (N=56) n (%)
Any concomitant medications	45 (76.3)	42 (75.0)
Beta blocking agents	16 (27.1)	12 (21.4)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	15 (25.4)	13 (23.2)
Analgesics	14 (23.7)	23 (41.1)
Vitamins	14 (23.7)	13 (23.2)
Agents acting on the renin-angiotensin system	13 (22.0)	20 (35.7)
Diuretics	12 (20.3)	12 (21.4)
Lipid modifying agents	11 (18.6)	7 (12.5)
Drugs for acid related disorders	10 (16.9)	15 (26.8)
Psychoanaleptics	10 (16.9)	11 (19.6)
Antiinflammatory and antirheumatic products	9 (15.3)	13 (23.2)
Antibacterials for systemic use	8 (13.6)	5 (8.9)
Psycholeptics	7 (11.9)	10 (17.9)
Drugs used in diabetes	7 (11.9)	6 (10.7)
Antithrombotic agents	6 (10.2)	14 (25.0)
Calcium channel blockers	6 (10.2)	9 (16.1)
Mineral supplements	6 (10.2)	6 (10.7)
Unspecified herbal and traditional medicine	6 (10.2)	2 (3.6)
Thyroid therapy	5 (8.5)	9 (16.1)
Antihistamines for systemic use	5 (8.5)	6 (10.7)
Ophthalmologicals	5 (8.5)	6 (10.7)
Antianemic preparations	5 (8.5)	5 (8.9)
Cough and cold preparations	5 (8.5)	3 (5.4)
Digestives, incl. enzymes	4 (6.8)	7 (12.5)
Drugs for functional gastrointestinal disorders	4 (6.8)	7 (12.5)
Antiemetics and antinauseants	4 (6.8)	4 (7.1)
Drugs for treatment of bone diseases	4 (6.8)	3 (5.4)
Drugs for obstructive airway diseases	3 (5.1)	6 (10.7)
Drugs for constipation	3 (5.1)	5 (8.9)
Corticosteroids for systemic use	3 (5.1)	4 (7.1)
Sex hormones and modulators of the genital system	3 (5.1)	2 (3.6)
Anti-parkinson drugs	3 (5.1)	1 (1.8)
Vasoprotectives	3 (5.1)	0
All other therapeutic products	2 (3.4)	3 (5.4)
Cardiac therapy	2 (3.4)	3 (5.4)
Urologicals	2 (3.4)	3 (5.4)
Antihypertensives	2 (3.4)	1 (1.8)
Corticosteroids, dermatological preparations	2 (3.4)	1 (1.8)
Nasal preparations	2 (3.4)	1 (1.8)
Other alimentary tract and metabolism products	2 (3.4)	1 (1.8)
Other nervous system drugs	2 (3.4)	0
Blood substitutes and perfusion solutions	1 (1.7)	3 (5.4)
Anesthetics	1 (1.7)	2 (3.6)
Antiepileptics	1 (1.7)	2 (3.6)

Antigout preparations	1 (1.7)	2 (3.6)
Antivirals for systemic use	1 (1.7)	1 (1.8)
Other gynecologicals	1 (1.7)	1 (1.8)

(Continued)

Therapeutic class	Lanreotide (N=59) n (%)	Placebo (N=56) n (%)
Antipruritics, incl. antihistamines, anesthetics, etc.	1 (1.7)	0
Bile and liver therapy	1 (1.7)	0
Contrast media	1 (1.7)	0
General nutrients	1 (1.7)	0
Immunostimulants	1 (1.7)	0
Immunosuppressants	1 (1.7)	0
Other respiratory system products	1 (1.7)	0
Otologicals	1 (1.7)	0
Pancreatic hormones	1 (1.7)	0
Stomatological preparations	0	3 (5.4)
Vaccines	0	2 (3.6)
Antibiotics and chemotherapeutics for dermatological use	0	1 (1.8)
Emollients and protectives	0	1 (1.8)
Endocrine therapy	0	1 (1.8)
Muscle relaxants	0	1 (1.8)
Peripheral vasodilators	0	1 (1.8)

Data Source: Table 14.1.4.3.1.
Note: World Health Organisation (WHO) Drug Dictionary, version June 2015, was used to code the concomitant medications. Subjects with more than one preferred term within a therapeutic class were only counted once for that therapeutic class. This table includes concomitant medications started used during the DB phase.

Statistical Analysis

The ITT, PP, and Safety Populations are presented in the following table. The ITT population included 115 patients (59 Somatuline, and 56 placebo) who received at least one scheduled injection. The safety population also had 115 patients with the difference of one subject removed from the Somatuline group. This was because the subject (I (b) (6)) was randomized to Somatuline group, but erroneously received placebo. The PP population included subjects in the ITT population for whom no major protocol violations/deviations occurred during the DB phase including the subjects who had early roll over to the open label phase.

Table 15: Analysis Populations for the Double-blind Treatment Period

	Lanreotide (N=59)	Placebo (N=56)	Total (N=115)
	n (%)		
ITT	59 (100.0)	56 (100.0)	115 (100.0)
Safety	58 (98.3)	57 (101.8)[a]	115 (100.0)
PP	54 (91.5)	46 (82.1)	100 (87.0)

Data Source: Table 14.1.1.1.
a For the placebo group, n=56 for the ITT population and n=57 for the safety population. This discrepancy can be attributed to the fact that subject (b) (6) was randomised to lanreotide Autogel, but erroneously received placebo, therefore was included in the safety population as per the actual treatment received.

Medical Officer Comments:
As a result of "early roll-over" of the pre-specified protocol, 14 (23.7%) subjects in the Somatuline group and 22 (39.3%) in the placebo group were early-roll-over to the open-label phase.
This produced an imbalance in breakthrough data between Somatuline and placebo groups. The placebo group had 8 more subjects (than the Somatuline group) whose breakthrough days were imputed to 0% usage of octreotide during the 12 weeks of the 16 weeks DB study period in favor of placebo group, while in fact these unsuccessful placebo subjects had more percentage of octreotide days than the imputed 0% usage.

Protocol Amendments

There were 9 amendments. The Applicant provided the rationale for amendment. All the changes were reviewed. These modifications did not change the integrity of the trial or reviewer's interpretation of the results.

Data Quality and Integrity: Sponsor's Assurance

The Applicant assured the data quality and integrity of Study 730. The study was conducted in accordance with Good Clinical Practice (GCP) as required by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

All study protocol amendments, written study patient information, informed consent form (ICF), and any other appropriate study-related information were reviewed and received approval of ethics committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC], or Ethics Review Committee [ERC]) before the study began. Institutional Review Board/IEC information for all study sites is submitted.

6.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that all the studies (730, 726, and 718) submitted to this NDA were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). The studies were conducted under IND 078749.

Financial Disclosure

The Applicant has adequately disclosed financial interests or arrangements with the clinical investigators (see Appendix 13.2). The sponsor stated that none of the clinical investigators received significant payments as defined in 21 CRG 54.2(a), (b), and (f).

Medical Officer Comments: The Applicant has reasonably disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not raise concerns which would possibly jeopardize the integrity of the data.

Patient Disposition

A total of 115 subjects were randomized in the DB phase to receive Somatuline (59 subjects) or placebo (56 subjects). The Somatuline group had a higher rate of completion of the DB phase than the placebo, 45 (76.3%) versus 34 (60.7%), respectively.

Table 16: Patient Disposition (Study 730)

	Lanreotide (N=59) n (%)	Placebo (N=56) n (%)	Total (N=115) n (%)
Screened			153
Failed screening			38
Completed DB phase[a]	45 (76.3)	34 (60.7)	79 (68.7)
Continued to IOL phase[b]	45 (76.3)	33 (58.9)	78 (67.8)
Did not continue to IOL phase	0	1 (1.8)	1 (0.9)
Did not complete DB phase	14 (23.7)	22 (39.3)	36 (31.3)
Continued to IOL phase (rolled over early)[c][d]	11 (18.6)	12 (21.4)	23 (20.0)
Did not continue to IOL phase	3 (5.1)	10 (17.9)	13 (11.3)
Entered IOL phase	56 (94.9)	45 (80.4)	101 (87.8)
Completed IOL phase	43 (72.9)	37 (66.1)	80 (69.6)
Continued to LTOLE phase	32 (54.2)	25 (44.6)	57 (49.6)
Did not continue to LTOLE phase	11 (18.6)	12 (21.4)	23 (20.0)
Did not complete IOL phase	13 (22.0)	8 (14.3)	21 (18.3)
Did not continue to LTOLE phase	13 (22.0)	8 (14.3)	21 (18.3)
Entered LTOLE phase[e]	32 (54.2)	25 (44.6)	57 (49.6)
Completed LTOLE phase	17 (28.8)	8 (14.3)	25 (21.7)
Discontinued during LTOLE phase	15 (25.4)	17 (30.4)	32 (27.8)
Primary reason for discontinuation during DB phase[f]			
Adverse Event	1 (1.7)	2 (3.6)	3 (2.6)
Lost to Follow-up	0	0	0
Patient Decision	1 (1.7)	5 (8.9)	6 (5.2)
Investigator Decision	0	0	0
Sponsor Decision	0	1 (1.8)	1 (0.9)
Death	0	0	0
Other	1 (1.7)	3 (5.4)	4 (3.5)
Primary reason for discontinuation during IOL phase			
Adverse Event	1 (1.7)	1 (1.8)	2 (1.7)
Lost to Follow-up	0	0	0
Patient Decision	4 (6.8)	3 (5.4)	7 (6.1)
Investigator Decision	3 (5.1)	2 (3.6)	5 (4.3)
Sponsor Decision	1 (1.7)	0	1 (0.9)
Death	0	0	0
Other	4 (6.8)	2 (3.6)	6 (5.2)
Study site not participating in extension	7 (11.9)	8 (14.3)	15 (13.0)
Primary reason for discontinuation during LTOLE phase[g]			
Adverse Event	7 (21.9)	3 (12.0)	10 (17.5)
Lost to Follow-up	0	0	0
Patient Decision	0	5 (20.0)	5 (8.8)
Investigator Decision	4 (12.5)	1 (4.0)	5 (8.8)
Sponsor Decision	2 (6.3)	1 (4.0)	3 (5.3)
Death	0	0	0
Other	2 (6.3)	7 (28.0)	9 (15.8)

Data Source: Table 14.1.1.1

N=total number of subjects in group; n=number of subjects with assessment; ITT=Intent-to-treat; PP=Per-protocol; DB=double-blind; IOL=initial open-label; LTOLE=long-term extension open-label.

Note: Treatment group refers to the group that a subject was randomised to receive during the DB phase. All subjects received lanreotide Autogel during the IOL and/or the LTOLE phases. Unless otherwise noted, percentages in this table were based on the number of ITT subjects.

Terminations due to disease progression were reported in the category Other - 'Other: Disease progression' or 'Other: tumour progression'.

Number of subjects who discontinued due to an AE includes subjects who died during the DB, IOL and LTOLE phases (see Section 12.3.3.1) as this was reported as a withdrawal with the reason given as an "AE" provided on the termination page.

*Subject (b) (6) was randomised to lanreotide Autogel, but erroneously received placebo, therefore was included in the safety population as per the actual treatment received.

a Subjects re-screened counted once.

b Subjects who received four double-blind study injections AND rolled over into the IOL phase OR had diary data at least up to the 21st day after the 4th DB injection (regardless of missing diary data before the 21st day).

c Subjects who received any open-label study injections.

d Based on data entered in the Subject Status – Completion of the Initial Open-label Phase CRF.

e Subjects who received any study drug injections at or after visit Week 48. The LTOLE phase will end when two years have elapsed from the time the last subject has completed his/her participation in the initial 32-week OL phase

f Thirteen subjects were considered early withdrawals in the DB phase. However, one placebo subject (b) (6) who completed the DB phase, but did not continue into the IOL phase.

g Percentages are based on the number of ITT subjects participating in the LTOLE phase.

Medical Officer Comments:
At the EOP2 meeting on July 15, 2008, the Applicant discussed an "early roll over" strategy of the protocol with the Division. The purpose of "early roll over" was (1) protecting patients from extensive unbearable suffering due to carcinoid syndrome, and (2) collecting essential information for efficacy analysis of Somatuline activity. As a result, 14 (23.7%) subjects in the Somatuline group and 22 (39.3%) in the placebo group were early rolled-over to the open-label phase. This produced an imbalance in breakthrough data between Somatuline and placebo groups. The placebo group had 8 more subjects than the Somatuline group, whose breakthrough days were imputed to 0% usage of octreotide during the 12 weeks (12/16) DB study period in favor of placebo group.

(b) (4)

(b) (4) The Division asked the Applicant to propose "an alternative imputation strategy." The Applicant accepted the recommendation, applying 0% usage to subjects who drop early. That is in favor of placebo.

Protocol Deviations (Study 730)

There were 17 subjects (17/59, 28%) in the Somatuline group and 19 subjects (19/56, 33%) in placebo group who had protocol deviations in the DB study (ITT population). The most commonly protocol deviation was "procedures violation" (7/59 vs. 7/56 for the treated and placebo, respectively), followed by "time window violation" (5/59 vs. 5/56), and "eligibility criteria violation" (4/59 vs. 6/56).

While these deviations could have impacted treatment efficacy and/or safety in the DBT Period, the Applicant did not believe these deviations had an impact on the overall study results.

Medical Officer Comment:
I agree with the investigator that the deviations had not major impact on the overall study results.

Treatment Compliance (Study 730)

The Applicant stated that "All injections of study treatment were administered by qualified unblinded study center personnel. Compliance was ensured by having all study treatments

administered at the study center. Study treatment administration date and time were recorded in the medical records and transcribed to the CRF."

Medical Officer Comments:
The listings of administration date and time (Listing 16.2.5.1), drug exposure (Listing 16.2.5.2), and visit status (Listing 16.2.5.4) were reviewed. No misconduct was found.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the percentage of days that any rescue octreotide was used in addition to Somatuline treatment for controlling carcinoid syndrome symptoms of diarrhea/flushing during the 16-week DB period. A treatment diary was recorded using IVRS/IWRS.

The results showed that the Somatuline group used rescue octreotide for significantly fewer days during the DB period as compared to the placebo. The least squares (LS) mean percentage of octreotide-rescue days of the Somatuline was 33.7%, while the placebo was 48.4% of days (p=0.016).

Table 17: Percentage of Days with Subcutaneous Octreotide as Rescue Medication during DB Period (ITT Population)

	N	LS Mean (SE)	95% CI	LS mean diff (Lanreotide – placebo)	95% CI LS mean diff (Lanreotide – placebo)	p-value
Lanreotide	59	33.72 (4.39)	(25.02, 42.42)	–14.76	(–26.78 –2.75)	0.0165
Placebo	56	48.49 (4.50)	(39.57, 57.40)			

Data Source: Table 14.2.1.2.1.
LS Mean=least squares mean (i.e., adjusted for stratification factors and covariates (octreotide usage, daily average of diarrhoea and daily average of flushing events at baseline) based on the ANCOVA model evaluation presented in the statistical appendix and in Table 14.2.1.3.1. Interaction between treatment and stratification factors was tested – no significance); SE=standard error; CI=confidence interval; ERO=roll over
This analysis does not include any imputation for the ERO subjects.

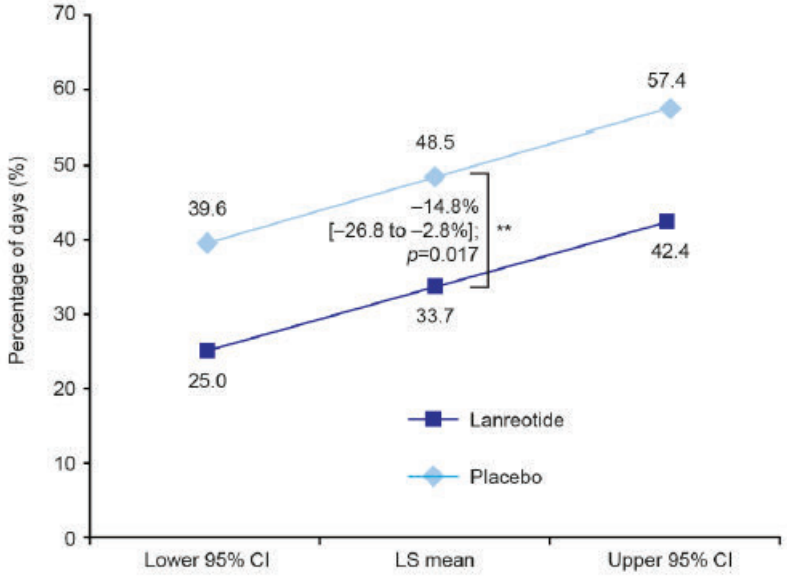
Medical Officer Comments:
Fourteen (23.7%) subjects in the Somatuline group and 22 subjects (39.3%) in the placebo group were early-rolled over to the open-label phase. This produced an imbalance in breakthrough data between Somatuline and placebo groups. The placebo group had 8 more subjects than the Somatuline group, whose breakthrough days were imputed to 0% usage of octreotide during the 12 weeks of 16 weeks DB study period. This was a huge deduction in favor of placebo group. Despite the imbalance, the Somatuline group showed the greater reduction of breakthrough days, and the reduction of octreotide use is clinically meaningful.

The percentage of days short-acting octreotide was used as a rescue therapy for controlling CS

diarrhea and flushing symptoms was plotted against the confidence interval of total days of rescue octreotide use. Least Squares Method was used to determine the equation of the curve that provides a "good fit" to the points. The Y-axis represents percentage of days of rescue octreotide use. The X-axis represents the confidence interval of total days of octreotide use for controlling CS symptom (Figure 5). The results show that the days of rescue octreotide use (upper line, placebo) are essentially proportional to the total days required for controlling carcinoid symptoms. The higher the capability of carcinoid tumors to generate CS diarrhea, the more days of rescue octreotide were required (Figure 5, upper line).

It is noted that the Somatuline group (lower line) had the similar slope of the octreotide, as determined by the Least Squares method. This observation is supported by the evidence that receptor binding and the biological response to Somatuline treatment are essentially similar to the octreotide.

Figure 5: Percentage of Days Short-Acting Octreotide was used as Rescue Therapy for Symptom Control



Data Source: Table 14.2.1.2.1.
Adjusted for baseline use of short-acting octreotide, symptoms, prior therapy, and region. **LS (adjusted) mean [95% CI] treatment difference = –14.8% [–26.8 to –2.8%]; p=0.017.

Medical Officer Comments:
The above figure was seriously criticized by the Statistical Reviewer. The clinical reviewer disagrees with the criticism, because (1) the figure included the 28-day DB data from the early rolled over subjects, thus, it provides a better picture for comparing breakthrough days between Somatuline and placebo groups; and (2) the figure is consistent with the fact that Somatuline and octreotide bind to the same group of somatostatin receptors (b) (4)

(b) (4)

Supportive Analysis of Primary Endpoint: Responder Analysis

A responder analysis was conducted for the last 4 weeks of the 16-week DB period. A complete responder was defined as no octreotide use during the 4 weeks; a partial responder was defined as the need for octreotide use for no more than 3 days (3/28) and a non-responder was defined as the need for octreotide use for more than 3 days during the 4 weeks following the 4th DB injection (the last 4 weeks). The results showed that 40.7% of patients in Somatuline group were complete responders, compared to 23.2% of the placebo. These results suggest that Somatuline treatment reduced the need for using octreotide.

Table 18: Summary Statistics of Subject Responder during the DB Phase (ITT Population)

	Lanreotide (N=59)	Placebo (N=56)
Subject responder [a]		
Treatment success		
n (%)	24 (40.7)	13 (23.2)
95% CI	(28.1, 54.3)	(13.0, 36.4)
Partial treatment success		
n (%)	4 (6.8)	3 (5.4)
95% CI	(1.9, 16.5)	(1.1, 14.9)
Treatment failure		
n (%)	31 (52.5)	40 (71.4)
95% CI	(39.1, 65.7)	(57.8, 82.7)

Data Source: Table 14.2.1.1.1.1.
Note: Only the observed data were used in the calculation. The missing data were excluded from the analysis.
a Treatment success=subcutaneous octreotide was not required as rescue during the 4 weeks following the 4th DB injection. Partial Treatment success=subcutaneous octreotide usage as rescue medication in 1 to 3 days during the 4 weeks following the 4th DB injection.
Treatment Failure=subcutaneous octreotide usage as rescue medication more than 3 days during the 4 weeks following the 4th DB injection (Week 12 through to Week 15). Subjects who received less than four DB study treatment injections were considered as treatment failures.
DB=double-blind; ITT=intent-to-treat; CI=confidence interval

Medical Officer Comments:
It is noted that placebo group had 23% of subjects who met the criterion of treatment success, while the Somatuline group had 40%. Whether the uncounted breakthrough days of the 8 more placebo subjects (than the Somatuline) during the 12 weeks of the 16 weeks study lead to the high rate of placebo responders is not clear. Despite the placebo had more breakthrough days uncounted, Somatuline group showed greater responder rate (40%) than the placebo (23%).

Data Quality and Integrity – Reviewer's Assessment

There are four factors that had potential impacts on the outcomes of the primary endpoint: (1) background frequency of diarrhea, (2) diarrhea frequency at DB phase, (3) the proportion of patients who had concomitant use of anti-diarrhea opioid during the DB phase, and (4) the proportion of patients who had concomitant use of opioid analgesics during the DB phase. These factors are evaluated as follows:

(1) The Somatuline group had slightly higher average daily frequency of diarrhea episodes at baseline than the placebo (2.13 and 1.57, respectively).
(2) The average daily diarrhea episodes during the DB phase were 1.56 and 1.35 for the Somatuline and placebo groups, respectively. There were numerical changes during the DB phase from baseline, and the changes were in favor of the Somatuline group.
(3) The proportion of patients who had anti-diarrhea loperamide use at baseline:
Somatuline group: 7/59 patients (11.9%)
Placebo group: 2/56 patients (3.6%).
Concomitant use of anti-diarrhea opioids during the DB phase included loperamide, Lomotil, and diphenoxylate hydrochloride.
Somatuline group: 15/59, (25.4%)
Placebo group: 12/56, (21.4%)
(4) Opioid analgesic use at baseline included codeine, morphine, oxycodone, and Vicodin. The proportion of patients who used opioid analgesics were as follows:
Somatuline group: 4/59 (6.7%)
Placebo group: 6/56 (10.7%)
Concomitant use of analgesics during the DB phase included codeine fentanyl, morphine oxycodone, pethidine tramadol, and Vicodin. The proportions of patients were as follows:
Somatuline group: 11/59 (18.6%)
Placebo group: 18/56 (32.1%)

Medical Officer Comment:
The investigator stated that the numerical differences in concomitant uses of opioid anti-diarrhea and analgesics do not appear to have major impact on the overall study results. Considering that these opioid antidiarrheal and analgesics were short-acting, and some values were in favor of placebo, the clinical reviewer agrees that major impact on the overall study is unlikely.

The Somatuline group had a slightly lower average frequency of flushing episodes at baseline than the placebo (1.53 and 2.20 per day, respectively). During the DB phase the average daily frequency of flushing events was lower in the Somatuline group than in the placebo (0.92 and 1.75, respectively). There was a difference in LS means of -0.42 with 95% CI (-0.79, -0.06). The percentage of days of rescue loperamide during the screening period in the Somatuline group was higher than the placebo group with 12.8 days and 8.3 days, respectively (Table 19).

Table 19: Summary of Average Daily Frequency of Diarrhea and Flushing Events during Screening and the DB Phase, and Percentage of Days with Other Concomitant Rescue Medications (ITT Population)

	Lanreotide (N=59)	Placebo (N=56)
Average daily frequency of Diarrhea events during Screening		
Median	1.57	0.86
Mean (SD)	2.13 (1.85)	1.57 (1.67)
95% CI	(1.65, 2.61)	(1.12, 2.02)
Min, max	0.0, 8.0	0.0, 6.7
Average daily frequency of Diarrhea events during DB phase		
Median	0.87	0.67
Mean (SD)	1.56 (1.83)	1.35 (1.45)
95% CI	(1.08, 2.04)	(0.96, 1.74)
Min, max	0.0,7.6	0.0,6.8
Average daily frequency of Flushing events during Screening		
Median	0.57	0.80
Mean (SD)	1.53 (1.98)	2.20 (3.27)
95% CI	(1.01, 2.04)	(1.32, 3.08)
Min, max	0.0,5.9	0.0, 15.5
Average daily frequency of Flushing events during DB phase		
Median	0.29	0.80
Mean (SD)	0.92 (1.45)	1.75 (2.26)
95% CI	(0.54, 1.30)	(1.15, 2.36)
Min, max	0.0,5.9	0.0,9.7
Percentage of days with other rescue medication during Screening		
Median	0.00	0.00
Mean (SD)	12.85 (28.63)	8.31 (23.69)
95% CI	(5.39, 20.32)	(1.96, 14.65)
Min, max	0.0,96.4	0.0,100.0
Percentage of days with other rescue medication during DB phase*		
Median	0.00	0.00
Mean (SD)	8.86 (19.34)	6.25 (17.48)
95% CI	(3.83, 13.90)	(1.57, 10.93)
Min, max	0.0,91.2	0.0,100.0
Number and proportion of subjects who rolled over early		
n (%)	11 (18.6)	12 (21.4)
95% CI	(9.7, 30.9)	(11.6, 34.4)

Data Source: Table 14.2.2.1.1, Table 14.2.2.2.1, Table 14.2.2.1.2.1, Table 14.2.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1 and Table 14.2.3.12.1
Note: Subjects who rolled over early were those who received less than four DB injections before receiving the first IOL injection.
* subjects were required to record the use and dose of s.c. octreotide, if any, as well as the use of other concomitant rescue medications (e.g. loperamide 2 mg tabs, and/or tincture of opium); DB=double-blind; ITT=intent-to-treat; SD=standard deviation; CI=confidence interval

While there were differences in the concomitant use of opioid anti-diarrhea and analgesics between lanreotide and placebo groups during the DB period, the Applicant did not believe these numerical differences had an impact on the overall study results.

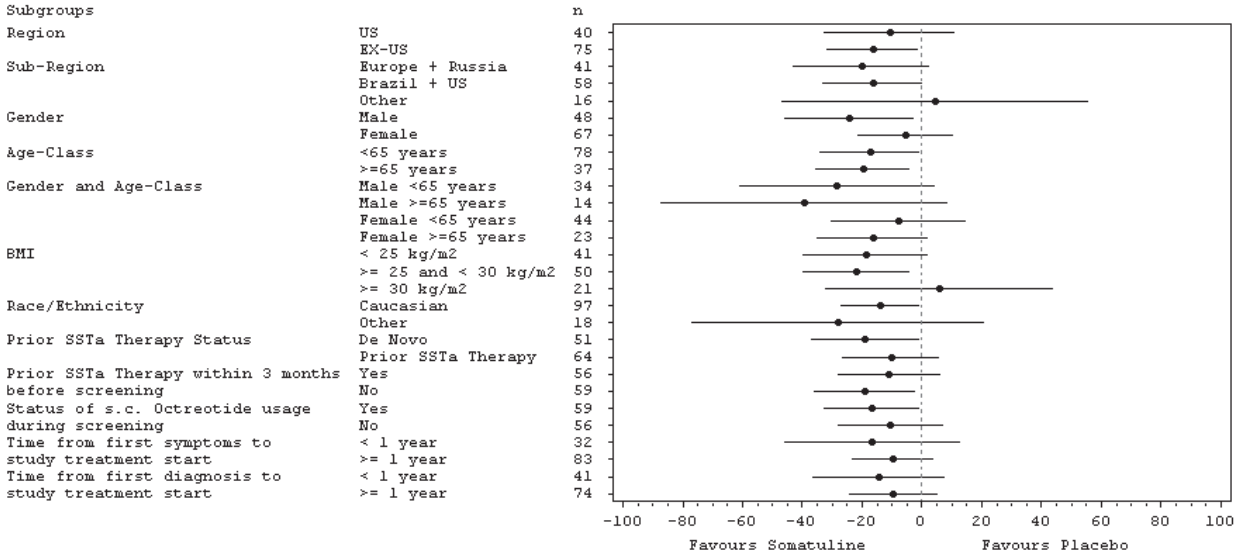
Medical Officer Comment:

I agree with the Applicant that the differences in concomitant uses of opioid anti-diarrhea and analgesics do not appear to have major impact on the overall study results.

Supplemental Analysis of the Primary Efficacy Endpoint

The subgroup analyses were conducted, and the results were consistent with the outcomes of primary efficacy endpoint. Figure 6 shows that there was a reduction in mean percentage of days in which rescue octreotide was administered irrespective of age, gender, race, ethnicity, time since diagnosis, and BMI (except for BMI>30 kg/m^2).

Figure 6: Forest Plot of the Subgroup Analyses for the Percentage of Days with Rescue Octreotide Use during DB Phase (ITT Population, Study 730)



Data Source: Study 730 Report, Figure 7, page 65 of 132.
ANCOVA=analysis of covariance; BMI=body mass index; DB=double-blind; ITT=intent-to-treat; SSTa=somatostatin analogue; s.c.=subcutaneous.
Note: Displayed LS mean differences for lanreotide–placebo together with 95% CIs are obtained from the subgroup ANCOVA analyses containing treatment, stratification factor(s) and baseline parameters (baseline octreotide, diarrhea, and flushing events).

Percentage of Days with Severe and Moderate/Severe Symptoms

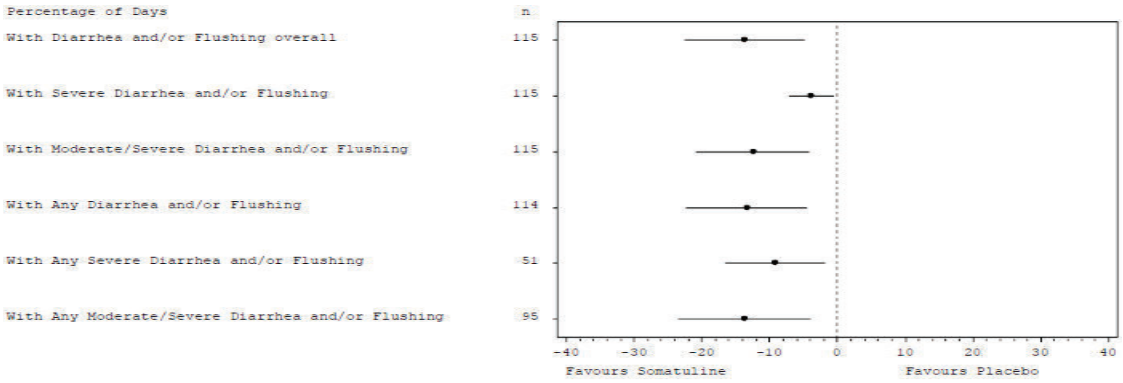
The percentage of days that subjects recorded moderate or severe symptoms during the 16-week DB phase was analyzed to define patient-reported symptomology between the Somatuline and placebo groups. The analyses are shown in Table 20.

Table 20: Post-Hoc Analyses of Percentage of Days with Severe or Moderate/Severe Symptoms during the Double-blind Phase (ITT Population)

Endpoints of Percentage of Days with Symptom(s):	Lanreotide Autogel	Placebo	Treatment Difference (Lanreotide Autogel - Placebo) (95% CI)	% Reduction in # of Days with Symptoms [a]	p-value
Any Moderate or Severe Symptom (Diarrhoea and/or Flushing)					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	23.43 (3.06)	35.83 (3.12)	-12.40 (-20.73, -4.07)	34.6	0.0039
N (Subgroup with Moderate/Severe Symptoms in DB)	49	46			
Percentage of Days; LS Mean (SE), %	29.06 (3.51)	42.76 (3.65)	-13.70 (-23.49, -3.90)	43.6	0.0066
Any Severe Symptom (Diarrhoea and/or Flushing)					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	3.86 (1.20)	7.62 (1.23)	-3.76 (-7.01,-0.52)	49.3	0.0233
N (Subgroup with Severe Symptoms in DB)	27	24			
Percentage of Days; LS Mean (SE), %	8.76 (2.45)	17.84 (2.81)	-9.08 (-16.41, -1.76)	50.9	0.0162
Moderate or Severe Diarrhoea					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	15.78 (2.62)	24.61 (2.66)	-8.83 (-15.99, -1.67)	35.9	0.0161
N (Subgroup with Moderate/Severe Diarrhoea in DB)	46	41			
Percentage of Days; LS Mean (SE), %	21.07 (3.27)	31.44 (3.43)	-10.37 (-19.67, -1.07)	33.0	0.0293
Moderate or Severe Flushing					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	13.23 (2.41)	21.66 (2.48)	-8.43 (-14.96, 1.90)	38.9	0.019
N (Subgroup with Moderate/Severe Flushing in DB)	27	36			
Percentage of Days; LS Mean (SE), %	26.66 (4.59)	35.98 (4.18)	-9.32 (-21.18, 2.54)	25.9	0.1213
Severe Diarrhoea					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	2.96 (0.83)	4.92 (0.85)	-1.96 (-4.20, 0.28)	39.8	0.0864
N (Subgroup with Severe Diarrhoea in DB)	22	21			
Percentage of Days; LS Mean (SE), %	7.04 (1.97)	12.23 (2.17)	-5.19 (-11.14, 0.76)	42.4	0.0853
Severe Flushing					
N (All Subjects)	59	56			
Percentage of Days; LS Mean (SE), %	1.65 (0.92)	3.51 (0.95)	-1.86 (-4.37, 0.64)	53.0	0.1437
N (Subgroup with Severe Flushing in DB)	13	14			
Percentage of Days; LS Mean (SE), %	10.65 (4.36)	16.91 (3.67)	-6.26 (-16.91, 4.40)	37.0	0.2359

From Study 730 Report, Table 25, page 82 of 132
DB=double-blind; LS Mean=least squares means based on ANCOVA model (adjusted for prior SST use, region, and respective baseline score); SE=standard error; CI=95% confidence intervals. In the models with 'All Subjects', the subjects without any severe (moderate/severe, respectively) symptoms are included with 0% percentage of days.
[a] Percent reduction in the number of days with symptoms for the lanreotide group was calculated by dividing the LS means difference (lanreotide minus placebo) in % of days with symptom(s) by the LS means for placebo and multiplying by 100%.

Figure 7: Forest Plot: Percentage of Days with diarrhea and/or flushing during the Double-blind Phase (ANCOVA, ITT Population)



From Study 730 Report, Figure 10, page 83 of 132.
LS Mean=least squares means difference adjusted for stratification factors at baseline and respective baseline value based on ANCOVA model (CI=95% confidence intervals)

Efficacy Results – Secondary endpoints

A hierarchical testing procedure for the secondary efficacy analyses was conducted per protocol and identified average frequency of diarrhea events per day during the DB phase as the first analysis to be performed. The difference in LS means for Somatuline versus placebo for the average daily frequency of diarrhea events during the DB phase was not significant (Table 21). Because this first comparison in the hierarchy was not significant, no meaningful statistical conclusions could be drawn for subsequent comparisons in the hierarchy. The results of the hierarchical testing procedure for the secondary efficacy analyses are provided in Table 21.

Table 21: Summary of Results of the Hierarchical Testing Procedure for the Secondary Efficacy Analyses (ITT Population, Study 730)

Rank	Criteria	n	Statistics	Result
1	Average Daily Frequency of Diarrhoea Events during DB Phase	115	LS Means difference (95% CI)	-0.21 (-0.58, 0.15) p-value=0.2544*
2	Average Daily Frequency of Flushing Events during DB Phase	115	LS Means difference (95% CI)	-0.42 (-0.79, -0.06)
3	Percentage of Days with Other Rescue Medications, during DB Phase	115	LS Means difference (95% CI)	0.45 (-4.68, 5.57)
4	Proportion of ERO patients	115	OR (95% CI)	0.83 (0.33, 2.10)
5	Changes from Baseline in Global Health Status/QoL Score during DB Phase	82	LS Means difference (95% CI)	4.05 (-2.09, 10.20)
6	Changes from Baseline in the G.I. Score during DB Phase	81	LS Means difference (95% CI)	-4.68 (-9.63, 0.26)
7	Changes from Baseline in Endocrine Symptoms Score during DB Phase	81	LS Means difference (95% CI)	-7.04 (-14.80, 0.73)
8	Absolute Changes from Baseline in Plasma CGA (µg/L) during DB Phase	69	LS Means difference (97.5% CI)	-2147.94 (-6574.03, 2278.14)
8	Absolute Changes from Baseline in Urinary 5-HIAA (µmol/day) during DB Phase	66	LS Means difference (97.5% CI)	-39.53 (-202.28, 123.22)

Data Source: Table 14.2.2.10.

*The p value is only displayed for the first secondary endpoint as it was not significant at the 5% level and therefore the hierarchical testing procedure was stopped. No formal statistical conclusion may be drawn for the rest of the secondary endpoints. ITT=intent-to-treat; OR=odds ratio; DB=double-blind; ERO=early rollover; LS=least square; CI=confidence interval; QoL=quality of life: CgA=Chromogranin A; GI=gastrointestinal; 5-HIAA=5-hydroxyindoleacetic acid

Changes from Baseline to Week 12 in Levels of Biochemical Markers of NETs

Changes from Baseline to Week 12 in levels of biochemical markers of NETs, plasma CgA (Chromogranin A) and urinary 5-HIAA were evaluated as secondary endpoints. Subjects treated with Somatuline showed reductions from Baseline in median values of CgA and 5-HIAA at Week 12, while increases in median values were observed for these biomarkers in the placebo group (Table 23). Subjects in the Somatuline group had greater median values of 5-HIAA at Baseline (73.0 µmol/day) compared with the placebo group (44.0 µmol/day), with a high degree of variability in this measure (Table 22).

Table 22: Summary of Plasma Chromogranin A and Urinary 5-HIAA during the DB Phase Subgroup of subjects with Assessment at Baseline and Week 12 (ITT Population, Study 730)

	Lanreotide (N=59)		Placebo (N=56)	
	Value	Change from Baseline	Value	Change from Baseline
Plasma CgA [µg/L] at Baseline				
n	51		50	
Median	784.0		1078.0	
Min, max	98,48902		49,782040	
Q1, Q3	343.0, 4410.0		441.0, 2793.0	
Mean (SD)	4092.0 (8504.4)		17692.9 (110363.0)	
95% CI	(1700.1, 6483.9)		(-13671.9, 49057.7)	
Plasma CgA [µg/L] at Week 12				
n	41	41	28	28
Median	539.0	-98.0	833.0	196.0
Min, max	49,108731	-10731,78400	98,13769	-4557,6174
Q1, Q3	294.0, 1666.0	-441.0, 49.0	294.0, 2989.0	-196.0, 1641.5
Mean (SD)	4261.8 (16964.6)	1125.8 (12579.4)	2383.5 (3267.5)	801.5 (2294.0)
95% CI	(-894.7, 8841.4)	(-2844.8, 5096.4)	(1116.5, 3650.5)	(-88.0, 1691.0)
Urinary 5-HIAA [µmol/d] at Baseline				
n	39		27	
Median	73.0		44.0	
Min, max	0,7175		13,722	
Q1, Q3	19.0, 187.0		20.0, 257.0	
Mean (SD)	388.0 (1195.9)		157.1 (200.7)	
95% CI	(0.3, 775.6)		(77.7, 236.5)	
Urinary 5-HIAA [µmol/d] at Week 12				
n	39	39	27	27
Median	36.0	-7.0	68.0	8.0
Min, max	2,2088	-6314,130	1,773	-449,272
Q1, Q3	17.0, 156.0	-64.0, 7.0	18.0, 322.0	-6.0, 138.0
Mean (SD)	186.6 (406.6)	-201.4 (1009.9)	193.4 (234.1)	36.3 (142.3)
95% CI	(54.8, 318.4)	(-528.7, 126.0)	(100.7, 286.0)	(-20.0, 92.6)

Data Source: Post-hoc Table 14.2.5.6.2.1, Post-hoc Table 14.2.5.5.7.2 and Post-hoc Table 14.2.5.6.7.2.
Note: "Week 12" consists of subjects who are still in the blinded phase.
Change from baseline=absolute change. Baseline is defined as the last non-missing observation obtained prior to the initiation of study treatment. Only the observed data are used in the calculation. The missing data are excluded from the analysis. CgA= Chromogranin A; CI=confidence interval; N=total number of subjects in group; n=number of subjects taken into account for the analysis; SD=standard deviation; 5-HIAA=5-hydroxyindoleacetic acid.

6.1 Supportive Study 718

6.1.1 Study Design

Study Title: "An Open, Multicenter, Phase 2/3, Dose-Titration Clinical Study to Evaluate the Efficacy and Safety of Lanreotide Autogel (60 mg, 90 mg or 120 mg) Administered Subcutaneously Once Monthly for Six Months in the Relief of Clinical Symptoms Associated with Carcinoid Neuroendocrine Tumors"

Primary and Key Secondary Objectives:

- Primary: To evaluate the efficacy of lanreotide, at doses of 60 mg, 90 mg or 120 mg, in the relief of clinical symptoms (diarrhea or flushing) after 6 months treatment in subjects with carcinoid NETs.
- To evaluate the efficacy of lanreotide in the relief of clinical symptoms (diarrhea and/or flushing) monthly
- To evaluate the safety of lanreotide and effect on biomarkers of tumor activity and Quality of Life assessments

Study Design:
Study 718 was a 6-month, open-label, dose-titration study in which all subjects received lanreotide (60 mg, 90 mg, or 120 mg) every 28 days by deep s.c. injection. Eligible subjects were ≥18 years of age diagnosed with a symptomatic carcinoid NET and documented three or more stools per 24-hour period and/or one or more moderate or severe flushes per 24-hour period. Subjects were either naïve to SST treatment or had clinical symptoms after sufficient washout. Of the 71 subjects who received study treatment, 55 subjects completed 6 months of treatment.
A responder was defined by a ≥50% decrease in the number of episodes of the target symptom from baseline. At the first dose titration responders were titrated down to 60 mg, and non-responders were titrated up to 120 mg. If the responders subsequently became non-responders on 60 mg, the dose was increased to 90 mg, and subsequently to 120 mg if necessary. Once a patient was on 120 mg, the dose could not be reduced.

6.2.2 Study Results

The primary efficacy endpoint was the proportion of responders at Month 6, as defined by a reduction from baseline of ≥50% in the average number of daily episodes of diarrhea or moderate/severe flushing (based on the target symptom identified by subjects). Twenty-seven of 71 subjects (38%) (95% CI: 28%, 50%) in the intent-to-treat (ITT) population were target symptom responders at Month 6. The proportion of target symptom responders at Month 6 using the last observation carried forward (LOCF) approach to missing data was higher (43% versus 38% in the ITT population). Of 40 subjects whose target symptom was diarrhea, seven (18%) responded at Month 6 (LOCF). Of 31 subjects whose target symptom was flushing, 20 (65%) responded at Month 6 (LOCF).

Based on secondary efficacy endpoints, the daily number of flushing target symptom episodes had decreased from 3.0 ±3.2 at baseline to 1.7 ±3.0 at Month 6, a difference of 1.3 (-56%) episodes per day. The mean daily number of diarrhea target symptom episodes had decreased from 5.0±2.7 at baseline to 3.9±2.2 at Month 6, a difference of 1.1 (-19%) episodes per day. Further analysis of the number of target symptom responders at Month 6 revealed that when mild episodes of flushing were included, the proportion of target symptom responders was

similar to the primary analysis at Month 6 (34% versus 38%). Of the 27 subjects who were target symptom responders at Month 6, 20 (74%) had responded after the first two lanreotide (90 mg) treatments. The mean severity of flushing decreased from 1.53 ±0.75 at baseline to 1.03 ±0.88 at Month 6, a decrease of 33%. Compared with baseline, decreases were seen in 5-HIAA (median decrease of 24% at Month 6) and CgA (decrease of 38% at Month 6). With the exception of the improvement in diarrhea (median improvement of 33.3), there were no notable changes in QoL (quality of life) assessed by EORTC-C30 questionnaire.

Lanreotide was generally well tolerated. Sixty-six out of the 71 subjects (93%) in the safety population reported at least one TEAE. The most common TEAEs were those affecting the GI system namely abdominal pain, diarrhea, vomiting and nausea. A total of 29 (41%) subjects had SAEs and few subjects had AEs that led to withdrawal (7%). Two subjects had fatal SAEs, neither of which was considered by the investigator to be related to lanreotide.

Overall Conclusion of Study 718 by Applicant:
This 71-subject open-label study provided evidence of clinical benefit of lanreotide administered via a deep s.c. injection once every 28 days (b) (4) (b) (4) Lanreotide was generally well tolerated with GI system AEs (abdominal pain, diarrhea, vomiting and nausea) being most commonly reported.

Medical Officer Comment:
I agree with the Applican (b) (4) (b) (4)

6.2 Supportive Study 726

6.2.1 Study Design

Title: Phase 3, Randomized, Double Blind, Stratified Comparative, Placebo Controlled, Parallel Group, Multicenter Study to Assess the Effect of Deep Subcutaneous Injections of Lanreotide 120 mg Administered every 28 Days on Tumor Progression Free Survival in Patients with Nonfunctioning Enteropancreatic Endocrine Tumor

Primary and Key Secondary Objectives:

- Primary: To assess the effect of lanreotide 120 mg administered every 28 days compared to placebo, on progression-free survival (PFS) in subjects with well or moderately differentiated nonfunctioning enteropancreatic NETs
- To assess overall survival in this subject population

- To assess the effect of lanreotide 120 mg compared to placebo on plasma CgA and on any other tumor peptide markers with elevated level at baseline
- To assess the clinical safety profile of lanreotide 120 mg

Study Design:
Study 726 consisted of a screening visit to assess for progressive disease, followed by a 96-week, DB, placebo-controlled, treatment phase in which subjects were randomized to receive either lanreotide (120 mg) or placebo every 28 days by s.c. injection. Two computed tomography or magnetic resonance imaging scans were performed prior to randomization; tumor progression was assessed every 12 weeks during the first year and every 24 weeks during the second year. Eligible subjects were least 18 years of age with a neuroendocrine tumor measurable by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (confirmed by centrally-assessed histological criteria), documented metastatic disease and/or locally advanced inoperable tumor, and who had nonfunctioning enteropancreatic NETs of unknown origin (or with a known primary localization in the pancreas, mid gut, or hind gut, or a gastrinoma adequately controlled by proton-pump inhibitors). Subjects were required to be naïve to SSA treatment at screening (or <15 days of prior SSA treatment). A total of 204 subjects were randomized and received study treatment (101 lanreotide, 103 placebo); 171 (84%) subjects completed the study.

6.2.2 Study Results (Study 726)

The primary efficacy endpoint was the time to either disease progression or death occurring within 96 weeks after treatment initiation (PFS, progression-free survival). Treatment with lanreotide led to a significant difference in PFS between the two treatment groups in favor of the lanreotide group (p=0.0002). After 96 weeks of treatment, median PFS was >96 weeks in the lanreotide group compared with 72.0 weeks (95% CI: 48.6, 96.0) in the placebo group. Based on the Kaplan-Meier estimates at the time of the last scan performed, 38% of subjects had progressed or died in the lanreotide group, compared with 78% of subjects in the placebo group. Treatment with lanreotide for 96 weeks reduced the risk of progression or death by 53% [Hazard Ratio (HR) = 0.47, 95% CI: 0.30, 0.73]. Overall survival was similar between treatment groups (HR = 1.05, 95% CI: 0.55, 2.03).

There was a significant decrease in CgA for subjects treated with lanreotide compared to placebo. At the last post baseline value, odds of having a 50% or more decrease in CgA levels from baseline were 15 times greater with lanreotide than placebo (OR = 15.2: 95% CI: 4.29, 53.9; logistic regression p<0.0001). In subjects with elevated biomarkers (i.e. CgA, gastrin, pancreatic polypeptide etc.) at baseline, the effect of lanreotide on extending PFS was consistent with that observed in subjects with normal levels.

The overall incidence of subjects with at least one TEAE in the lanreotide and placebo groups was similar at 88.1% and 90.3%, respectively. The most commonly reported types of events were GI disorders reported in 67.3% and 63.1% of subjects in the lanreotide and placebo groups, respectively. The majority of reported events was mild to moderate in severity and was not serious. The proportion of subjects who experienced at least one TEAE leading to withdrawal from the study was similar in each group (lanreotide: 3.0%; placebo: 2.9%). Two deaths occurred during the study in the lanreotide group and were considered by the Investigator to be unrelated to study treatment. Administration of lanreotide 120 mg for up to two years had no adverse impact on assessed parameters relating to clinical laboratory parameters, vital signs and ECG function in this population.

Overall Conclusion by Applicant:
Lanreotide (120 mg) was effective in improving PFS in subjects with nonfunctioning enteropancreatic NET. In the subjects with elevated baseline biomarkers, the changes of biomarkers were consistent with the changes of PFS.

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy across Trials

7.1.1 Primary Endpoints

The primary efficacy endpoint of the pivotal placebo-controlled trial, Study 730, was to measure the "the percentage of days that short-acting octreotide was used as rescue medication for breakthrough symptoms during the 16-week DB phase". Reduction of octreotide use for controlling breakthrough of CS diarrhea and flushing symptoms served as a surrogate endpoint. "Breakthrough day" is proportional to the capability of carcinoid tumors to generate carcinoid diarrhea and flushing. Therefore, it qualifies to serve as the primary efficacy endpoint.

The results of the primary efficacy analysis (ANCOVA) are presented in Table 16. The least squares (LS) mean percentage of days on which s.c. octreotide was administered as rescue medication during the DB phase was significantly lower in favor of the Somatuline group (33.72% of days) compared with the placebo group (48.49% of days) (p = 0.0165). The absolute difference in LS means (95% confidence interval) was –14.76% (-26.78, -2.75). These results show that Somatuline significantly reduced the percentage of breakthrough days, and the primary efficacy endpoint was met.

Table 23: Percentage of Days with Subcutaneous Octreotide as Rescue Medication during DB

Period (ITT Population)

	N	LS Mean (SE)	95% CI	LS mean diff (Lanreotide – placebo)	95% CI LS mean diff (Lanreotide – placebo)	p-value
Lanreotide	59	33.72 (4.39)	(25.02, 42.42)	–14.76	(–26.78 –2.75)	0.0165
Placebo	56	48.49 (4.50)	(39.57, 57.40)			

Data Source: Table 14.2.1.2.1.

LS Mean=least squares mean (i.e., adjusted for stratification factors and covariates (octreotide usage, daily average of diarrhea and daily average of flushing events at baseline) based on the ANCOVA model evaluation presented in the statistical appendix and in Table 14.2.1.3.1. Interaction between treatment and stratification factors was tested – (no significance); SE=standard error; CI=confidence interval; ERO=roll over. This analysis does not include any imputation for the ERO subjects.

Responder analysis was conducted during the last 4 weeks of the 16-week DB period. Responder = Complete responder + Partial responder. A complete responder was defined as no octreotide use during the 4 weeks; a partial responder was defined as the need for octreotide use for no more than 3 days (3/28). A non-responder was defined as the need for octreotide use for more than 3 days during the 4 weeks following the 4th DB injection (Week 12 through to Week 15). The results showed that 47% of patients in Somatuline group were responder, as compared 28% of the placebo. These results suggest that Somatuline treatment reduced the need for the rescue medication octreotide for the treatment of breakthrough carcinoid diarrhea and flushing syndromes.

Table 24: Summary Statistics of Subject Responder during the DB Phase (ITT Population)

	Lanreotide (N=59)	Placebo (N=56)
Responder to Lanreotide	47.4% (28/59)	28.5% (16/56)
Treatment failure	52.5% (31/59)	71.4% (40/56)

From the reviewer's notes based on Study 730 Report; Note: Only the observed data were used in the calculation. The missing data were excluded from the analysis. Responder=subcutaneous octreotide was not required as rescue during the 4 weeks following the 4th DB injection; or subcutaneous octreotide usage as rescue medication in 1 to 3 days during the 4 weeks following the 4th DB injection.
Treatment Failure=subcutaneous octreotide usage as rescue medication more than 3 days during the 4 weeks following the 4th DB injection (Week 12 through to Week 15). Subjects who received less than four DB study treatment injections were considered as treatment failures.
DB=double-blind; ITT=intent-to-treat; CI=confidence interval

7.1.2 Key Secondary Endpoints of Study 730

Average Daily Frequency of diarrhea and Flushing

The average daily frequency of diarrhea and flushing events during the DB phase are presented in Table 5. There was no statistically significant difference between the Somatuline and placebo groups in LS means for daily frequency of diarrhea events.

Table 25: Average Daily Frequency of Diarrhea and Flushing Events during the DB Phase (ANCOVA, ITT Population)

	Somatuline (N=59)	Placebo (N=56)	LS Mean Difference (Somatuline – Placebo)	p-value
Average Daily Frequency of Diarrhoea Events				
Baseline Mean (SD)	2.13 (1.85)	1.57 (1.67)	—	—
DB Phase:				
LS Means (±SE)	1.34 (0.13)	1.55 (0.14)	-0.21	0.2544[a]
95% CI	1.07, 1.61	1.28, 1.82	-0.58, 0.15	
Average Daily Frequency of Flushing Events				
Baseline Mean (SD)	1.53 (1.98)	2.20 (3.27)	—	—
DB Phase:				
LS Means (±SE)	1.04 (0.13)	1.46 (0.14)	-0.42	0.0229
95% CI	0.77, 1.30	1.19, 1.74	-0.79, -0.06	

Data Source: Study 730, Tables 14.2.2.1.1, 14.2.2.1.2.2, 14.2.2.2.1, and 14.2.2.2.2.2

LS Mean=least squares means based on ANCOVA model (adjusted for daily average of diarrhea and flushing events at baseline, prior SSA use, and region); SE=standard error; CI=95% confidence intervals.

Biochemical Markers of Neuroendocrine Tumors

Changes from baseline to Week 12 in levels of biochemical markers of carcinoid tumors, CgA and 5-HIAA, were evaluated as secondary endpoints in Study 730. Subjects in the Somatuline group had greater mean (SD) values of 5-HIAA at baseline [388.0 µmol/d (1195.9 µmol/d)] as compared with the placebo group [157.1 µmol/d (200.7 µmol/d)], with a high degree of variability in this measure.

Subjects treated with Somatuline showed reductions from baseline in median values of CgA and 5-HIAA at Week 12, while the placebo showed increases from baseline in median values at Week 12 (Table 6).

Table 26: Changes from Baseline in Plasma CgA and Urinary 5-HIAA at Week 12 of the DB Phase (ITT Population)

	Somatuline (N=59)		Placebo (N=56)	
	Value	Change from Baseline	Value	Change from Baseline
Plasma CgA [µg/L] at Week 12				
n	41	41	28	28
Median	539.0	-98.0	833.0	196.0
Min, max	49,108731	-10731,78400	98,13769	-4557,6174
Mean (SD)	4261.8 (16964.6)	1125.8 (12579.4)	2383.5 (3267.5)	801.5 (2294.0)
95% CI	-894.7, 8841.4	-2844.8, 5096.4	1116.5, 3650.5	-88.0, 1691.0
Urinary 5-HIAA [µmol/d] at Week 12				
n	39	39	27	27
Median	36.0	-7.0	68.0	8.0
Min, max	2, 2088	-6314, 130	1, 773	-449, 272
Mean (SD)	186.6 (406.6)	-201.4 (1009.9)	193.4 (234.1)	36.3 (142.3)
95% CI	54.8, 318.4	-528.7, 126.0	100.7, 286.0	-20.0, 92.6

CgA= Chromogranin A; CI=confidence interval; SD=standard deviation; 5-HIAA=5-hydroxyindoleacetic acid.
Data Source: Table 14.2.5.5.7.2 and Table 14.2.5.6.7.2.
Note: 'Week 12' consists of subjects who are still in the blinded phase.
Change from baseline=absolute change. Baseline is defined as the last non-missing observation obtained prior to the initiation of study treatment. Only the observed data are used in the calculation. The missing data are excluded from the analysis.

7.1.3 Subpopulations

Pooled analyses of subpopulations were not conducted.

7.1.4 Dose and Dose-Response

An integrated analysis of all data that pertain to the dose-response relationships was not conducted. Somatuline 120 mg s.c. monthly was used in Study 730.

7.1.5 Onset, Duration, and Durability of Efficacy Effects

Statistically convincing evidence of onset, duration, and durability of efficacy effects were not studied.

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

Subgroup analyses of Study 730 showed that the patients with body mass index (BMI) ≥30 kg/m^2 did not respond to Lanreotide treatment (Figure 4). It is not clear whether these patients

require higher doses of Somatuline Depot.

7.2.2 Other Relevant Benefits

Dosing schedule or route of administration that may be a relevant benefit to patients was not studied.

7.3 Integrated Assessment of Effectiveness

The Applicant has provided substantial evidence of effectiveness of Somatuline treatment. The effectiveness is supported by one placebo controlled phase 3 trial (Study 730), one open-label dose-titration trial (Study 718), and one placebo controlled phase 3 trial (Study 726) for pooled analysis of 5-HIAA and CgA.

The clinically-meaningful benefits are shown in three analyses: (1) monthly Somatuline injections of 120 mg reduce the daily injection frequency (2 to 4 injections per day) of the FDA approved active drug octreotide acetate for treating CS diarrhea and flushing; (2) the reductions correlated with the reduction of clinical breakthrough events in patients with metastatic carcinoid tumors; and (3) the reductions correlated with 40% of treated patients who were free of using the active drug octreotide during the last 4 weeks of 16-week DB study period.

In addition, both 5-HIAA and CgA studies with Somatuline show reductions of tumor secretory biomarkers.

(b) (4) The reduction of rescue octreotide days in response to clinical CS symptoms break-through should be presented in the label.

8 Review of Safety

8.1 Safety Review Approach

The safety review is based on the database from one pivotal study (Study 730), 5 supportive studies (Studies 726, 718, 216, 166, and 729), and postmarketing surveillance report.

The pivotal study had DB phase and two open-label phases (the initial open-label phase and the long term open-label extension phase). The review relies on the safety reporting of AEs, vital

signs, and laboratory data. Supportive studies contained symptomatic and non-symptomatic subjects. To facilitate the safety review, symptomatic subjects (pivotal plus supportive studies) and All subjects are reviewed separately in the following sections.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The key safety data are derived from the pivotal, double-blind, placebo-controlled study (Study 730). A total of 58 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for 16 weeks in the DB phase; 101 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for 32 weeks in the IOL phase; and 57 subjects were treated with 120 mg Somatuline s.c. every 4 weeks for at least 2 years in the LTOLE phase.

Supportive safety data are derived from 5 phases 2, 3, and 4 controlled and uncontrolled studies. All of the supportive safety data are based on administration of Somatuline at 60, 90, and 120 mg, respectively with deep s.c. injection every 4 weeks in subjects with symptomatic and asymptomatic carcinoid tumors.

Table 27: Summary of Pivotal and Supportive Studies for Safety Assessment

Study number (abbreviated number)/ Location of CSR in dossier	Study design	Lanreotide Autogel dose (duration of treatment) Study status	Comparator	Number of subjects treated with Somatuline Depot
Pivotal				
2-SS-52030-730 (730)/ Module 5.3.5.1 Study 730	Phase III, DB, randomised placebo controlled study of the efficacy and safety of Somatuline Depot 120 mg in the treatment of symptoms associated with carcinoid syndrome	120 mg / 4 weeks (DB=16 weeks) (IOL=32 weeks) (LTOLE= 2 years[a]) Completed	Placebo (only during the DB)	58 subjects treated with Somatuline Depot in DB phase Included in the IOL phase: 101 Included in LTOLE phase: 57 All subjects with symptomatic NETs
Supportive				
2-SS-52030-726 (726)/ Module 5.3.5.1 Study 726	Phase III, randomised, DB, comparative, placebo controlled, parallel group, multicentre study.	120 mg / 4 weeks (96 weeks) Completed	Placebo	101 subjects with asymptomatic NETs
E-47-52030-718 (718)/ Module 5.3.5.2 Study 718	Open-label, phase II/III, multicentre, dose titration study of the efficacy and safety of s.c. Somatuline Depot in the relief of clinical symptoms associated with carcinoid syndrome (symptomatic NETs)	60, 90, 120 mg / 4 weeks (6 months) Completed	None	71 subjects with symptomatic NETs
A-99-52030-216 (216)/ Module 5.3.5.2 Study 216	Phase IV, international, open-label, randomised, cross over study of subject preference and health economy in subjects with NETs treated with self administered Somatuline Depot	90 or 120 mg / 4 weeks (7 or 8 months) Completed	None	26 subjects with symptomatic NETs
A-92-52030-166 (166)/ Module 5.3.5.2 Study 166	Phase II, open, single group, multicentre study of the safety and efficacy of Somatuline Depot on tumour growth stabilisation in subjects not eligible for treatment with either surgery or chemotherapy	120 mg / 4 weeks (92 weeks) Completed	None	30 subjects. Subjects with symptomatic NETs: 19 Subject with asymptomatic NETs: 11
2-SS-52030-729 (729)/ Module 5.3.5.2 Study 729	Phase III, open-label extension study of Somatuline Depot 120 mg in subjects with nonfunctioning enteropancreatic endocrine tumours (extension of Study 726)	120 mg / 4 weeks (maximum approximately 8 years) Completed	None	89 subjects with asymptomatic NETs

From Summary of Clinical Safety, NDA 022074; CSR=clinical study report; DB=double-blind; IOL=initial open-label; ISS=Integrated Summary of Safety; LTOLE=long term open-label extension; NET=neuroendocrine tumor; SAP=statistical analysis plan. Data Source: Module 5.3.5.1 and 5.3.5.2 CSRs. The LTOLE phase of the study was planned to end when 2 years had elapsed from the time the last subject completed his/her participation in the 32-

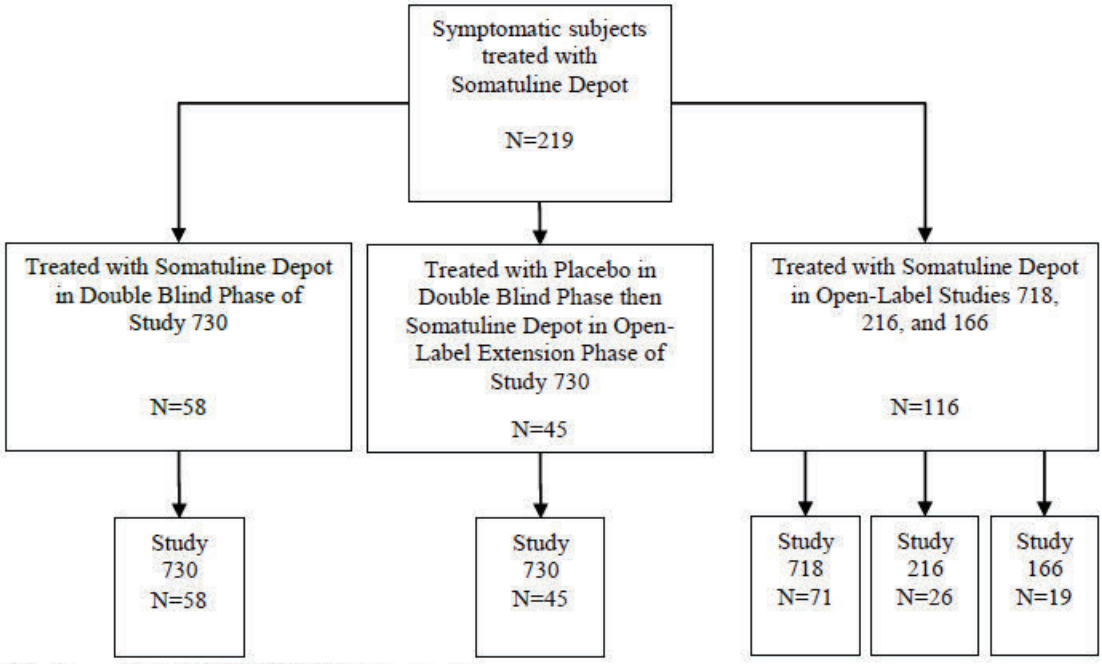
week IOL phase, or when marketing approval was obtained in the respective countries (whichever occurred first) or at any time the study was to be terminated by the Sponsor.

Subjects with Symptomatic NETs

The pooled analyses of symptomatic subjects with NETs treated with Somatuline Depot administered by deep s.c. injection once every 4 weeks included 219 subjects (Figure 8). Subjects were counted in each column depending on their study treatment or study phase, but only once in the All phases analysis.

Of the 219 symptomatic subjects, 58 were treated with Somatuline Depot 120 mg in the DB, placebo controlled Study 730. There were 45 subjects treated with placebo during the DB phases who then received Somatuline Depot in the IOL phase of Study 730. There were 116 symptomatic subjects treated with Somatuline Depot in the OL Study 718 (71 subjects), Study 216 (26 subjects) and Study 166 (19 subjects). A total of 219 symptomatic subjects received Somatuline Depot 120 mg.

Figure 8: Symptomatic subjects Disposition Pooled Studies



Data Source: Module 5.3.5.3 ISS SAP Tables 3 and 5.

Exposure of Subjects with Symptomatic NETs

The 219 symptomatic subjects received a mean ±SD of 14.9±14.43 injections of Somatuline Depot during the studies. The mean duration of treatment with Somatuline Depot in symptomatic subjects, All Phases was 65.25 weeks (Table 28). A total of 68 subjects (37.8%) were treated ≤6 months, 47 subjects (26.1%) were treated 6 months to 1 year and 65 (36.1%) were treated >1 year. Subjects received a mean of 14.9 injections and a mean cumulative dose

of 1,727.3 mg of Somatuline Depot. Treatment interruptions were recorded in five subjects (2.6%).

In the 16-week DB phase of Study 730, subjects treated with Somatuline Depot 120 mg received a mean of 3.6 injections and a mean cumulative dose of 426.2 mg.
Subjects in the placebo group received a mean of 3.1 injections. Treatment interruptions were recorded in no symptomatic subjects treated with either Somatuline Depot or placebo (Table 28). During the IOL phase of Study 730, 101 subjects received a mean 7.6 injections of Somatuline Depot and a mean cumulative dose of 910.1 mg (Module 5.3.5.1 clinical study report (CSR) 730. During the LTOLE phase of Study 730, 57 subjects received a mean 25.1 injections with mean cumulative dose of 3012.6 mg.

In the OL Studies 718, 216, and 166, the majority of subjects [55 (71.4%)] were treated for 6 months or less and received a mean cumulative dose of 775.1 mg. No treatment interruptions were recorded in these subjects.

Table 28: Exposure: Pooled Studies - Subjects with Symptomatic NETs

	All phases[a] lanreotide Autogel all doses N=219	Double-blind phase[b] Lanreotide Autogel 120 mg N=58	Double-blind phase[b] Placebo N = 57	Open-label[c] studies lanreotide Autogel all doses N = 116
Total duration of treatment exposure (weeks)				
Mean (SD)	60.44 (58.401)	14.55 (3.936)	12.58 (5.059)	30.27 (18.427)
Median (Range)	32.29 (4.1 to 282.3)	16.14 (4.1 to 18.3)	16.14 (4.1 to 17.3)	24.29 (4.1 to 97.3)
Duration of treatment, n (%)				
Less than or equal to 6 months	88 (40.2%)	58 (100.0%)	57 (100.0%)	75 (64.7%)
Between 6 months and 1 year	66 (30.1%)	0 (0.0%)	0 (0.0%)	30 (25.9%)
More than 1 year	65 (29.7%)	0 (0.0%)	0 (0.0%)	11 (9.5%)
Exposure to lanreotide Autogel 120 mg (weeks)				
	n=180	n=58	NA	n=77
Mean (SD)	65.25 (63.906)	14.55 (3.936)	NA	26.24 (24.654)
Median (Range)	36.43 (4.1 to 282.3)	16.14 (4.1 to 18.3)	NA	16.14 (4.1 to 97.3)
Duration of exposure to lanreotide Autogel 120 mg, n (%)				
	n=180	n=58	NA	n=77
Less than or equal to 6 months	68 (37.8%)	58 (100.0%)	NA	55 (71.4%)
Between 6 months and 1 year	47 (26.1%)	0 (0.0%)	NA	11 (14.3%)
More than 1 year	65 (36.1%)	0 (0.0%)	NA	11 (14.3%)
Number of injections, n (%)				
Mean (SD)	14.9 (14.43)	3.6 (0.96)	3.1 (1.22)	7.4 (4.49)
Median (Range)	8.0 (1 to 70)	4.0 (1 to 4)	4.0 (1 to 4)	6.0 (1 to 23)
1 to 4	28 (12.8%)	58 (100.0%)	57 (100.0%)	19 (16.4%)
5 to 8	93 (42.5%)	0 (0.0%)	0 (0.0%)	74 (63.8%)
9 to 12	33 (15.1%)	0 (0.0%)	0 (0.0%)	12 (10.3%)
13 to 16	5 (2.3%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
>16	60 (27.4%)	0 (0.0%)	0 (0.0%)	9 (7.8%)
Cumulative Dose (mg)				
Mean (SD)	1727.3 (1768.31)	426.2 (115.00)	0.0 (0.00)	775.1 (570.21)
Median (Range)	960.0 (90 to 8400)	480.0 (120 to 480)	0.0 (0 to 0)	660.0 (90 to 2760)
Subjects with treatment interruption (n (%))[d]				
	n=193	n=58	n=57	n=90
Yes	5 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

ISS=Integrated Summary of Safety; N=number of subjects; n=number of subjects with data; NA=not applicable; SD=standard deviation.

a Included Studies 730 (any study phase), 718, 216, and 166 (subjects with symptomatic NETs only).

b Included double-blind Study 730.

c Included Studies 718, 216 and 166 (subjects with symptomatic NETs only).

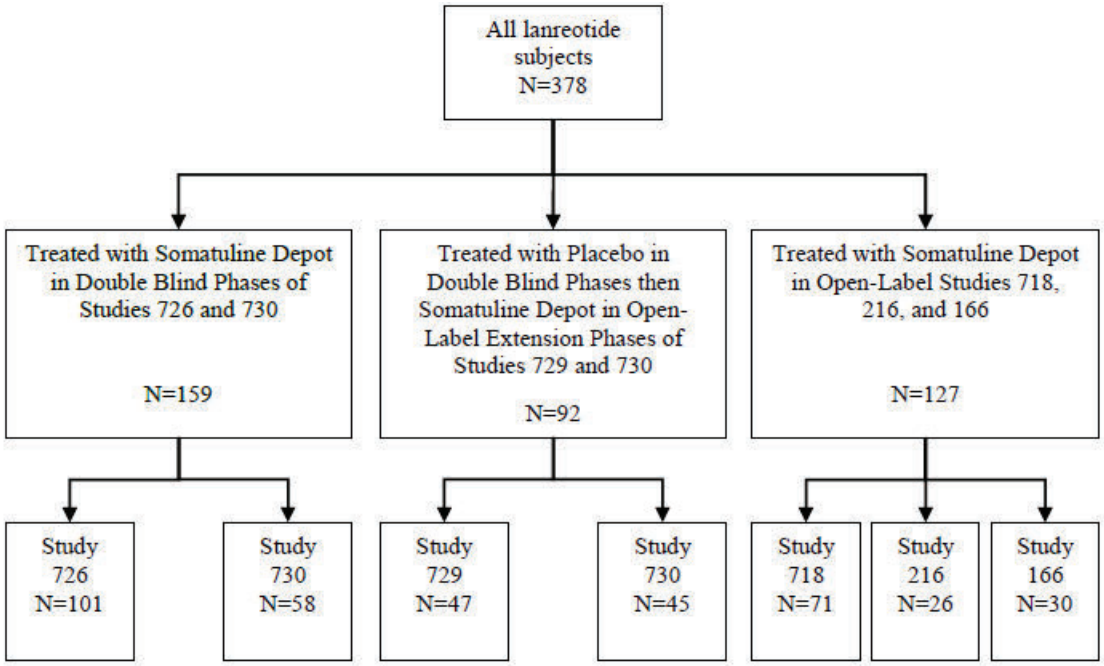
d Treatment interruption was not calculated for Study 216.

All Subjects Safety Database

The pooled analyses of subjects with NETs treated with Somatuline Depot administered by deep s.c. injection once every 4 weeks included 378 subjects (Figure 9). Of these 378 subjects, 159 were treated with Somatuline Depot 120 mg in the DB phase of the controlled Study 730 and Study 726. The remaining 219 subjects received Somatuline Depot in the OL Studies 729, 718, 216, and 166 or in the OL phases of Study 730.

The total number of subjects in the All phases analysis is not the sum of the other columns. This is because not all placebo treated subjects continued in the OL phases (IOL and LTOLE) of Study 730 (N=45 entered the IOL phase) or in the OLE Study 729 (N=47 subjects from Study 726 continued in the OLE Study 729) (Figure 7).

Figure 9: All Subject Disposition Pooled Studies



Data Source: Module 5.3.5.3 ISS SAP Tables 3 and 5.
ISS=Integrated Summary of Safety; N=number of subjects; SAP=statistical analysis plan.

All Subjects Exposure

The 378 subjects in the All Subjects population received a mean ±SD of 20.8 ±20.96 injections of Somatuline Depot during the studies. The mean duration of treatment with Somatuline Depot in All Subjects, (All Phases all doses) was 89.64 weeks (Table 8). A total of 98 subjects (28.9%) were treated for 6 months or less, 76 subjects (22.4%) were treated 6 months to 1 year and 165 (48.7%) were treated for more than 1 year. Subjects received a mean of 20.8 injections and a mean cumulative dose of 2,465.5 mg of Somatuline Depot. Treatment interruptions were recorded in 10 subjects.

Similar results were seen in the DB phases of Study 726 and 730 and OL studies where the injections were administered every 4 weeks. The maximum dose administered in 39 subjects treated in the crossover Study 216 or in the dose titration Study 718 was 90 mg. This was approximately 10% of the pooled population of subjects treated with Somatuline Depot.

In the DB phase of Studies 726 and 730, subjects treated with Somatuline Depot 120 mg received a mean of 12.5 injections and a mean cumulative dose of 1,494.3 mg. Subjects in the placebo group received a mean of 11.0 injections. Treatment interruptions were recorded in very few subjects treated with either Somatuline Depot [two subjects (1.3%)] or placebo [four subjects (2.5%)].

In the OL Studies 718, 216, and 166, the majority of subjects [82 (64.6%)] were treated for 6 months or less and received a mean cumulative dose of 793.0 mg. No treatment interruptions were recorded in these subjects.

Table 28: Exposure: All Subjects

	All phases[a] lanreotide Autogel all doses N=378	Double-blind phase[b] Lanreotide Autogel 120 mg N=159	Double-blind phase[b] Placebo N=160	Open-label studies[c] lanreotide Autogel all doses N=127
Total duration of treatment exposure (weeks)				
Mean (SD)	84.34 (84.460)	50.43 (37.922)	44.65 (33.978)	30.65 (19.527)
Median (Range)	45.86 (4.1 to 404.1)	36.14 (4.1 to 101.1)	31.50 (4.1 to 100.9)	24.29 (4.1 to 100.3)
Duration of treatment, n (%)				
Less than or equal to 6 months	118 (31.2%)	75 (47.2%)	70 (43.8%)	82 (64.6%)
Between 6 months and 1 year	95 (25.1%)	16 (10.1%)	35 (21.9%)	32 (25.2%)
More than 1 year	165 (43.7%)	68 (42.8%)	55 (34.4%)	13 (10.2%)
Exposure to lanreotide Autogel 120 mg (weeks)				
	n=339	n=159	NA	n=88
Mean (SD)	89.64 (87.837)	50.43 (37.922)	NA	27.29 (25.298)
Median (Range)	52.14 (4.1to404.1)	36.14 (4.1to101.1)	NA	16.21 (4.1to100.3)
Duration of exposure to lanreotide Autogel 120 mg, n (%)				
	n=339	n=159	NA	n=88
Less than or equal to 6 months	98 (28.9%)	75 (47.2%)	NA	62 (70.5%)
Between 6 months and 1 year	76 (22.4%)	16 (10.1%)	NA	13 (14.8%)
More than 1 year	165 (48.7%)	68 (42.8%)	NA	13 (14.8%)
Number of injections, n (%)				
Mean (SD)	20.8 (20.96)	12.5 (9.40)	11.0 (8.44)	7.5 (4.68)
Median (Range)	11.5 (1 to 101)	8.0 (1 to 24)	7.5 (1 to 24)	6.0 (1 to 23)
1 to 4	50 (13.2%)	72 (45.3%)	65 (40.6%)	22 (17.3%)
5 to 8	114 (30.2%)	8 (5.0%)	16 (10.0%)	78 (61.4%)
9 to 12	43 (11.4%)	7 (4.4%)	17 (10.6%)	14 (11.0%)
13 to 16	16 (4.2%)	8 (5.0%)	14 (8.8%)	2 (1.6%)
>16	155 (41.0%)	64 (40.3%)	48 (30.0%)	11 (8.7%)
Cumulative Dose (mg)				
Mean (SD)	2465.5 (2539.83)	1494.3 (1128.34)	0.0 (0.00)	793.0 (592.34)
Median (Range)	1380.0 (90 to 12120)	960.0 (120 to 2880)	0.0 (0 to 0)	660.0 (90 to 2760)
Subjects with treatment interruption (n (%))[d]				
	n=352	n=159	n=160	n=101
Yes	10 (2.8%)	2 (1.3%)	4 (2.5%)	0 (0.0%)

ISS=Integrated Summary of Safety; N=number of subjects; n=number of subjects with data; NA=not applicable; SD=standard deviation.
Data Source: Module 5.3.5.3 ISS Tables EX-A.1, EX-A.2, and EX-A.3.

a Included Studies 730, 726, 718, 216, 166, and 729.

b Included double-blind Studies 730 and726.

c Included open-label Studies 718, 216 and 166.

d Treatment interruption was not calculated for Study 216.

8.2.2 Relevant characteristics of the safety population:

Demographics and baseline characteristics of subjects with symptomatic NETs

The mean (SD) age of symptomatic subjects treated with Somatuline Depot was 59.7 (11.35) years and 86 subjects (39.2%) were >65 years of age (65 to 74 years: 66 subjects, 30.1% and ≥75 years: 20 subjects, 9.1%; Table 29). Males and females (47.9% versus 52.1%) were balanced. The majority of symptomatic subjects were White (90.7%). The majority of symptomatic subjects were overweight (BMI 25-30: 43.2%) or obese (BMI ≥30: 18.9%). One-third of subjects for pivotal Study 730 were recruited from the U.S., and overall, the majority of subjects were recruited outside the U.S. (83.6%).

There were no notable differences between the Somatuline Depot 120 mg and placebo treatment groups with respect to demographic parameters in the DB phase of Study 730.

Table 29: Subject Demographics: Pooled Studies - Subjects with Symptomatic NETs

Demographic characteristic	All phases[a] lanreotide Autogel all doses N=219	Double-blind phase[b] (Study 730)		Open-label studies[c] lanreotide Autogel all doses N=116
		Lanreotide Autogel 120 mg N=58	Placebo N=57	
Age (years) at entry				
Mean (SD)	59.7 (11.35)	57.8 (10.64)	59.5 (11.50)	60.7 (11.43)
Median (Range)	61.0 (27.0 to 85.0)	58.5 (38.0 to 77.0)	61.0 (27.0 to 85.0)	62.0 (28.0 to 80.0)
18 to 29 years n (%)	2 (0.9)	0 (0.0)	1 (1.8)	1 (0.9)
30 to 49 years n (%)	41 (18.7)	14 (24.1)	11 (19.3)	18 (15.5)
50 to 64 years n (%)	90 (41.1)	28 (48.3)	23 (40.4)	45 (38.8)
65 to 74 years n (%)	66 (30.1)	13 (22.4)	17 (29.8)	39 (33.6)
≥75 years n (%)	20 (9.1)	3 (5.2)	5 (8.8)	13 (11.2)
Gender				
Male n (%)	105 (47.9)	26 (44.8)	22 (38.6)	61 (52.6)
Female n (%)	114 (52.1)	32 (55.2)	35 (61.4)	55 (47.4)
Race				
N	193	58	57	90
Black Or African American [d] n (%)	8 (4.1)	3 (5.2)	6 (10.5)	1 (1.1)
American Indian Or Alaska Native n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian n (%)	9 (4.7)	6 (10.3)	3 (5.3)	0 (0.0)
Native Hawaiian Or Other Pacific Islander n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White n (%)	175 (90.7)	48 (82.8)	48 (84.2)	89 (98.9)
Other n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple n (%)	1 (0.5)	1 (1.7)	0 (0.0)	0 (0.0)
Region				
US n (%)	36 (16.4)	21 (36.2)	19 (33.3)	0 (0.0)
NON-US n (%)	183 (83.6)	37 (63.8)	38 (66.7)	116 (100.0)
Height (cm)				
Mean (SD)	166.3 (9.49)	166.3 (9.02)	165.9 (10.44)	165.7 (8.16)
Median (Range)	166.2 (143.0 to 188.0)	166.0 (152.0 to 183.0)	163.8 (143.0 to 188.0)	167.0 (150.0 to 178.0)
Missing n	107	1	1	105
Weight (kg)				
Mean (SD)	73.61 (16.659)	74.08 (15.297)	74.56 (17.494)	72.05 (16.340)

Demographic characteristic	All phases[a] lanreotide Autogel all doses N=219	Double-blind phase[b] (Study 730)		Open-label studies[c] lanreotide Autogel all doses N=116
		Lanreotide Autogel 120 mg N=58	Placebo N=57	
Median (Range)	70.45 (37.00 to 42.80)	71.00 (39.70 to 110.00)	70.00 (38.00 to 42.80)	70.10 (37.00 to 13.00)
Missing n	35	2	0	33
Body Mass Index (kg/m²)				
Mean (SD)	26.82 (4.990)	26.69 (5.189)	26.99 (4.686)	25.42 (3.794)
Median (Range)	26.61 (16.31 to 45.20)	26.33 (16.31 to 45.20)	26.82 (18.58 to 40.42)	24.44 (17.73 to 31.07)
Missing n	108	2	1	105
<18.5 n (%)	2 (1.8)	1 (1.8)	0 (0.0)	1 (9.1)
≥18.5 to 25 n (%)	40 (36.0)	20 (35.7)	20 (35.7)	5 (45.5)
≥25 to 30 n (%)	48 (43.2)	24 (42.9)	26 (46.4)	4 (36.4)
≥30 n (%)	21 (18.9)	11 (19.6)	10 (17.9)	1 (9.1)

ISS=Integrated Summary of Safety; N=number of subjects; n= number of subjects in a specific group; NET=neuroendocrine tumour; SD=standard deviation; US=United States.
Data Source: Module 5.3.5.3 ISS Table BL-A1.1-1.
a Included Studies 730 (any study phase), 718, 216, and 166 (subjects with symptomatic NETs only).
b Included Double-blind Study 730.
c Included Studies 718, 216 and 166 (subjects with symptomatic NETs only).
d Includes Afro-Caribbean subjects from Study 166.

Demographics and baseline characteristics for All subjects

The mean (SD) age of subjects treated with Somatuline Depot was 60.7 (10.83) years and 156 subjects (41.3%) were >65 years (65 to 74 years: 121 subjects, 32.0% and ≥75 years: 35 subjects, 9.3%; Table 30). There were similar percentages of males and females (49.7% versus 50.3%) and the majority of subjects were White (92.9%). The majority of subjects were overweight (38.8%) or obese (22.7%). The majority of subjects were recruited outside the U.S. (84.9%).

There were no notable differences between the Somatuline Depot 120 mg and placebo treatment groups with respect to demographic parameters in the DB phase of Studies 730 and 726. The demographic profile of subjects with symptomatic NETs (Table 30) was similar to that of the overall pooled population. Recruitment of all subjects treated in the OL studies was outside the U.S.

Table 30: Patient Demographics: All Subjects

Demographic characteristic	All phases[a] lanreotide Autogel all doses N=378	Double-blind phase[b]		Open-label studies[c] lanreotide Autogel all doses N=127
		Lanreotide Autogel 120 mg N=159	Placebo N=160	
Age (years) at entry				
Mean (SD)	60.7 (10.83)	61.3 (10.41)	61.2 (11.30)	60.7 (11.19)
Median (Range)	62.0 (27.0 to 85.0)	62.0 (30.0 to 83.0)	62.5 (27.0 to 92.0)	62.0 (28.0 to 80.0)
18 to 29 years n (%)	2 (0.5)	0 (0.0)	1 (0.6)	1 (0.8)
30 to 49 years n (%)	56 (14.8)	21 (13.2)	24 (15.0)	19 (15.0)
50 to 64 years n (%)	164 (43.4)	73 (45.9)	68 (42.5)	51 (40.2)
65 to 74 years n (%)	121 (32.0)	48 (30.2)	51 (31.9)	43 (33.9)
≥75 years n (%)	35 (9.3)	17 (10.7)	16 (10.0)	13 (10.2)
Gender				
Male n (%)	188 (49.7)	79 (49.7)	76 (47.5)	66 (52.0)
Female n (%)	190 (50.3)	80 (50.3)	84 (52.5)	61 (48.0)
Race				
N	352	159	160	101
Black Or African American [d] n (%)	10 (2.8)	5 (3.1)	8 (5.0)	1 (1.0)
American Indian Or Alaska Native n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian n (%)	14 (4.0)	8 (5.0)	8 (5.0)	0 (0.0)
Native Hawaiian Or Other Pacific Islander n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White n (%)	327 (92.9)	145 (91.2)	144 (90.0)	100 (99.0)
Other n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple n (%)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)
Region				
US n (%)	57 (15.1)	37 (23.3)	33 (20.6)	0 (0.0)
NON-US n (%)	321 (84.9)	122 (76.7)	127 (79.4)	127 (100.0)
Height (cm)				
Mean (SD)	167.4 (9.48)	167.6 (9.15)	167.5 (10.43)	165.0 (7.16)
Median (Range)	167.0 (143.0 to 193.0)	167.0 (148.0 to 193.0)	167.0 (143.0 to 194.0)	167.0 (150.0 to 178.0)
Missing n	117	6	5	107
Weight (kg)				
Mean (SD)	74.92 (17.102)	76.37 (16.060)	75.33 (18.516)	71.44 (16.251)
Median (Range)	73.00 (37.00 to 42.80)	75.00 (39.70 to 128.00)	72.00 (38.00 to 142.80)	70.00 (37.00 to 113.00)
Missing n	36	2	1	34
Body Mass Index (kg/m^2)				
Mean (SD)	26.95 (5.224)	27.09 (4.992)	26.78 (5.467)	25.51 (5.637)
Median (Range)	26.35 (14.00 to 46.02)	26.68 (16.31 to 45.20)	25.99 (16.02 to 46.02)	24.42 (14.00 to 38.21)
Missing n	118	7	5	107
<18.5 n (%)	4 (1.5)	1 (0.7)	5 (3.2)	2 (10.0)
≥18.5 to 25 n (%)	96 (36.9)	54 (35.5)	58 (37.4)	9 (45.0)
≥25 to 30 n (%)	101 (38.8)	62 (40.8)	55 (35.5)	6 (30.0)
≥30 n (%)	59 (22.7)	35 (23.0)	37 (23.9)	3 (15.0)

ISS=Integrated Summary of Safety; N=number of subjects; n= number of subjects in a specific group; SD=standard deviation; US=United States.
Data Source: Module 5.3.5.3 ISS Table BL-A.1.

a Included Studies 730, 726, 718, 216, 166, and 729.
b Included double-blind Studies 730 and 726.
c Included open-label Studies 718, 216 and166.
d Includes Afro-Caribbean subjects from Study 166.

8.2.3 Adequacy of the safety database:

Considering carcinoid syndrome occurs in < 10% of gastrointestinal carcinoid tumors, the size of safety database is acceptable. The exposure to Somatuline Depot, duration of treatment, and patient demographics are adequate.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

The safety review was primarily based on Study 730. The safety database includes the double-blind placebo controlled data and the open-label extension data. Adverse events were collected at the weekly and/or monthly clinical visits. The data integrity and submission quality are acceptable. Assessment of the consistency of data did not identify safety issues.

OSI (Office of Scientific Investigations) did not audit of this submission. OCS (Office of Computational Science) did not conduct data fitness assessment.

8.3.2 Categorization of Adverse Events

The Applicant's approach to categorize of adverse events is reasonable.

- The Applicant provided adequate definition of AEs and serious adverse events in the protocols.
- The definition of TEAE (treatment emergent adverse events) was appropriate.
- MedDRA (Versions 18.1) was used to code AEs.
- AEs were collected at the clinical visits.
- AEs and SAEs were followed up until events returned to baseline.
- The AE assessment methods were appropriate.

8.3.3 Routine Clinical Tests

The routine clinical tests included hematology, chemistry and urinalysis. Clinically significant laboratory values, as well as clinically significant shifts in laboratory values, were required to be reported as TEAEs per study protocols. The assessment methods and time points of routine laboratory evaluations were reasonable.

8.4 Safety Results of Placebo-Controlled Study 730

8.4.1 Deaths during Controlled Phase of Study 730

In the placebo-controlled double-blind phase of Study 730, 2 patients in the placebo group died. There was no death in the Somatuline group.

8.4.2 Serious Adverse Events during Controlled Phase of Study 730

The proportion of subjects who experienced SAEs was low in both treated and placebo groups. Fewer subjects experienced SAEs in the Somatuline group as compared with placebo: 2 (3.4%) versus 5 (8.8%), respectively.

The most commonly reported SAEs were in the GI disorders SOC, reported in 1(1.7%) subject in the Somatuline group and in 2 (3.5%) subjects in the placebo group (Table 31).

Two SAEs were judged by the investigator to be related to study treatment. One was an event of cerebral ischemia experienced by a subject who had received placebo and the other was a serious case of "deafness permanent" experienced by one subject (PID (b) (6) in the Somatuline group.

> Narrative of SAE (PID (b) (6)): 62 years old female with carcinoid syndrome received Lanreotide 120 mg deep subcutaneous injections for 2 months before being diagnosed as breast cancer. She also suffered from partial deafness on the left ear at the same time. Concomitant medications included flunarizine, dihydroergocryptine, nimodipine, and thiamine, pyridoxine, and cyanocobalamin. She discontinued Lanreotide 2 months later. The investigator considered the partial irreversible deafness was probably related to the Lanreotide treatment. He thought “there may be somatostatin receptors in the semi-circular canal cells in the inner-ear leading to necrosis and or apoptosis.”

Medical Officer Comment: The clinical reviewer did not find any scientific evidence to support Lanreotide treatment causing semi-circular canal cell damages.

Table 31: Summary of SAEs during DB Phase by SOC and PT (Safety Population)

SOC PT	Lanreotide (N=58) n(%) [N]	Placebo (N=57) n(%) [N]
Any SAE	**2 (3.4) [6]**	**5 (8.8) [10]**
Gastrointestinal disorders	**1 (1.7) [3]**	**2 (3.5) [5]**
Small intestinal obstruction	1 (1.7) [3]	0
Vomiting	0	1 (1.8) [2]
Abdominal pain	0	1 (1.8) [1]
Diarrhoea	0	1 (1.8) [1]
Intestinal obstruction	0	1 (1.8) [1]
Infections and infestations	**1 (1.7) [1]**	**1 (1.8) [1]**
Urinary tract infection	1 (1.7) [1]	1 (1.8) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.7) [1]**	**1 (1.8) [1]**
Invasive ductal breast carcinoma	1 (1.7) [1]	0
Metastases to central nervous system	0	1 (1.8) [1]
Ear and labyrinth disorders	**1 (1.7) [1]**	**0**
Deafness permanent	1 (1.7) [1]	0
Nervous system disorders	**0**	**2 (3.5) [2]**
Cerebral ischaemia	0	1 (1.8) [1]
Hydrocephalus	0	1 (1.8) [1]
Musculoskeletal and connective tissue disorders	**0**	**1 (1.8) [1]**
Back pain	0	1 (1.8) [1]

Data Source: Table 14.3.1.1.2.9.
SAE= serious adverse event; DB=double-blind; SOC=system organ class; PT=preferred term; n (%) [N]=number of subjects (percent of subjects) [number of occurrences]
Note: MedDRA Version: 18.1, was used to map the verbatim terms.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

TEAEs leading to discontinuation of study drug for the placebo-controlled phase were low (Table 32).

Table 32: Summary of TEAEs during the DB Phase Leading to Withdrawal of Treatment (Safety Population)

SOC PT	Lanreotide (N=58) n(%) [N]	Placebo (N=57) n(%) [N]
Any TEAE	**1 (1.7) [1]**	**1 (1.8) [1]**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.7) [1]**	**0**
Invasive ductal breast carcinoma	1 (1.7) [1]	0
Nervous system disorders	**0**	**1 (1.8) [1]**
Cerebral ischaemia	0	1 (1.8) [1]

Data Source: Table 14.3.1.1.2.8.
TEAE=treatment-emergent adverse event; DB=double-blind; SOC=system organ class; PT=preferred term; n (%) [N]=number of subjects (percent of subjects) [number of occurrences].
Note: Any subject who experienced the same PT more than once is counted only once (except for the number of occurrences). System organ classes (SOCs) and PTs within SOCS are sorted by descending order of frequency for the lanreotide Autogel group during the double-blind phase.

8.4.4 Common Adverse Events

Symptomatic Subjects

Table 33 presents the most frequent TEAEs that occurred in symptomatic subjects in pooled studies (incidence >5% for SOC and PT in All Phases). Gastrointestinal disorders were the most frequent TEAEs and were reported by over half of the symptomatic subjects (52.5%, Table 33). TEAEs (PTs) within the GI disorder SOC that were reported by more than 5% of the subjects were abdominal pain (22.4%), abdominal pain upper (10.0%), nausea (11.9%), vomiting (10.5%), and constipation (7.8%). Diarrhea events were reported by 34/173 symptomatic subjects, 19.7% (not shown in Table 33).

Other most frequent PTs in other SOCs reported by >10% symptomatic subjects included: headache (12.8%), fatigue (12.8%), and asthenia (11.4%).

In the DB phase, headache, dizziness, and muscle spasms had higher than 5% frequency difference (i.e. a difference of at least three subjects) in the symptomatic subjects treated with Somatuline Depot compared with the symptomatic subjects treated with placebo.

Table 33: Most Frequent Treatment Emergent Adverse Events (Incidence in >5% Subjects, All Phases)

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System organ class[a] *High level term* Preferred term	All phases[b] lanreotide Autogel all doses N=219	Double-blind phase[c]		Open-label studies lanreotide Autogel all doses[d] N=116
		Lanreotide Autogel 120 mg N=58	Placebo N=57	
	n (%)	n (%)	n (%)	n (%)
Any TEAE	191 (87.2)	31 (53.4)	34 (59.6)	104 (89.7)
Gastrointestinal disorders	115 (52.5)	19 (32.8)	18 (31.6)	62 (53.4)
Gastrointestinal and abdominal pains (excl oral and throat)	65 (29.7)	7 (12.1)	9 (15.8)	37 (31.9)
Abdominal pain	49 (22.4)	5 (8.6)	8 (14.0)	28 (24.1)
Abdominal pain upper	22 (10.0)	1 (1.7)	1 (1.8)	11 (9.5)
Nausea and vomiting symptoms	39 (17.8)	7 (12.1)	8 (14.0)	18 (15.5)
Nausea	26 (11.9)	5 (8.6)	5 (8.8)	10 (8.6)
Vomiting	23 (10.5)	4 (6.9)	3 (5.3)	10 (8.6)
Flatulence, bloating and distension	18 (8.2)	3 (5.2)	1 (1.8)	8 (6.9)
Gastrointestinal atonic and hypomotility disorders NEC	18 (8.2)	2 (3.4)	2 (3.5)	6 (5.2)
Constipation	17 (7.8)	2 (3.4)	2 (3.5)	6 (5.2)
General disorders and administration site conditions	100 (45.7)	9 (15.5)	11 (19.3)	53 (45.7)
Asthenic conditions	50 (22.8)	5 (8.6)	4 (7.0)	25 (21.6)
Fatigue	28 (12.8)	2 (3.4)	4 (7.0)	12 (10.3)
Asthenia	25 (11.4)	2 (3.4)	1 (1.8)	15 (12.9)
Injection site reactions	21 (9.6)	2 (3.4)	2 (3.5)	14 (12.1)
General signs and symptoms NEC	22 (10.0)	2 (3.4)	0 (0.0)	10 (8.6)
Pain and discomfort NEC	12 (5.5)	1 (1.7)	2 (3.5)	5 (4.3)
Musculoskeletal and connective tissue disorders	66 (30.1)	8 (13.8)	7 (12.3)	29 (25.0)
Musculoskeletal and connective tissue pain and discomfort	40 (18.3)	4 (6.9)	5 (8.8)	18 (15.5)
Back pain	16 (7.3)	1 (1.7)	4 (7.0)	5 (4.3)
Musculoskeletal pain	12 (5.5)	0 (0.0)	1 (1.8)	6 (5.2)
Joint related signs and symptoms	20 (9.1)	0 (0.0)	1 (1.8)	7 (6.0)
Arthralgia	17 (7.8)	0 (0.0)	1 (1.8)	4 (3.4)
Muscle related signs and symptoms NEC	12 (5.5)	3 (5.2)	0 (0.0)	1 (0.9)
Infections and infestations	65 (29.7)	9 (15.5)	9 (15.8)	25 (21.6)
Upper respiratory tract infections	20 (9.1)	3 (5.2)	5 (8.8)	4 (3.4)
Urinary tract infections	12 (5.5)	2 (3.4)	2 (3.5)	2 (1.7)
Nervous system disorders	58 (26.5)	13 (22.4)	5 (8.8)	23 (19.8)
Headaches NEC	28 (12.8)	7 (12.1)	3 (5.3)	10 (8.6)
Headache	28 (12.8)	7 (12.1)	3 (5.3)	10 (8.6)
Neurological signs and symptoms NEC	20 (9.1)	4 (6.9)	0 (0.0)	9 (7.8)
Dizziness	18 (8.2)	4 (6.9)	0 (0.0)	7 (6.0)
Metabolism and nutrition disorders	48 (21.9)	2 (3.4)	5 (8.8)	17 (14.7)
Appetite disorders	19 (8.7)	1 (1.7)	1 (1.8)	6 (5.2)
Decreased appetite	19 (8.7)	1 (1.7)	1 (1.8)	6 (5.2)
Hyperglycaemic conditions NEC	14 (6.4)	0 (0.0)	1 (1.8)	2 (1.7)
Hyperglycaemia	12 (5.5)	0 (0.0)	1 (1.8)	2 (1.7)
Respiratory, thoracic and mediastinal disorders	42 (19.2)	2 (3.4)	5 (8.8)	14 (12.1)
Breathing abnormalities	14 (6.4)	0 (0.0)	4 (7.0)	5 (4.3)
Dyspnoea	14 (6.4)	0 (0.0)	4 (7.0)	5 (4.3)
Coughing and associated symptoms	12 (5.5)	2 (3.4)	1 (1.8)	3 (2.6)
Investigations	39 (17.8)	3 (5.2)	5 (8.8)	7 (6.0)
Physical examination procedures and organ system status	13 (5.9)	1 (1.7)	0 (0.0)	3 (2.6)
Weight decreased	12 (5.5)	1 (1.7)	0 (0.0)	3 (2.6)

System organ class[a] *High level term* Preferred term	All phases[b] lanreotide Autogel all doses N=219	Double-blind phase[c]		Open-label studies lanreotide Autogel all doses[d] N=116
		Lanreotide Autogel 120 mg N=58	Placebo N=57	
	n (%)	n (%)	n (%)	n (%)
Skin and subcutaneous tissue disorders	31 (14.2)	5 (8.6)	3 (5.3)	12 (10.3)
Hepatobiliary disorders	23 (10.5)	0 (0.0)	2 (3.5)	11 (9.5)
Cholecystitis and cholelithiasis	13 (5.9)	0 (0.0)	1 (1.8)	5 (4.3)
Cholelithiasis	13 (5.9)	0 (0.0)	1 (1.8)	5 (4.3)
Renal and urinary disorders	20 (9.1)	5 (8.6)	4 (7.0)	6 (5.2)
Psychiatric disorders	22 (10.0)	2 (3.4)	4 (7.0)	6 (5.2)
Injury, poisoning and procedural complications	16 (7.3)	2 (3.4)	2 (3.5)	7 (6.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (7.3)	2 (3.4)	3 (5.3)	5 (4.3)
Cardiac disorders	15 (6.8)	1 (1.7)	2 (3.5)	6 (5.2)
Vascular disorders	18 (8.2)	0 (0.0)	1 (1.8)	4 (3.4)
Vascular hypertensive disorders NEC	13 (5.9)	0 (0.0)	1 (1.8)	2 (1.7)
Hypertension	13 (5.9)	0 (0.0)	1 (1.8)	2 (1.7)
Eye disorders	15 (6.8)	1 (1.7)	2 (3.5)	4 (3.4)
Blood and lymphatic system disorders	16 (7.3)	1 (1.7)	0 (0.0)	2 (1.7)
Anaemias NEC	14 (6.4)	1 (1.7)	0 (0.0)	2 (1.7)
Anaemia	13 (5.9)	0 (0.0)	0 (0.0)	2 (1.7)

Note: if there were no preferred terms or high level terms with incidence >5%, then these terms are not included and just the higher term(s) are included.
excl=excluding; incl=including; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects receiving study treatment in a specific group; n=number of subjects with event(s); NEC=not elsewhere classified; TEAE=treatment emergent adverse event.
Data Source: Module 5.3.5.3 ISS Tables AE-A1.2-1.

a Coded using MedDRA Version 18.1.
b Studies 730, 718, 216, and 166.
c Double-blind phase of Study 730.
d Studies 716, 216 and 166.

All Subjects

Table 34 presents the most frequent TEAEs that occurred in all subjects in pooled studies (incidence >5% for any SOC, or PT in All Phases). Gastrointestinal disorders were the most frequent TEAEs and were reported by over half of the subjects (55.8%), Table 32. TEAEs (PTs) within the GI disorder SOC that were reported by more than 5% of the subjects were abdominal pain (23.0%), abdominal pain upper (11.9%), vomiting (14.6%), nausea (13.0%), flatulence (6.9%) and constipation (10.1%).

Diarrhea events were reported by 92/332 subjects, 27.7% (not shown in Table 34). Other most frequent PTs in other SOCs reported by >10% subjects included: fatigue (12.2%), and asthenia (10.8%), back pain (10.6%), headache (13.5%), and cholelithiasis (10.8%).

In the DB phase, vomiting, headache and dizziness had higher than 5% frequency difference (i.e. a difference of at least eight subjects) in the subjects treated with Somatuline Depot (14.5%, 15.1%, and 8.8%, respectively) compared with the subjects treated with placebo (7.5%, 8.8%, and 1.3%, respectively).

Table 34: Most Frequent Treatment Emergent Adverse Events (Incidence in >5% Subjects, All Phases) Excluding Diarrhea and Flushing: All Subjects

System organ class[a] *High level term* Preferred term	All phases[b]	Double-blind phase[c]		Open-label studies[d]
	Lanreotide Autogel all doses N=378	Lanreotide Autogel 120 mg N=159	Placebo N=160	Lanreotide Autogel All doses N=127
	n (%)	n (%)	n (%)	n (%)
Any TEAE	330 (87.3)	119 (74.8)	126 (78.8)	112 (88.2)
Gastrointestinal disorders	211 (55.8)	78 (49.1)	73 (45.6)	68 (53.5)
Gastrointestinal and abdominal pains (excl oral and throat)	119 (31.5)	38 (23.9)	33 (20.6)	38 (29.9)
Abdominal pain	87 (23.0)	29 (18.2)	25 (15.6)	28 (22.0)
Abdominal pain upper	45 (11.9)	9 (5.7)	10 (6.3)	12 (9.4)
Nausea and vomiting symptoms	80 (21.2)	34 (21.4)	24 (15.0)	20 (15.7)
Vomiting	55 (14.6)	23 (14.5)	12 (7.5)	12 (9.4)
Nausea	49 (13.0)	20 (12.6)	19 (11.9)	10 (7.9)
Flatulence, bloating and distension	42 (11.1)	18 (11.3)	12 (7.5)	9 (7.1)
Flatulence	26 (6.9)	15 (9.4)	10 (6.3)	7 (5.5)
Gastrointestinal atonic and hypomotility disorders NEC	40 (10.6)	14 (8.8)	18 (11.3)	7 (5.5)
Constipation	38 (10.1)	14 (8.8)	16 (10.0)	7 (5.5)
General disorders and administration site conditions	159 (42.1)	44 (27.7)	55 (34.4)	59 (46.5)
Asthenic conditions	85 (22.5)	24 (15.1)	23 (14.4)	28 (22.0)
Fatigue	46 (12.2)	12 (7.5)	19 (11.9)	12 (9.4)
Asthenia	41 (10.8)	10 (6.3)	6 (3.8)	18 (14.2)
Injection site reactions	47 (12.4)	17 (10.7)	8 (5.0)	17 (13.4)
Injection site pain	23 (6.1)	9 (5.7)	5 (3.1)	7 (5.5)
General signs and symptoms NEC	27 (7.1)	3 (1.9)	5 (3.1)	10 (7.9)
Infections and infestations	137 (36.2)	52 (32.7)	57 (35.6)	27 (21.3)
Upper respiratory tract infections	47 (12.4)	17 (10.7)	30 (18.8)	5 (3.9)
Nasopharyngitis	27 (7.1)	12 (7.5)	18 (11.3)	3 (2.4)
Urinary tract infections	30 (7.9)	13 (8.2)	12 (7.5)	2 (1.6)
Urinary tract infection	24 (6.3)	11 (6.9)	11 (6.9)	2 (1.6)
Lower respiratory tract and lung infections	29 (7.7)	10 (6.3)	8 (5.0)	3 (2.4)
Musculoskeletal and connective tissue disorders	123 (32.5)	43 (27.0)	32 (20.0)	31 (24.4)
Musculoskeletal and connective tissue pain and discomfort	80 (21.2)	28 (17.6)	19 (11.9)	20 (15.7)
Back pain	40 (10.6)	13 (8.2)	15 (9.4)	7 (5.5)
Musculoskeletal pain	23 (6.1)	7 (4.4)	4 (2.5)	6 (4.7)
Joint related signs and symptoms	41 (10.8)	12 (7.5)	11 (6.9)	7 (5.5)
Arthralgia	35 (9.3)	10 (6.3)	10 (6.3)	4 (3.1)
Muscle related signs and symptoms NEC	20 (5.3)	9 (5.7)	4 (2.5)	1 (0.8)
Nervous system disorders	104 (27.5)	46 (28.9)	24 (15.0)	24 (18.9)
Headaches NEC	51 (13.5)	24 (15.1)	14 (8.8)	10 (7.9)
Headache	51 (13.5)	24 (15.1)	14 (8.8)	10 (7.9)
Neurological signs and symptoms NEC	35 (9.3)	14 (8.8)	2 (1.3)	10 (7.9)
Dizziness	33 (8.7)	14 (8.8)	2 (1.3)	8 (6.3)
Metabolism and nutrition disorders	109 (28.8)	36 (22.6)	24 (15.0)	19 (15.0)
Appetite disorders	37 (9.8)	12 (7.5)	10 (6.3)	7 (5.5)
Decreased appetite	37 (9.8)	12 (7.5)	10 (6.3)	7 (5.5)
Hyperglycaemic conditions NEC	27 (7.1)	7 (4.4)	1 (0.6)	3 (2.4)
Hyperglycaemia	23 (6.1)	6 (3.8)	1 (0.6)	3 (2.4)
Skin and subcutaneous tissue disorders	66 (17.5)	27 (17.0)	24 (15.0)	12 (9.4)
Investigations	78 (20.6)	22 (13.8)	18 (11.3)	8 (6.3)
Physical examination procedures and organ system status	30 (7.9)	12 (7.5)	9 (5.6)	3 (2.4)
Weight decreased	25 (6.6)	9 (5.7)	8 (5.0)	3 (2.4)
Respiratory, thoracic and mediastinal disorders	72 (19.0)	19 (11.9)	20 (12.5)	15 (11.8)

(Continued)

System organ class[a] *High level term* Preferred term	All phases[b] Lanreotide Autogel all doses N=378 n (%)	Double-blind phase[c] Lanreotide Autogel 120 mg N=159 n (%)	Double-blind phase[c] Placebo N=160 n (%)	Open-label studies[d] Lanreotide Autogel All doses N=127 n (%)
Breathing abnormalities	24 (6.3)	7 (4.4)	8 (5.0)	5 (3.9)
Dyspnoea	23 (6.1)	6 (3.8)	5 (3.1)	5 (3.9)
Coughing and associated symptoms	23 (6.1)	7 (4.4)	6 (3.8)	3 (2.4)
Cough	21 (5.6)	7 (4.4)	4 (2.5)	3 (2.4)
Hepatobiliary disorders	60 (15.9)	20 (12.6)	12 (7.5)	12 (9.4)
Cholecystitis and cholelithiasis	41 (10.8)	14 (8.8)	8 (5.0)	5 (3.9)
Cholelithiasis	41 (10.8)	14 (8.8)	8 (5.0)	5 (3.9)
Vascular disorders	50 (13.2)	19 (11.9)	12 (7.5)	4 (3.1)
Vascular hypertensive disorders NEC	35 (9.3)	13 (8.2)	6 (3.8)	2 (1.6)
Hypertension	35 (9.3)	13 (8.2)	6 (3.8)	2 (1.6)
Psychiatric disorders	42 (11.1)	17 (10.7)	12 (7.5)	7 (5.5)
Injury, poisoning and procedural complications	36 (9.5)	10 (6.3)	18 (11.3)	8 (6.3)
Renal and urinary disorders	38 (10.1)	14 (8.8)	10 (6.3)	6 (4.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	33 (8.7)	8 (5.0)	11 (6.9)	6 (4.7)
Blood and lymphatic system disorders	34 (9.0)	9 (5.7)	8 (5.0)	3 (2.4)
Anaemias NEC	27 (7.1)	7 (4.4)	2 (1.3)	3 (2.4)
Anaemia	25 (6.6)	6 (3.8)	2 (1.3)	3 (2.4)
Eye disorders	29 (7.7)	10 (6.3)	11 (6.9)	4 (3.1)
Cardiac disorders	29 (7.7)	7 (4.4)	9 (5.6)	6 (4.7)
Reproductive system and breast disorders	21 (5.6)	8 (5.0)	4 (2.5)	4 (3.1)

Note: if there were no preferred terms or high level terms with incidence >5%, then these terms are not included and just the higher term(s) are included.
excl=excluding; incl=including; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects receiving study treatment in a specific group; n=number of subjects with event (s); NEC=not elsewhere classified; TEAE=treatment emergent adverse event.
Data Source: Module 5.3.5.3 ISS Table AE-A.2-1.

a Coded using MedDRA Version 18.1.
b Studies: 730, 726, 718, 216, 166, and 729.
c Double-blind phase of Studies 726 and 730.
d Studies 716, 216 and 166.

8.4.5 Laboratory Findings

Laboratory evaluations included hematology, chemistry and urinalysis. Clinically significant laboratory values, as well as clinically significant shifts in laboratory values, were reported as TEAEs. In the Somatuline group, during the DB phase, hemoglobin decreased, blood viscosity increased (one subject each) were reported, and were considered related to study treatment, while in the placebo group, blood glucose increased was reported and considered related to the study treatment.

8.4.6 Vital Signs

All vital sign parameters (heart rate, systolic and diastolic blood pressure, respiratory rate, weight, and BMI) were monitored during each phase of studies. No clinically significant abnormalities were identified.

8.4.7 Electrocardiograms (ECGs)

ECG evaluations include heart rate, PR duration, QRS duration, and QT interval. The evaluation had no significant or clinical meaningful findings.

8.4.8 Immunogenicity

No assessment of immunogenicity for Somatuline Depot was performed.

8.5 Analysis of Submission-Specific Safety Issues

No new safety issues of drug class effect, non-clinical signal, or uncertainty about novel moiety were found.

8.6 Specific Safety Studies/Clinical Trials

No Specific study was conducted to evaluate a specific safety concern.

8.7 Additional Safety Explorations

8.7.1 Human Carcinogenicity or Tumor Development

No potential issues related to human carcinogenicity or tumor development were identified.

8.7.2 Human Reproduction and Pregnancy

Human reproduction and pregnancy were not evaluated during the development program.

8.7.3 Pediatrics and Assessment of Effects on Growth

Pediatric trials and assessment of effects on growth were not evaluated during the development program, because Orphan Drug Designation was approved on September 8, 2011.

8.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose, drug abuse potential, withdrawal, and rebound were not studied.

8.8 Safety in the Postmarket Setting

8.8.1 Safety Concerns Identified Through Postmarket Experience

Postmarketing Data
The postmarketing experience with lanreotide extends to 19 years of use for a variety of indications. From its approval on May 16, 1994 to May 31, 2013, a total o (b) (4) units of

lanreotide [including (b) (4) units of Prolonged Release (PR) formulations an (b) (4) units of Autogel formulations] have been sold. This equates to a cumulative patient exposure of approximatel (b) (4) treatment months based on an estimated dosing regimen of two PR injections (30 mg or 60 mg) per month or one Autogel injection (60 mg, 90 mg or 120 mg) per month.

Description of Postmarketing Adverse Events

Between the first approval of lanreotide on May 16, 1994 and March 31, 2013, 2,684 serious and nonserious postmarketing cases (with 5,893 AEs) have been reported. Of these AEs, 3,761 relate to use in acromegaly and 1,038 to use in other approved indications (peritoneal carcinomatosis, neuroendocrine tumors, digestive fistulae and thyroid adenoma). The remaining 1,094 AEs are associated with use of lanreotide for conditions for which it is not approved.

Postmarketing AEs for lanreotide are presented by SOC in Table 35.

The most common postmarketing AEs were in the SOCs of gastrointestinal disorders, and general disorders and administration site conditions [31.2% (1,839/5,893) and 24.3% (1,432/5,893) of all postmarketing AEs, respectively]. In the SOC of gastrointestinal disorders, the most frequently reported AEs were diarrhea (9.4%), abdominal pain (3.9%), nausea (3.8%) and flatulence (2.2%), and in the SOC of general disorders and administration site conditions were injection site pain (3.6%), injection site nodule (3.3%) and fatigue (2.3%). In the SOC of nervous system disorders, headache was also frequently reported (2.3%). For all other PTs, fewer than 100 AEs (<2% of all postmarketing AEs) were reported.

In total, 988 postmarketing SAEs were reported. Of these SAEs, 785 occurred during use of lanreotide for approved indications, including 543 SAEs in patients with acromegaly. Ninety one postmarketing cases with a fatal outcome have been reported with lanreotide treatment, including 31 cases of patients with acromegaly, 35 cases associated with use of lanreotide in other approved indications, and 25 cases associated with the use of lanreotide for conditions for which it is not approved. Of the 91 deaths, 31 concerned cases where the cause of death was either unknown or not reported (including nine patients with acromegaly). Eighteen deaths were considered to be due to disease progression, including three patients with acromegaly (progression of pituitary carcinoma, progression of metastatic colon cancer, and progression of duodenal carcinoma in one patient each). Seven patients with acromegaly died from myocardial infarction or cardiac arrest, and cardiac arrest was reported as the cause of death for one case associated with the use of lanreotide for conditions for which it is not approved. In total, four of the fatal cases were considered to be related to treatment by the reporter (including two patients with acromegaly), 41 were considered not related by the reporter, while a causality assessment in the remaining 46 cases was not reported.

The safety of lanreotide is regularly monitored, with data presented in Periodic Safety Update Reports (PSURs).

Table 35: Postmarketing AEs by SOC (All Indications)

SOC	All indications									Total[a]
	Acromegaly			Other approved indications[b]			Off label use			
	S	NS	T	S	NS	T	S	NS	T	
Blood and lymphatic system disorders	2	9	11	2	0	2	5	4	9	22
Cardiac disorders	33	25	58	10	6	16	7	7	14	88
Congenital, familial and genetic disorders	1	2	3	0	0	0	0	0	0	3
Ear and labyrinth disorders	2	5	7	0	1	1	0	0	0	8
Endocrine disorders	9	6	15	2	1	3	1	1	2	20
Eye disorders	6	20	26	1	3	4	2	5	7	37
Gastrointestinal disorders	93	1171	1264	38	238	276	43	256	299	1839
General disorders and administration site conditions	58	779	837	51	241	292	36	267	303	1432
Hepatobiliary disorders	62	39	101	12	6	18	7	7	14	133
Immune system disorders	0	3	3	0	0	0	3	1	4	7
Infections and infestations	33	55	88	11	10	21	14	17	31	140
Injury, poisoning and procedural complications	19	99	118	3	57	60	6	64	70	248
Investigations	17	254	271	16	53	69	5	29	34	374
Metabolism and nutrition disorders	16	64	80	20	24	44	10	14	24	148
Musculoskeletal and connective tissue disorders	28	132	160	8	22	30	3	30	33	223
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	35	2	37	16	1	17	6	1	7	61
Nervous system disorders	45	233	278	15	39	54	19	46	65	397
Pregnancy, puerperium and perinatal conditions	3	10	13	0	0	0	4	4	8	21
Psychiatric disorders	7	50	57	7	15	22	3	14	17	96
Renal and urinary disorders	8	14	22	9	0	9	7	2	9	40
Reproductive system and breast disorders	10	21	31	1	4	5	1	6	7	43
Respiratory, thoracic and mediastinal disorders	13	29	42	4	11	15	5	8	13	70
Skin and subcutaneous tissue disorders	12	147	159	7	36	43	10	76	86	288
Social circumstances[c]	0	1	1	0	0	0	0	0	0	1
Surgical and medical procedures	21	6	27	4	4	8	0	22	22	57
Vascular disorders	10	42	52	5	24	29	6	10	16	97
Total	543	3218	3761	242	796	1038	203	891	1094	5893

NS=nonserious; S=serious; SOC=system organ class; T=total.

a Postmarketing AEs include worldwide reports of nonserious and serious, related and not related, listed and unlisted, medically confirmed and consumer reports from spontaneous, literature, health authority and solicited sources for all dosage forms of lanreotide, excluding comanifestations.

b Approved indications include peritoneal carcinomatosis, neuroendocrine tumours, digestive fistulae and thyroid adenoma.

c Stress at work.

From Postmarketing Reports of NDA 022,074.

Medical Officer Comments:
The adverse event profile of the postmarketing report was consistent with that observed in the clinical studies. The most frequent AEs were gastrointestinal disorders and general disorders and administration site conditions. No new safety signal was identified.

Review of 120-day Safety Update

The 120-day Safety Update summarizes additional safety information between the data extraction date for the NDA submission on 4/1/2016 and the 120-day safety update date on 8/31/2016. A total of 872 new postmarketing surveillance (PMS) cases of Somatuline Depot were reported. The safety profile of Somatuline in patients with CS remained unchanged.

Table 36: Somatuline Depot 120 mg Number of AEs (Incidence >5%) for Patients with NETs- Pooled by Causality - PMS Data

System organ class[a] *High level term* Preferred term	M=872 Causality Overall	Related [b]	Unclassified [c]	Unrelated [d]
Any Adverse Event	872 (100.0%)	551 (63.2%)	2 (0.2%)	319 (36.6%)
Gastrointestinal disorders	204 (23.4%)	166 (19.0%)	0 (0.0%)	38 (4.4%)
Diarrhoea (excl infective)	56 (6.4%)	54 (6.2%)	0 (0.0%)	2 (0.2%)
Diarrhoea	54 (6.2%)	53 (6.1%)	0 (0.0%)	1 (0.1%)
General disorders and administration site conditions	185 (21.2%)	118 (13.5%)	0 (0.0%)	67 (7.7%)
Injection site reactions	51 (5.8%)	51 (5.8%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	74 (8.5%)	56 (6.4%)	0 (0.0%)	18 (2.1%)
Maladministrations	48 (5.5%)	47 (5.4%)	0 (0.0%)	1 (0.1%)
Investigations	54 (6.2%)	31 (3.6%)	0 (0.0%)	23 (2.6%)
Musculoskeletal and connective tissue disorders	45 (5.2%)	37 (4.2%)	0 (0.0%)	8 (0.9%)
Nervous system disorders	45 (5.2%)	36 (4.1%)	0 (0.0%)	9 (1.0%)

AE=adverse events, M=Number of adverse events (percentages are of total adverse events and are rounded as appropriate), NETs=neuroendocrine tumours, PMS=postmarketing surveillance.

Data Source: ISS 120 day update Table AE-C.4-1

Note: Data from the reporting window 01 April 2016 to 31 August 2016

a Adverse events have been coded using MedDRA version 19.0

b Related when causality is "Possible", "Probable", "Related" and "Reasonable Possibility".

c Unclassified when causality is "Not Reported", "Not assessable", "Unclassified" or missing.

d Not related when causality is "Not related", "Unlikely" or "No reasonable possibility".

Serious Adverse Events

Of the 872 PMS AEs, a total of 260 SAEs (Table 37) have been received during the reporting window of this 120-day safety update. The profile of the SAE postmarketing surveillance reports is consistent with that seen in the updated Integrated Summary of Safety.

Table 37: Somatuline Depot 120 mg Number of Postmarketing Surveillance SAEs (Incidence >1%) for Patients with NETs- Pooled by Causality - PMS Data

System organ class[a] *High level term* Preferred term	M=872 Causality Overall	Related [b]	Unclassified [c]	Unrelated [d]
Any Serious Adverse Event	260 (29.8%)	60 (6.9%)	0 (0.0%)	200 (22.9%)
General disorders and administration site conditions	53 (6.1%)	6 (0.7%)	0 (0.0%)	47 (5.4%)
General signs and symptoms NEC	25 (2.9%)	1 (0.1%)	0 (0.0%)	24 (2.8%)
Disease progression	17 (1.9%)	1 (0.1%)	0 (0.0%)	16 (1.8%)
Death and sudden death	14 (1.6%)	0 (0.0%)	0 (0.0%)	14 (1.6%)
Death	14 (1.6%)	0 (0.0%)	0 (0.0%)	14 (1.6%)
Gastrointestinal disorders	42 (4.8%)	18 (2.1%)	0 (0.0%)	24 (2.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (3.2%)	0 (0.0%)	0 (0.0%)	28 (3.2%)
Metabolism and nutrition disorders	21 (2.4%)	10 (1.1%)	0 (0.0%)	11 (1.3%)
Surgical and medical procedures	16 (1.8%)	1 (0.1%)	0 (0.0%)	15 (1.7%)
Therapeutic procedures NEC	9 (1.0%)	0 (0.0%)	0 (0.0%)	9 (1.0%)
Infections and infestations	13 (1.5%)	0 (0.0%)	0 (0.0%)	13 (1.5%)
Injury, poisoning and procedural complications	13 (1.5%)	0 (0.0%)	0 (0.0%)	13 (1.5%)
Investigations	12 (1.4%)	3 (0.3%)	0 (0.0%)	9 (1.0%)
Respiratory, thoracic and mediastinal disorders	11 (1.3%)	2 (0.2%)	0 (0.0%)	9 (1.0%)
Hepatobiliary disorders	9 (1.0%)	7 (0.8%)	0 (0.0%)	2 (0.2%)
Nervous system disorders	9 (1.0%)	4 (0.5%)	0 (0.0%)	5 (0.6%)

AE=adverse events, M=Number of adverse events (percentages are of total adverse events and are rounded as appropriate), NEC=not elsewhere classified, NETs=neuroendocrine tumours, PMS=postmarketing surveillance

Percentages are of total adverse events (M) and are rounded as appropriate.

Data Source: ISS 120 day update Table AE-C.5-1

Note: Data for the reporting window 01 April 2016 to 31 August 2016

a Adverse Events have been coded using MedDRA version 19.0

b Related when causality is "Possible", "Probable", "Related" and "Reasonable Possibility".

c Unclassified, when causality is. "Not reported", "Not assessable" and "Unclassified" or missing.

d Not related when causality is "Not related", "Unlikely" or "No reasonable possibility".

Deaths

There were 38 SAEs in 33 patients that led to death during the reporting window. These SAEs were all assessed as unrelated to treatment with the exception of two SAEs (coagulopathy and cerebral hemorrhage) that occurred in one patient as described below.

Case 2016-04421: Cerebral bleed/intracerebral hemorrhage

A 64-year-old male patient had a medical history of prostate cancer and S/P mechanical aortic valve placement. Concomitant medications included warfarin and octreotide for NET. O (b) (6) (b) (6) the patient started treatment with Somatuline Depot 120 mg for NET. Eleven days after treatment with Somatuline Depot, the patient developed coagulation disturbance and a large cerebral bleed. His International Normalized Ratio (INR) was >9. On the same day the patient died due to intracerebral hemorrhage and coagulation disturbance. The physician assessed the causality as possibly related, and the Applicant stated that the most likely cause of the cerebral hemorrhage was the high INR (>9) secondary to warfarin use. The presence of intestinal NETs and prostate cancer were also confounding factors. There is no known drug-drug interaction between lanreotide and warfarin.

Medical Officer Comments:
I agree with the Applicant. It appears that the intracerebral hemorrhage was caused by warfarin overdosing. There was no sufficient evidence to support Somatuline causing intracerebral hemorrhage.

Summary of Safety 120-Day Update by Applicant
The safety profile of Somatuline Depot 120 mg in patients with NETs and symptoms associated with carcinoid syndrome is consistent with the profile and conclusions in the updated Integrated Summary of Safety. No safety signals have been observed in the PMS data during the period covered by this 120-day safety update.

8.8.2 Expectations on Safety in the Postmarket Setting

No evidence raises safety concerns in the postmarket setting.

8.9 Additional Safety Issues From Other Disciplines

Potential issues such as drug formulation, delivery, product quality were not identified.

8.10 Integrated Assessment of Safety by Applicant

A total of 378 patients with carcinoid tumor (219 patients with carcinoid diarrhea and flushing) were treated by Somatuline Depot. The mean duration was approximate 20 months and the highest dose was 120 mg deep s.c. injection every 4 weeks. There was no significant safety signal reported.

The most frequently reported events by >5% of all the symptomatic subjects in the DB phase of the pivotal Study 730 were GI disorders (abdominal pain, vomiting, and nausea). The most frequently reported TEAEs for all symptomatic subjects treated with Somatuline Depot (excluding diarrhea and flushing) treated in all phases and studies (>10%) were: abdominal pain (22.4%), fatigue (12.8%), headache (12.8%), nausea (11.9%), asthenia (11.4%), and vomiting (10.5%).

In the DB phase of Study 730, headache, dizziness, and muscle spasms had higher than 5% frequency difference (i.e. a difference of at least three subjects) in the symptomatic subjects treated with Somatuline Depot compared with the symptomatic subjects treated with placebo.

There were 12/219 symptomatic subjects treated with Somatuline Depot who experienced a serious TEAE that led to death; none of them was considered related to study treatment. There

were 17/219 (7.8%) of the symptomatic subjects treated with Somatuline Depot who withdrew due to a TEAE. One of them (ID (b) (6) Study 730) withdrew from the Somatuline treatment due to irreversible hearing loss.

The AE profile of Somatuline Depot 120 mg in subjects with symptomatic NETs was consistent with the All Subjects population and with the known safety profile in the use of the product in other indications. The safety profile in Study 730 was similar to that seen in the analysis of All Subjects. An analysis of the TEAE profile in subjects naïve to SSA therapy compared to those previously treated with SSAs showed that previous SSA therapy did not have an effect on TEAEs, except diarrhea. Two symptomatic subjects (0.9%) experienced bradycardia following treatment with Somatuline Depot. The proportion of symptomatic subjects with cholelithiasis increased with longer exposure to Somatuline Depot.

In summary, the safety profile of Somatuline Depot 120 mg administered to subjects with NETs and symptoms of CS diarrhea and flushing, is consistent with the profile previously reported in other indications. No new emerging safety concerns have been identified that change the benefit-risk balance of Somatuline Depot.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations was held.

10 Labeling Recommendations

10.1 Prescribing Information

Labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS was not recommended.

12 Postmarketing Requirements and Commitments

Postmarketing requirement and commitments were not recommended.

13 Appendices

13.1 References

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13.2 Financial Disclosure

A total of 454 clinical investigators participated in the covered clinical Study 730 of Somatuline

Depot. The covered clinical study is defined in 21 CFR 54.2(e) which is used to establish the effectiveness. No investigators were part- or full-time employees of the Applicant. The Applicant certified the names of the 454 clinical investigators who did not enter into any financial agreements with the Applicant (Section 1.3.4.1 Financial Certification of Clinical Investigators).

Table 38: Covered Clinical Study: Study 2-55-52030-730 (Study 730)

Was a list of clinical investigators provided:	Yes √	No ☐ (Request list from Applicant) N/A
Total number of investigators identified: 454		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	N/A	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	N/A	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	N/A	No ☐ (Request explanation from Applicant) N/A

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

/s/

WEN-YI GAO
06/05/2017

VICTOR C BAUM
06/05/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	022-074
Supplement #:	S-017
Drug Name:	Somatuline depot (lanreotide acetate)
Indication:	(b) (4)
Applicant:	Ipsen Biopharmaceuticals, Inc.
Dates:	Received date: 8/15/2016; Filing date: 10/14/2016; Mid-cycle date: 2/15/2017; Review completed date:6/6/2017
Review Priority:	Standard
Biometrics Division:	III
Statistical Reviewers:	Ling Lan, Ph.D.
Concurring Reviewers:	George Kordzakhia, Ph.D; Yeh-Fong Chen, Ph. D. (team leader).
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team:	Wen-Yi Gao, M.D.; Victor Baum, M.D. (team leader)
Project Manager:	Benjamin Vali

Keywords: missing data, single study application, rare disease

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1 EXECUTIVE SUMMARY

Somatuline Depot (lanreotide acetate) is a long-acting synthetic cyclical octapeptide somatostatin analogue (SSTa) developed by Ispe (b) (4) (b) (4). Carcinoid syndrome, one type of NETs and a rare disease, often occurs as a result of hepatic metastases and evoked by the release of hormones directly into the systemic circulation.

Lanreotide has been approved in the US under NDA 22-074, originally for acromegaly on August 30, 2007, and for the improvement on progression-free survival in patients with gastroenteropancreatic NETs on December 16, 2014. Lanreotide was designated as an orphan drug for the treatment of symptoms associated with carcinoid syndrome on September 8, 2011.

This submission included three studies to support efficacy claims, a pivotal phase 3, randomized (1:1 randomization ratio), double-blind (DB), placebo-controlled, multi-center study in patients with carcinoid syndrome (Study 2-55-52030-730, hereafter referred to as Study 730); and two supportive studies, one uncontrolled Phase 2 European study and one biomarker study pooling from the pivotal Phase 3 study mentioned above and a Phase 3 study in non-functioning enteropancreatic endocrine tumor. This statistical review focused on the pivotal study 730 in patients with carcinoid syndrome.

In the pivotal study 730, a total of 115 subjects were randomized to receive lanreotide 120mg (n=59) or placebo (n=56) via deep subcutaneous injection every 28 ± 3 days in 39 centers during the 16-week DB phase in order to demonstrate the efficacy of lanreotide compared to placebo on symptom control of diarrhea and/or flushing associated with carcinoid syndrome. The primary endpoint was the percent of days with octreotide use as a rescue medication during the DB phase, and the key secondary endpoints were the average daily frequencies of diarrhea events and flushing events.

The primary analysis was based on the observed number of days with octreotide use divided by the number of non-missing diary days, which is essentially the prorated measurement for each patient; this approach is based on the assumption of missing at random (i.e., MAR).

Based on the pre-specified primary analysis using an ANCOVA model, the lanreotide arm (30.7%) had a significant 14.8% reduction (the 95% confidence interval: -26.8, -2.8) in days of octreotide use in comparison to the placebo arm (48.5%) with *p*-value of 0.0165. The study failed to show efficacy of lanreotide 120 mg in the first key secondary endpoint, i.e., average daily frequency of diarrhea (p-value of 0.254). The results for the second key secondary endpoint, i.e., the average frequency of flushing episodes, reached nominal significance; (b) (4)

We noted a high dropout rate (36/115 or 31% of patients did not complete the DB treatment period) as well as the noticeably different missing data pattern in treatment arms (lanreotide 24% and placebo 39%) in study 730. The statistical review team performed several types of sensitivity analyses for dealing with missing data, including best case imputation and worst case imputation. Our results did not support the robustness of the primary efficacy results. Sensitivity analyses resulted in widely varying point estimates for the mean percentage difference in octreotide use between the drug and placebo arms (see Table 7 for details).

We further explored the impact of missing data focusing on shorter assessment periods (i.e., from day 1 until the day of second injection). Of note, placebo patients' early rollover/dropout rate at this time points were about twice as large as for the Lanreotide patients. We found the impact of missing data and dropouts still cannot be ignored, even in the shorter duration, and there is no strong evidence to support the lanreotide's efficacy with a nominal p-value greater than 0.05.

In conclusion, Study 730 did not provide substantial evidence in supporting the efficacy of lanreotide fo (b) (4) (b) (4)

2 INTRODUCTION

2.1 Overview

Somatuline Depot (lanreotide acetate) is a long-acting synthetic cyclical octapeptide somatostatin analogue (SSTa) developed by Ispen [redacted] (b) (4) [redacted] (b) (4) The proposed dosage of lanreotide is 120 mg deep subcutaneous (s.c.) injection every 28 ± 3 days.

NETs originate from pancreatic islet neuroendocrine cells, diffuse gastroenteric neuroendocrine cells, and/or neuroendocrine cells elsewhere in the body. Those arising from the diffuse neuroendocrine system are known as carcinoid tumors, which could be asymptomatic or symptomatic. Carcinoid syndrome, flushing, diarrhea, and wheezing, occurs as a result of hepatic metastases and evoked by the release of hormones directly into the systemic circulation. Carcinoid syndrome is a rare disease.

Lanreotide has been approved in the US under New Drug Application (NDA) 22-074, originally for the long-term treatment of acromegaly on August 30, 2007, and for the treatment of patients with gastroenteropancreatic NETs (GEP-NETs) to improve progression-free survival on December 16, 2014. Lanreotide has also been approved for the treatment of symptoms associated with NETs in the European Union and named lanreotide autogel outside the US. The sponsor submitted original IND 63,239 on November 17, 2003. Lanreotide was designated as an orphan drug for the treatment of symptoms associated with carcinoid syndrome on September 8, 2011.

During the pre-NDA meeting on September 10, 2015, the Agency raised the following two major statistical concerns:

1. *The ability of a single trial to support approval will be a review issue.*
2. *FDA requested inclusion in the NDA of a thorough and careful exploratory analysis of diary data on flushing and diarrhea to support the primary endpoint.*

In this submission (SN 0039), the sponsor included reports for a pivotal Phase III, randomized (1:1), double-blind (DB), placebo-controlled, multi-center study (Study 2-55-52030-730, hereafter referred to as Study 730), one supportive, uncontrolled Phase II European study (Study E-47-52030-718, hereafter referred to as Study 718) and one exploratory pooled biomarker data of Study 730 and Study 2-55-52030-726 (hereafter referred to as Study 726), a randomized Phase III, DB, placebo-controlled study for indication of GEP-NETs. Detailed summary for these three studies refers to the Appendix.

After consulting with the clinical review team, the pivotal Study 730 is selected for full review and evaluation. This review will not discuss the uncontrolled Phase II study and the pooled biomarker study with heterogeneous study populations and biomarkers not directly related to the primary endpoint. Key information for Study 730 is presented in Table 1 below.

Table 1 Overall summary of Study 730

Phase and Design	Treatment Period	Follow-up Period	Efficacy Endpoints	Study Population
Phase III multicenter, DB, placebo-controlled randomized (1:1) clinical trial	16 weeks DB, 120 mg lanreotide (n=59) or placebo (n=56) s.c. every 4 weeks	Lanreotide in 32 weeks initial open-label phase and at least 2 years long term open-label extension	Primary: % of days using octreotide Key secondary: average daily frequency of diarrhea/flushing	Patients at least 18 years of age with carcinoid tumor or, a carcinoid tumor of unknown location with liver metastases, and a history of carcinoid syndrome (flushing and/or diarrhea), with documented absence of tumor progression for > 9 months, that are either naïve to treatment with an SSTa or responsive to octreotide.

2.2 Data Sources

Data sets for Study 730 were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:
\\CDSESUB1\evsprod\NDA022074\0039\m5\datasets\2-55-52030-730\analysis\adam\datasets
The electronic data sets (ADXD) generally represented the efficacy data described in the study report.

The electronic link to the sponsor's exploratory sensitivity analysis results as a response to the Agency's information request (IR) issued on April 25, 2017:
\\CDSESUB1\evsprod\NDA022074\0055\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnet\5351-stud-rep-contr\25552030730\2-55-52030-730\csr

The full list of statistical related IR issued is listed in Table 2 with EDR paths.

Table 2 Related information requests to the sponsor

Issued	Responded	Issue	Path
2/10/17	4/7/17	Additional analyses on key secondary endpoints	\\CDSESUB1\evsprod\NDA022074\0053
3/9/17	4/7/17	Sensitivity analyses for missing data	\\CDSESUB1\evsprod\NDA022074\0053
4/7/17	4/11/17	Calculation of primary endpoint and duration	\\CDSESUB1\evsprod\NDA022074\0054
4/23/17	4/28/17	Additional sensitivity analyses for primary, key secondary endpoints	\\CDSESUB1\evsprod\NDA022074\0055
4/26/17	5/4/17	Description of reasons for discontinuation	\\CDSESUB1\evsprod\NDA022074\0056
5/5/17	5/8/17	Figures for LS means of primary endpoint along with legacy dataset primary efficacy dataset	\\CDSESUB1\evsprod\NDA022074\0057
5/5/17	5/11/17	Summary of all rescue medication usage	\\CDSESUB1\evsprod\NDA022074\0058
5/5/17	5/11/17	Figure of missing diary data per day for screening and DB phase	\\CDSESUB1\evsprod\NDA022074\0058 Note: Submitted forest plot instead.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The primary dataset for efficacy analyses was ADXD with 269,281 records for 115 subjects in study 730. ADXD contains most information needed for the review, but it was not straightforward to replicate the derived primary and secondary endpoints based on the structure of the submitted dataset.

There was no information on the underlying tumor severity/stage or progression such as, time to progression free survival; although the eligible subjects were stable on carcinoid tumors at baseline. Lanreotide is proposed [redacted] (b) (4) [redacted] (b) (4) Without tumor severity, the proposed study cannot be used to examine whether missing data was associated with disease severity or adjust the efficacy findings by severity of the tumor.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 730 was a Phase III, randomized, DB, placebo-controlled, multicenter study that consisted of a screening period (a minimum of 4 weeks), followed by a 16-week DB phase in which 115 subjects were randomized (1:1), by prior history of SSTa and region (US versus non-US), to receive either lanreotide 120 mg or placebo 28±3 days by s.c. injection. The DB phase ranges from 100-124 days. Subjects could enter a 32-week initial open label (IOL) phase and a long-term open-label extension phase (≥2 years) in which all subjects received lanreotide 120 mg. Note that the subjects were allowed to use octreotide during the screening period.

Following instruction, daily frequency and severity of symptoms (diarrhea and flushing) and octreotide use were recorded by the subject at the end of each day using an Interactive Voice Response System (IVRS) (during screening, DB, and IOL phase).

Eligible subjects were at least 18 years of age with carcinoid tumor or, a carcinoid tumor of unknown location with liver metastases, and a history of carcinoid syndrome (flushing and/or diarrhea), with documented absence of tumor progression for > 9 months, that are either naïve to treatment with an SSTa or responsive to octreotide. Octreotide is one type of SSTa. No specific level of symptoms at baseline was required for eligibility.

The primary study objective was to evaluate the efficacy of lanreotide for the control of symptoms (diarrhea and/or flushing) associated with carcinoid syndrome compared with placebo, as measured by the percentage (hereafter referred to as %) of days of using octreotide during the DB phase. This primary endpoint served as a bridge for symptom control. Key secondary endpoints included average daily frequency of diarrhea events and flushing events.

3.2.2 Statistical Methodologies

For the statistical analysis of the primary and key secondary endpoints, the sponsor pre-specified ANCOVA model with the following covariates in addition to treatment factor, randomization stratification factors (prior history of SSTa and region (US versus EX-US)) and baseline % of days using octreotide, baseline average daily frequency of diarrhea and flushing. The sponsor calculated % of days using octreotide for each patient by counting the number of days with octreotide usage divided by each patient's non-missing days during the double blind period as illustrated in Section 3.2.2.1 of this review. Double-blind period ranged from 100 to 124 days per protocol.

Key secondary endpoints were analyzed based on the same ANCOVA model as used for analyzing the primary endpoint. The primary and secondary endpoints were tested sequentially in the following order: % of days of octreotide use, frequency of diarrhea and frequency of flushing. The type I error would be controlled at a two-tailed significance level of 0.05 at each step.

3.2.2.1 Derivation of the primary endpoint

As noted earlier, the % of days using octreotide was calculated as patients' number of days with octreotide use divided by total number of days with a diary record during DB phase. This was indeed the prorated data where patients' missing diary days were ignored from the analyses.

Table 3 presents an example to illustrate the prorated calculation and the best/worst cases imputation for % of days using octreotide when it is not clear whether missing data were at random (i.e., MAR). This review used the minimum duration of the DB phase, 100 days, as a cutoff for missing definition after consulting the clinical review team. In other words, when patients had less than 100 days of diary data in DB, they were treated as having missing data. For the calculation of % days of octreotide usage during DB phase, we considered: 1) the number of days with octreotide use divided by the total number of diary days in subjects with at least 100 days data available; or 2) the number of days using octreotide divided by 100 in subjects with less than 100 days diary records. The best case/worst case imputations were defined as follows.

I. Worst case types of imputation:
    a. Impute any one missing diary day as usage of octreotide in both study arms.
    b. For Somatuline arm, impute any one missing diary day as usage of octreotide; and impute "no octreotide use" for any missing diary day data in placebo arm.

II. Best case types of imputation:
    a. Impute any one missing diary day as no usage of octreotide in both study arms.
    b. For Somatuline arm, impute any missing diary day as no usage of octreotide; and impute "octreotide use" for any missing diary day data in placebo arm.

For example, there was a patient who was randomized to placebo arm and reported only 6 available diary days' records during DB phase ranging from 100 to 124 days per protocol.

Table 3 An example of missing data and best case/worst case imputations

	Numerator	Denominator	% of days with octreotide use
Sponsor's prorated data	6	6	100%
Missing octreotide use and the diary days can be imputed as below			
Worst case imputations			
Placebo no & LAN yes	6	100	6%
Yes for both arms	100	100	100%
Best case imputations			
No for both arms	6	100	6%
Placebo yes & LAN no	100	100	100%

Source: reviewer's analysis

3.2.3 Patient Disposition, Demographic, Baseline Characteristics and Missing Data

3.2.3.1 Patient disposition, dropouts and missing data

3.2.3.1.1 Patient disposition and summary of dropouts

The study was conducted in 39 countries, 31 ex-US and 8 inside the US. A total of 115 subjects were randomized to two treatment arms, lanreotide 59, and placebo 56. This constitutes the intent-to-treat (ITT) population, the primary efficacy analysis population. Subject overall disposition and reasons of dropouts for the DB phase are presented in Table 4 below.

Table 4 Subject disposition for the DB phase

	Lanreotide (n=59)	Placebo (n=56)	Total (n=115)
Completed DB phase	45 (76.3)	34 (60.7)	79 (68.7)
Did not complete DB phase	14 (23.7)	22 (39.3)	36 (31.3)
Continued to IOL phase (rolled over early)	11 (18.6)	12 (21.4)	23 (20.0)
Did not continue to IOL phase	3 (5.1)	10 (17.9)	13 (11.3)
Primary reason for discontinuation during DB phase			
Adverse Event	1 (1.7)	2 (3.6)	3 (2.6)
Lost to Follow-up	0	0	0
Patient Decision	1 (1.7)	5 (8.9)	6 (5.2)
Sponsor Decision	0	1 (1.8)	1 (0.9)
Death	0	0	0
Other	1 (1.7)	3 (5.4)	4 (3.5)

Reported are n (%)
Source: Table 5 on page 40 of clinical study report (CSR)

Based on the data submitted, a patient is categorized as dropout if he/she had withdrew during the DB phase (100-124 days per protocol). Table 5 indicated that when patients were determined to be dropouts during DB phase, there were more missing in placebo arm (39%) compared to the treatment arm (24%), and more dropouts were not due to early roll over (ERO) in the placebo arm (18%) than that in the lanreotide arm (5%). It is not feasible to evaluate the association between dropouts and the severity of the symptom or underlying tumor without tumor severity information (stage, etc.). We also explored dropout rates prior to second injection (approximately Day 28 of the DB phase). There were 16 (14%) patients who received only one injection during the DB phase. Placebo arm had about twice dropout rates (20%) than that in the lanreotide arm (8%).

Table 5 Summary of dropouts in DB phase by treatment arm

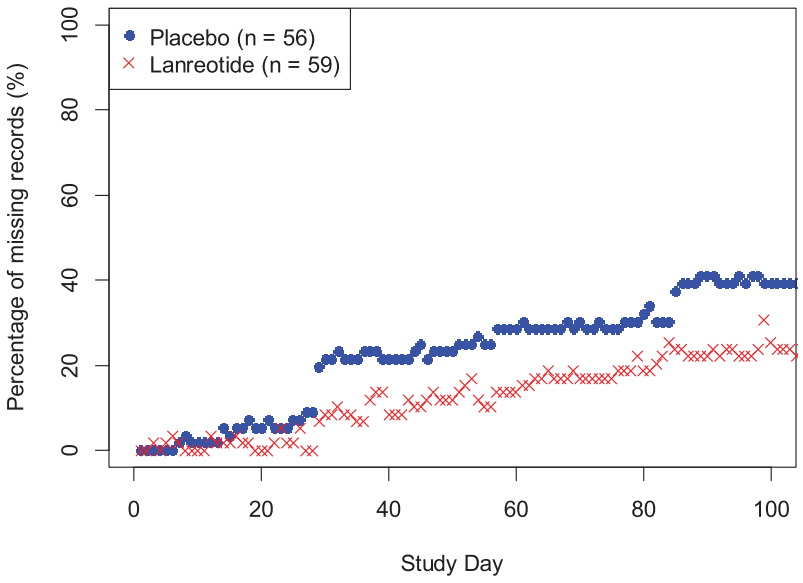
	Lanreotide N = 59		**Placebo N = 56**		**Total N=115**	
Total number of days with diary record						
Median (min, max)	111 (28, 126)		110 (6, 121)		111 (6, 126)	
Mean ± SD	98.6±28.0		86.2±37.7		92.5±33.5	
Number of dropout patients during DB phase (%)						
	14 (24%)		22 (39%)		36 (31%)	
	ERO*	Not ERO	ERO	Not ERO	ERO	Not ERO
	11 (19%)	3 (5%)	12 (21%)	10 (18%)	23 (20%)	12 (10%)
Number of dropout patients prior to the second injection (%)						
	5 (8%)		11 (20%)		16 (14%)	
	ERO	Not ERO	ERO	Not ERO	ERO	Not ERO
	5 (8%)	0	7 (13%)	4 (7%)	12 (10%)	4 (3%)

* ERO: After at least 4 weeks in the DB phase, subjects were allowed to roll over into the IOL phase and receive lanreotide 120 mg if they self-administered s.c. octreotide for at least 21 days out of the 28 day cycle between treatment injections, and used a dose ≥300 μg per day for at least 14 out of the 21 days, regardless of the presence or absence of symptoms.
Source: reviewer's analyses

3.2.3.1.2 Missing daily diary data

The daily diary data was collected via eDiary for octreotide usage, frequency of flushing and diarrhea events. To further explore the pattern of missing daily diary data, we produced the following Figure 1 for the number of missing octreotide data for each day over the entire DB period by treatment group. As seen from the figure, there are more patients in placebo group who had missing daily data than the lanreotide group throughout the DB period and it appears placebo group had more patients dropped much earlier than lanreotide group.

Figure 1 Percentage of missing daily diary data by study day during the double-blind phase (Day 1- Day100)

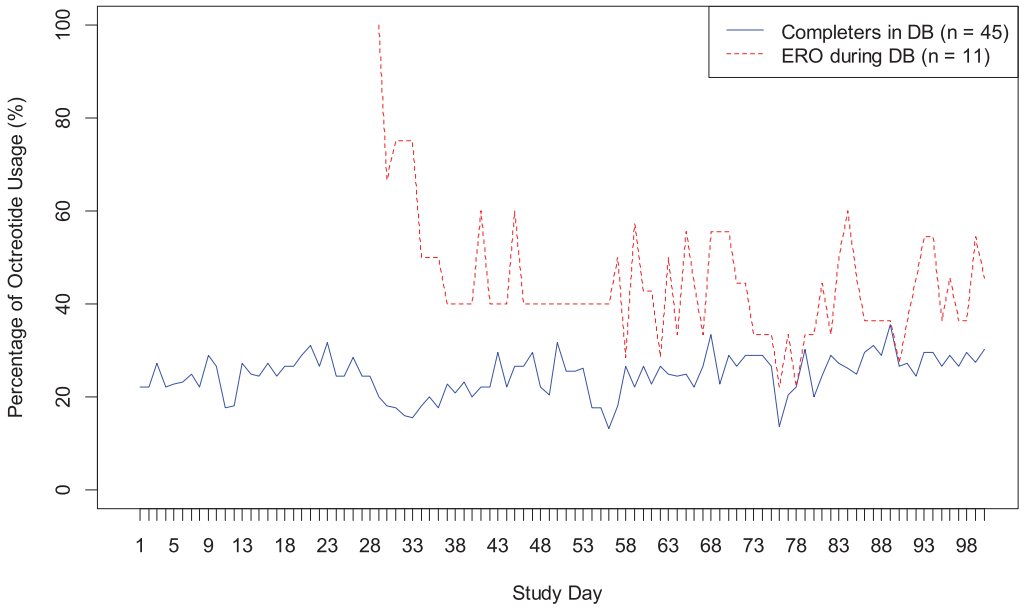


Source: Reviewer's analyses

3.2.3.1.3 Exploration of octreotide use in completers and EROs in the lanreotide arm

We explored the % of subjects using octreotide each day in the group of 45 completers and 11 ERO patients in the lanreotide arm during Day 1–Day 100. Based on the observed data in Figure 2, % of subjects on octreotide each day was noticeably higher in the group of dropouts as compared to completers. Note that there was no EROs in the lanreotide arm until Day 28. This suggested that patients who dropped out were different from patients who stayed until Day 100 in terms of octreotide use. Whether the data were missing at random is questionable.

Figure 2 Percentage of subjects using octreotide each day in completers and ERO patients during Day 1-Day 100



Source: Reviewer's analyses

3.2.3.2 Patient Demographic and Baseline Characteristics

Overall, 58.3% of the subjects were female and most were white (76.5%) with mean age of 58.6 years ranging from 27 to 85 years. No subjects had been previously treated with other SSTa medication other than octreotide LAR (48.7%) and short acting octreotide (20.9%).

Baseline demographics and characteristics were not balanced between treatment arms in gender and average daily frequency of diarrhea or flushing. Numerically more male patients were in the lanreotide arm (45.8%) than the placebo arm (37.5%). Subjects in the lanreotide arm experienced numerically more diarrhea events per day (mean (SD): 2.13(1.85)) during the screening period compared with those received placebo (1.57 (1.67)). Subjects received lanreotide had numerically fewer flushing events per day (mean (SD): 1.53 (1.98)) during the screening period compared with those in the placebo group (2.20 (3.27)).

Per protocol population consisted of 102 patients in the ITT population for whom no major protocol deviations occurred during the DB phase determined by the investigator.

Table 6 Baseline demographics and characteristics

	Lanreotide (n=59)	Placebo (n=56)
Age in years	57.9 (10.6)	59.3 (11.6)
Male	27 (45.8%)	21 (37.5%)
White	44 (74.6%)	44 (78.6%)
BMI	26.75 (5.16)	26.93 (4.71)
Country (US)	21 (35.6%)	19 (33.9%)
Prior SSTa history	33 (55.9%)	31 (55.4%)
Prior SSTa usage within 3 months	28 (47.5%)	28 (50%)
Baseline characteristics		
Average daily frequency of diarrhea	2.13 (1.85)	1.57 (1.67)
Average daily frequency of flushing	1.53 (1.98)	2.20 (3.27)
% days of octreotide usage	35.8 (41.1)	37.0 (42.5)
Ever used octreotide during screening period	30 (51%)	29 (52%)
% days using other rescue medicine	12.85 (28.63)	8.31 (23.69)

* Mean (SD) or median (min, max) for continuous variables and N (%) for categorical variables
Source: Table 7, 8, 9, 10 and 11 of CSR, verified by the reviewer.

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Primary endpoint

3.2.4.1.1 Primary and sensitivity analyses during DB phase

The sponsor reported the primary efficacy result based on the observed diary days for each patient. Due to the concern of high dropout rates and differential dropouts between two study arms, the reviewer conducted sensitivity analyses for in ITT population using the worst and best case imputations (see Section 3.2.2.1 for details) with minimum DB duration 100 days as the cutoff. The following Table 7 included all of the results and these results, except those for the non-parametric methods, had been confirmed by the sponsor.

It appears that the analyses results on the % of days on octreotide were not consistent across various sensitivity analyses with LS-means differences between lanreotide arm and the octreotide arm ranging from -30.53% to 3.23% (Table 7) .

Since the deterministic worst/best case imputations may affect empirical distribution of the primary variable (leading to heavy tails, skewness, higher variability), the statistical review team

also considered sensitivity analysis options based on ranks. The analyses used Wilcoxon rank sum test stratified by prior history of SSTa and region (US versus EX-US)), and rank ANCOVA model with the same terms as the primary analysis ANCOVA model. The results of the exploratory rank analyses were consistent with the results based on the primary analysis model, (ANCOVA) as reported in Table 7.

Table 7 Primary and sensitivity analyses on the primary endpoint and the best/worst case imputation data (ITT population)

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Primary endpoint (percent of octreotide usage calculated using available diary days)					
ANCOVA: LS Means	33.72 (4.39)	48.49 (4.50)	-14.76	(-26.75, -2.78)	0.0165
Exploratory rank analysis: rank ANCOVA					0.0164
Exploratory rank analysis: Stratified Wilcoxon Rank Sum test					0.0463
Hodges-Lehmann est. of treatment difference			-7.24	(-28.6, 0.0)	
Worst case imputations					
Placebo "No" & LAN "Yes"					
ANCOVA: LS means	35.46 (4.38)	32.23 (4.48)	3.23	(-8.75, 15.21)	0.594
Rank ANCOVA					0.88
Stratified Wilcoxon Rank Sum test					0.98
"Yes" for both arms					
ANCOVA: LS means	35.70 (4.72)	54.81 (4.84)	-19.11	(-32.03, -6.18)	0.004
Rank ANCOVA					0.0063
Stratified Wilcoxon Rank Sum test					0.0189
Best case imputations					
"No" for both arms					
ANCOVA: LS means	24.53 (3.69)	32.72 (3.77)	-8.19	(-18.28, 1.90)	0.110
Rank ANCOVA					0.076
Stratified Wilcoxon Rank Sum test					0.22
Placebo "Yes" & LAN "No"					
ANCOVA: LS means	24.77 (4.11)	55.30 (4.20)	-30.53	(-41.76, -19.3)	< 0.0001
Rank ANCOVA					< 0.0001
Stratified Wilcoxon Rank Sum test					0.0001

Source: reviewer's analyses and Table 16 on page 62 of CSR

3.2.4.1.2 Exploratory efficacy analysis based on truncated DB treatment period

Additional sensitivity analyses have been summarized per clinical reviewer's request because they anticipated that there should have been less missing data prior to the second injection when patients received injections every 28±3 days per protocol.

We noted that the dropout rates in the first 4 weeks of the DB phasewere lower than at the end of the DB phase but were still noticeable. There were 16 patients (out of 115 randomized) who rolled over to the open-label phase or dropped out before having a second injection. In addition, the Placebo early rollover plus dropout rate at this time point was twice as large as for the lanreotide arm (Table 5).

Table 8 below examined the characteristics of 16 subjects who received only one injection during DB phase, which corresponds to the decline, especially in the placebo arm, during approximately Day 1- Day 30 time period, illustrated in Figure 1.

Table 8 Summary of subjects who dropped out prior to the second injection during DB

	Lanreotide (n=5)	Placebo (n=11)
Baseline demographics		
Age in years	60.8 (14)	58.9 (12)
Male	3 (60%)	6 (54.5%)
White	0 (0%)	3 (27.3%)
BMI	25 (5.2)	25.8 (4.4)
Country (US)	1 (20%)	3 (27.3%)
Prior SSTa history	4 (80%)	5 (45.5%)
Prior SSTa usage within 3 months	3 (60%)	5 (45.5%)
Baseline characteristics		
Average daily frequency of diarrhea	4.0 (4.0)	1.4 (1.6)
Average daily frequency of flushing	2.4 (2.0)	2.5 (2.3)
% days of octreotide usage	55.7 (51)	39.0 (46)
Ever used octreotide during screening period	3 (60%)	5 (45.5%)
Reason for drop out		
Early roll over	5 (100%)	7 (63.6%)

* Mean (SD) for continuous variables and N (%) for categorical variables
Source: Reviewer's analyses.

As seen in Table 9, the absolute observed treatment effect of the first injection only was smaller than that of the primary analysis over the 16 week DB phase. Note that the difference between the lanreotide and placebo arms was not nominally significant at 0.05 level.

Table 9 Analyses of the octreotide usage using available diary data prior to the second injection

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Based on available days until the second injection					
ANCOVA: LS-means (SE)	33.2 (4.4)	44.4 (4.5)	-11.2	(-23.1, 0.8)	0.066

Source: Reviewer's analyses

3.2.4.1.3 Efficacy analyses in per protocol population and the population of completers

Treatment effect also was explored in the "per protocol" (PP) population, and the population of "completers". In comparison to the primary analysis based on ITT, the magnitude of treatment difference was larger in the PP population and smaller in "completers" subgroup. These analyses are purely exploratory because the explored subpopulations are not deterministic (outcome based).

Table 10 Analyses of the octreotide usage in ITT, PP and completers populations using available data during DB phase

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Analysis using available # of days as denominator (no imputation)					
ITT (115)	33.72 (4.39)	48.49 (4.50)	-14.76	(-26.75, -2.78)	0.0165
PP (100)	32.1 (4.7)	49.6 (5.0)	-17.5	(-30.8, -4.3)	0.010
Completers (79)	20.6 (4.5)	34.7 (5.2)	-14.1	(-27.4, -0.9)	0.037

Source: Reviewer's analyses

3.2.4.1.4 Exploratory efficacy analyses in the initial open label phase population

There were 101 subjects in the DB phase continued to the IOL phase including 45 randomized to placebo and 56 in lanreotide arm.

This review also examined the primary endpoint and % of subjects using octreotide each day during IOL phase. Patients randomized to lanreotide arm were on octreotide during 25.7% of the IOL days, which was numerically greater, 4.9% (95% CI, -7.9% - 17.8%), than that in the placebo-lanreotide arm (20.8%) reported in Table 11. Note that this difference in the primary endpoint, i.e., % of subjects with octreotide use, is in the opposite direction from the efficacy findings during the DB phase (-14.8%).

For % of subjects using octreotide each day during IOL phase, Figure 3 illustrates that more subjects randomized to lanreotide arm were on octreotide than those in placebo-lanreotide arm during Day 113 to Day 224, which corresponding to Week 17–Week 32. This finding is contradictory to the findings during DB phase as sponsor reported in Figure 4. The corresponding primary analyses during the same time period reported an increase % of octreotide usage, 6.7%, in lanreotide arm compared to the placebo arm (Table 11).

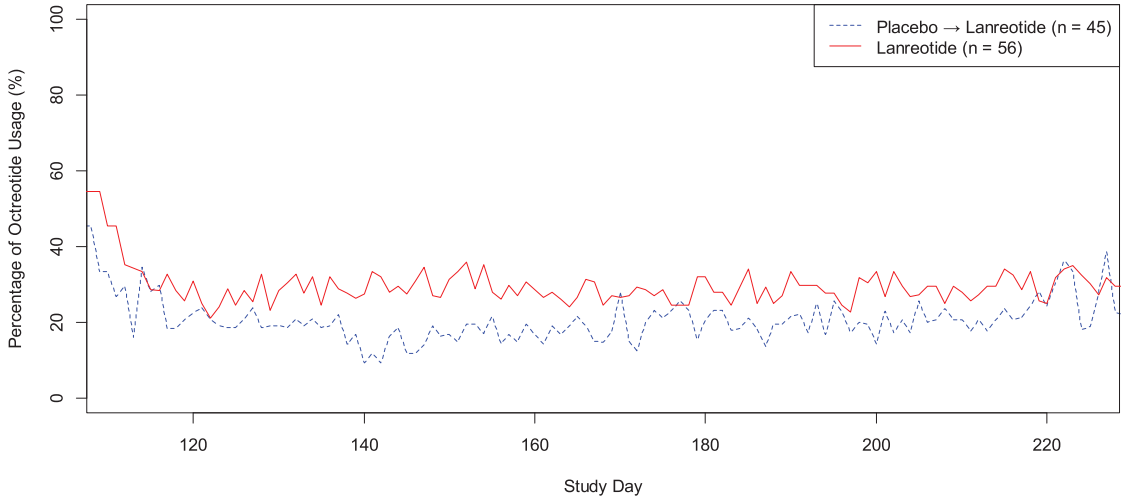
Therefore the long-term treatment effect of lanreotide did not sustain during the IOL phase, with more subjects using octreotide and more % of octreotide usage in lanreotide arm than those in the placebo-lanreotide arm, unlike the treatment effect shown in the DB phase.

Table 11 Analyses of the octreotide usage during the IOL phase

	Lanreotide n = 56	Placebo n = 45	LAN vs placebo LS-means difference (95% CI)		P-value
Based on available days during the IOL phase					
ANCOVA: LS-means (SE)	25.7 (4.5)	20.8 (5.0)	4.9	(-7.9, 17.8)	0.448
Based on available days during Day 113 to Day 224					
ANCOVA: LS-means (SE)	26.2 (4.8)	19.5 (5.6)	6.7	(-7.3, 20.7)	0.346

Source: reviewer's analyses

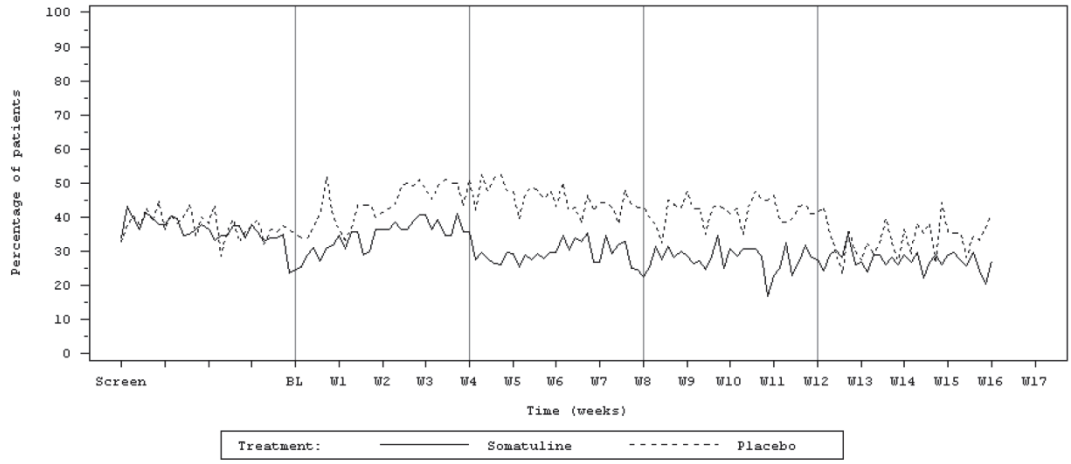
Figure 3 Percentage of subjects using octreotide during in IOL phase (Day 113 – Day 224)



Source: Reviewer's analyses

For comparison, we include respective sponsor's plot for the DB phase below.

Figure 4 Percentage of subjects using octreotide during the DB phase (Day 1- Day 112)



Source: Figure 3 on page 63 of CSR

3.2.4.2 Key secondary endpoints

The study did not succeed on the key secondary efficacy analyses according to the pre-specified testing hierarchy. The comparison in the first key secondary endpoint (average daily frequency of diarrhea) was not statistically significant (p=0.2544), and therefore, no meaningful statistical conclusions could be drawn for subsequent comparisons in the hierarchy on flushing per SAP. The differences in LS means (95% CI) between the lanreotide and placebo arms were -0.21 (-0.58, 0.15) for average daily frequency of diarrhea and -0.42 (-0.79, -0.06) for average daily frequency of flushing (Table 12 and Table 13).

On April 23, 2017, FDA requested to conduct sensitivity analysis to missing data based on best and worst case imputations. For the imputation of diarrhea/flushing, the minimum number of daily episodes of diarrhea/flushing for each subject through the DB phase was used as the best case, and the maximum number of daily episodes of the same subject as the worst case. For the diarrhea endpoint, neither imputation approach showed significant treatment effect. For flushing endpoint, best case imputation approach had nominal p-value less than 0.05, however, worst imputation did not produce significant finding.

Table 12 Primary and best/worst case sensitivity analyses for average daily frequency of diarrhea

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Baseline Mean (SD)	2.13 (1.85)	1.57 (1.67)	-	-	-
Sponsor's analysis using available # of days as denominator					
DB Phase LS Mean (SE)	1.34 (0.13)	1.55 (0.14)	-0.21	(-0.58, 0.15)	0.254
Worst case imputations (for both arms)					
DB Phase LS Mean (SE)	1.77 (0.21)	2.26 (0.22)	-0.49	(-1.06, 0.09)	0.0954
Best case imputations (for both arms)					
DB Phase LS Mean (SE)	1.28 (0.13)	1.41 (0.14)	-0.13	(-0.49, 0.23)	0.489

Source: Table 4 on page 20 of clinical overview; Sponsor's response to statistical IR request dated April 23, 2017

Table 13 Primary and best/worst case sensitivity analyses for average daily frequency of flushing events

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)		P-value
Baseline Mean (SD)	1.53 (1.98)	2.20 (3.27)	-	-	-
Sponsor's analysis using available # of days as denominator					
DB Phase LS Mean (SE)	1.04 (0.13)	1.46 (0.14)	-0.42	(-0.79, -0.06)	0.023
Worst case imputations (for both arms)					
DB Phase LS Mean (SE)	1.52 (0.22)	2.01 (0.23)	-0.49	(-1.11, 0.12)	0.115
Best case imputations (for both arms)					
DB Phase LS Mean (SE)	0.93 (0.13)	1.36 (0.14)	-0.43	(-0.78, -0.07)	0.019

Source: Table 4 on page 20 of clinical overview; Sponsor's response to statistical IR request dated April 23, 2017.

3.2.4.3 Conclusion

Based on the primary efficacy ANCOVA analysis in Study 730 for patients with carcinoid syndrome, a significant reduction in percent of days on octreotide use was observed in lanreotide arm when compared with the placebo arm (difference of 15%) during the DB phase. However, this review concluded that the efficacy results for this primary endpoint were not robust due to the extensive dropout rates (31% overall). The dropout rates were also noticeably different between treatment arms. As a result, sensitivity analyses resulted in widely varying point estimates for the mean percentage difference in octreotide use between the drug and placebo arms (Table 7).

The results for the average daily frequency of diarrhea, the first key secondary endpoint, were not significant. The second key secondary endpoint, the average daily frequency of flushing events, could not be tested due to the pre-specified sequential testing procedure. Even though the sponsor's results for flushing were nominally significant, due to the amount of missing data, the results were not stable based on sensitivity analyses (best/worst imputation).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region and Other Subgroup Populations

Figure 5 illustrates sponsor's subgroup analyses results by region, gender, age class, BMI, race and other baseline characteristics. Reduction in mean % days on octreotide for the treatment arm compared with placebo was observed in all subgroups of age, gender, race, ethnicity and time since diagnosis except for "Other" region and BMI>30 groups. Missing data distribution in each subgroup of interest is described in Table 14, where missing is defined as less than 100 days of available daily diary data during the DB phase.

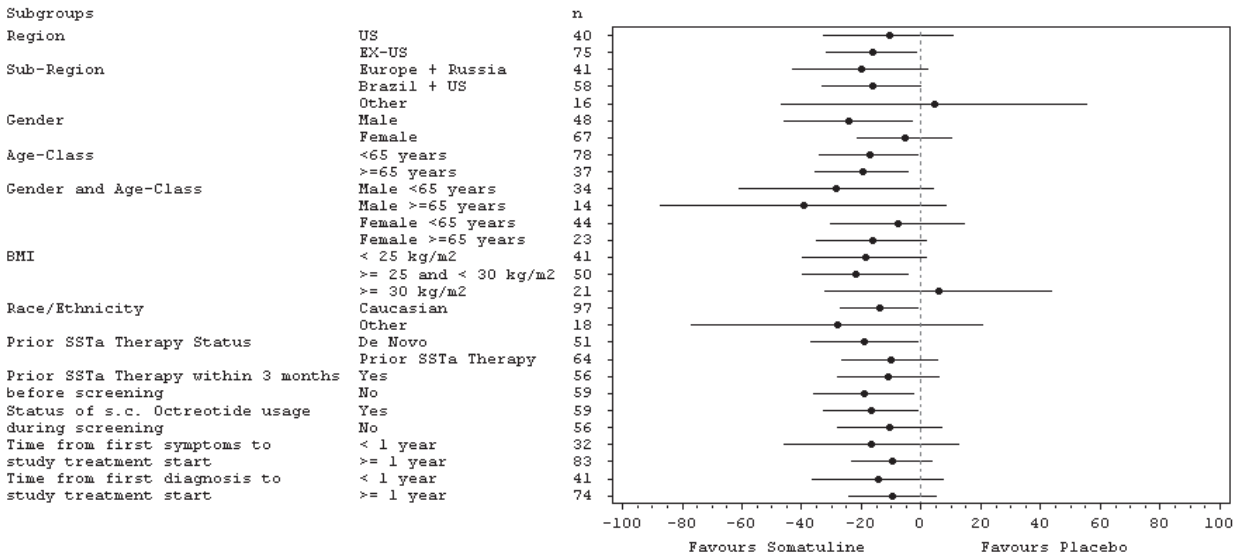
The statistical reviewer conducted subgroup analyses for prior SSTa usage history, octreotide usage during the screening period and gender using primary analysis ANCOVA model. Results are shown in Table 15. Numerically, the lanreotide arm performed better than the placebo arm in all explored subgroups. The LS-means differences in % days on octreotide for patients who had prior SSTa history was -10.3, as opposed to -18.9 in the naïve subgroup; -19.4 for subjects who used octreotide during screening phase and -10.4 for those who did not use; -24.1 in male subjects and only -5.4 in female patients. We noted that gender subgroups had very different outcomes. One factor that could contribute to this phenomenon was higher proportion of missing data in male placebo arm (Table 14).

For prior SSTa history subgroup, different sensitivity analyses resulted in various LS-mean difference between subjects with prior history versus naïve patients, 1) prorated analyses: -10.3 versus -18.9, 2) best case imputation: -8.4 versus -7.8, and 3) worst case imputation: -16.9 versus -20.0. The major differences among various sensitivity analyses presented in Table 15

appeared to be driven by the differential missing data/dropouts between treatment arms in both subgroups (with and without prior SSTa usage) (Table 14).

Subgroup analyses by prior SSTa history was also conducted using data from Day 1 to Day of the second injection (requested by clinical review team). We still observed numerically greater reduction in octreotide usage in the SSTa naïve group compared to the non-naïve subgroup using shorter period of time prior to second injection which was similar to the results in the DB phase (Table 16).

Figure 5 Forest plot of the subgroup analyses for the percentage of days with octreotide use during the double-blind phase (ITT Population)



Source: CSR page 65 Figure 4

Table 14 Missing data in subgroups by treatment arm

	Lanreotide	Placebo
Prior SSTa usage (n = 64)	n=33	n=31
	8 (24%)	12 (39%)
No Prior SSTa usage (n = 51)	n=26	n=25
	5 (19%)	10 (40%)
Octreotide usage in screening period (n = 59)	n=30	n=29
	7 (23%)	11 (38%)
No octreotide use in screening period (n = 56)	n=29	n=27
	6 (21%)	11 (41%)
Male (n=48)	n=27	n=21
	6 (22%)	10 (48%)
Female (n=67)	n=32	n=35
	7 (22%)	12 (34%)

Source: Reviewer's analyses

Table 15 Subgroup analyses and LS-means estimates

	Lanreotide LS-means (SE)	Placebo LS-means (SE)	Lanreotide - placebo LS-means difference (95% CI)
Prior SSTa usage			
Yes (n = 64)	**33.9 (5.6)**	**44.2 (5.8)**	**-10.3 (-26.5, 5.9)**
Best case imputation	23.2 (4.4)	31.6 (4.5)	-8.4 (-21.1, 4.2)
Worst case imputation	35.6 (6.3)	52.5 (6.5)	-16.9 (-34.9, 1.2)
No (n = 51)	**25.3 (9.3)**	**44.3 (9.3)**	**-18.9 (-37.0, -0.89)**
Best case imputation	22.9 (8.7)	30.7 (8.8)	-7.8 (-24.8, 9.2)
Worst case imputation	26.8 (9.6)	46.9 (9.7)	-20.0 (-38.8, -1.3)
Octreotide usage in screening period			
Yes (n = 59)	42.4 (8.5)	61.8 (8.4)	-19.4 (-38.8, 0.1)
No (n = 56)	25.7 (6.5)	36.1 (6.7)	-10.4 (-27.9, 7.1)
Gender			
Male (n = 48)	36.7 (21.6)	60.8 (7.5)	-24.1 (-45.7, -2.5)
Female (n = 67)	33.7 (22.0)	39.1 (27.5)	-5.4 (-21.5, 10.7)

Source: Reviewer's analyses

Table 16 Analyses of the octreotide usage by SSTa history using available diary data prior to the second injection

	Lanreotide n = 59	Placebo n = 56	LAN vs placebo LS-means difference (95% CI)
Prior SSTa Usage, LS-means (SE)			
Yes	29.6 (5.2)	38.1 (5.4)	-8.5 (-23.7, 6.6)
No	24.1 (10.2)	38.2 (10.2)	-14.1 (-34.0, 5.7)

Source: Reviewer's analyses

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

After evaluation, we identified the following statistical issues:

1. Study 730 had significant amount of dropout rates (31 % dropouts). We also noted significant imbalanced missing days and differential dropouts between two arms (24% in lanreotide and 39% in placebo).

2. In dealing with missing data, we conducted several sensitivity analyses including different types of imputation as well as non-parametric methods. We found that the efficacy results for the primary endpoint were not robust with point estimates for the percentage difference (in ANCOVA model) varying a lot. In addition, we conducted analyses for the short early study duration (first month, first cycle) when missing data were anticipated to be less. We found that the impact of missing data and dropouts still cannot be ignored, even in the shorter duration, and there is no strong evidence to support lanreotide's efficacy with a nominal p-value greater than 0.05.

3. In presence of extensive missing-data and dropouts, the sponsor's primary efficacy analyses were performed based on the prorated data, which hinges upon a strong MAR assumption. In particular, the primary endpoint, i.e., percent of days when patients on octreotide usage, was derived using the total available diary days divided by the number of patients' non-missing days during the DB phase, which ranged from 6 to 126 days as compared to the duration of DB phase of 100-124 days.

4. We explored patients' performance after rolling over to the open-label phase. We found that patients who rolled over from the drug arm in the DB phase had more octreotide usage than those rolled over from the placebo in DB phase daily, which indicates that the effectiveness of the lanreotide does not sustain after the DB phase.

5. The most clinically relevant two secondary endpoints, i.e., frequency of diarrhea and flushing did not show efficacy findings; the diarrhea results were not statistically significant at 0.05 level and due to the pre-specified sequential testing procedure, the flushing could not be tested. Although flushing had nominally significant results, the same missing data concerns cannot be ignored.

5.2 Collective Evidence

The sponsor reported the primary efficacy result based on patients' observed diary days with the least squares (LS) mean difference between lanreotide arm and placebo arm of –14.76% (p-value= 0.0165) in % of days on octreotide administered as rescue medication during the DB phase. However, we noted that there were 31% dropouts/early rollovers on the primary endpoint (39% in the placebo arm and 24% in lanreotide arm) and thus conducted several sensitivity analyses for assessing the impact of the missing data, including best/worst case imputations with minimum DB duration of 100 days as the cutoff for missing data as well as non-parametric method. We found that the primary efficacy results were not consistent across various missing data imputation strategies with LS-means differences between lanreotide arm and the octreotide arm ranging from -30.53 to 3.23, and p-values ranging from < 0.0001 to 0.594.

We further explored the impact of missing data focusing on shorter assessment periods (i.e., from day 1 until the day of second injection). Of note, placebo patients' early rollover/dropout rate at this time points were about twice as large as for the lanreotide patients. We found the impact of missing data and dropouts still cannot be ignored, even in the shorter duration, and there is no strong evidence to support the lanreotide's efficacy with a nominal p-value greater than 0.05.

The study also did not demonstrate evidence of efficacy on the two most important key secondary efficacy endpoints, i.e., the frequency of diarrhea and flushing. According to the pre-specified testing hierarchy, since the comparison between lanreotide arm and placebo arm on average daily frequency of diarrhea was not statistically significant (p=0.254), no formal statistical testing for the frequency of flushing could be conducted. For the frequency of flushing,

we noted that the difference in LS means (95% CI) between the lanreotide and placebo arms was -0.42 (-0.79, -0.06), but due to the missing data and dropouts, results were also not robust.

5.3 Conclusions and Recommendations

The sponsor claimed that Study 730 demonstrated statistically significant reduction in the primary endpoint, % of days on octreotide, in lanreotide arm compared to the placebo arm during the DB phase. However, with more than 30% patients who dropped out early during the DB phase, differential dropout rates and widely varying point estimates for the mean percentage difference in octreotide use between the drug and placebo arms in sensitivity analyses, we concluded that Study 730 did not provide substantial evidence to suppor (b) (4) (b) (4) In addition, the sponsor did not provide (b) (4) (b) (4)

APPENDIX

Table A 1 Summary of studies submitted for sNDA 22-074

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings (Sponsor)
730	MC, R, DB, PG, PC trial (DB:16 wks; IOL phase: 32 wks; LTOLE phase: At least 2 years after last subject completed IOL phase)	Somatuline (120 mg every 4 wks) /N=59 Placebo/N=56	Primary: percentage of days s.c. octreotide was used as rescue medication to control symptoms associated with carcinoid syndrome during the DB phase/ANCOVA Key Secondary: to characterize the effect of lanreotide Autogel versus placebo on biochemical markers of tumour activity	A significantly lower percentage of days of rescue medication use was observed for the somatuline group compared with the placebo group (LS Means: 33.7% versus 48.5%, respectively; p=0.0165) The comparison in average frequency of diarrhoea events per day was not statistically significant (p=0.2544), therefore, no meaningful statistical conclusions could be drawn for subsequent comparisons in the secondary efficacy hierarchy.
718	MC, open-label, dose titration Phase II/III trial (6 mons)	Somatuline (60 mg, 90 mg and 120 mg ; monthly) / N=71	Primary: Proportion of target symptom responders (either diarrhoea or flushing) at Month 6 in subjects with carcinoid syndrome /responder analysis	A clinically relevant proportion of subjects (38%) met the criteria for target symptom responders (≥50% reduction from baseline in mean number of daily target symptom episodes) at Month 6.
726	MC, R, DB, PG, PC trial (96 wks)	Somatuline (120 mg every 28 days) /N=101 Placebo/N=103	Related objective: to assess the effect of lanreotide compared to placebo on plasma CgA and on any other tumour peptide markers with elevated level at baseline in subjects with non-functioning entero pancreatic endocrine tumor	Significant reduction in both urinary 5-HIAA and plasma CgA was observed with Somatuline Depot.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

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06/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	022074/S-017
Link to EDR	\\CDSESUB1\evsprod\NDA022074\022074.enx
Submission Date	8/15/2016
Submission Type	Efficacy Supplement
Brand Name	Somatuline Depot
Generic Name	Lanreotide acetate
Dosage Form and Strength	120 mg/0.5 mL single-use prefilled syringes, 120 mg
Route of Administration	Deep subcutaneous injection
Proposed Indication	(b) (4)
Applicant	Ipsen Pharma SAS
Associated IND	63,239
OCP Primary Reviewer	Elizabeth Shang, Ph.D., R.Ph.
OCP Secondary Reviewer	Insook Kim, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Lanreotide is a synthetic cyclical octapeptide with a biological activity similar to naturally occurring somatostatin. Lanreotide (Somatuline Depot) injection 60 mg, 90 mg, and 120 mg is indicated for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. Lanreotide injection 120 mg is indicated for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival. In this efficacy supplement submission (S-17), the sponsor proposes a new indication for the 120 mg dosage for

(b) (4)

The clinical program for the proposed indication consisted of a pivotal placebo-controlled phase 3 study (Study 730) in patients with GEP-NETs with history of symptomatic carcinoid syndrome, supportive placebo-controlled phase 3 study (Study 726) in patients with asymptomatic enteropancreatic NETs, and supportive uncontrolled study (Study 718) in patients with carcinoid NETs. Studies 726 and 718 were completed and previously included in the Efficacy Supplement 11 (S-11) which was reviewed and approved on December 16, 2014. Study 730, while it was still ongoing, was included in S-11. Refer to current approved label for the pharmacokinetic characteristics of lanreotide. The incidence of anti-drug antibody (ADA) in Study 730 was 1/107 (0.93%) when it was reviewed in 2014. In this submission, one additional subject in Study 730 was found to have detectable ADA. Thus, the incidence rate is 2/108 (1.85%).

1.1 Recommendations

The Division of Clinical Pharmacology 3 has reviewed this application and found this supplemental NDA acceptable from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Lanreotide, the active component of Somatuline Depot, is an octapeptide analog of natural somatostatin. 120 mg administered every 4 weeks by deep subcutaneous injection is approved for the treatment of patients with unresectable, well or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

Refer to the product label for detailed PK and PD information as well as the effects of intrinsic and extrinsic factors on lanreotide PK and related dose adjustment. An excerpt of clinical PK information relevant to patients with GEP-NET is summarized here based upon the approved product label.

"Section 12.3 Pharmacokinetics

After a single, deep subcutaneous administration, the mean absolute bioavailability of Somatuline Depot in healthy subjects was 73.4, 69.0, and 78.4% for the 60 mg, 90 mg, and 120 mg doses, respectively. Mean Cmax values ranged from 4.3 to 8.4 ng/mL during the first day. Single-dose linearity was demonstrated with respect to AUC and Cmax, and showed high inter-subject variability. Somatuline Depot showed sustained release of lanreotide with a half-life of 23 to 30 days. Less than 5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in feces, indicative of some biliary excretion.

In patients with GEP-NETs treated with Somatuline Depot 120 mg every 4 weeks, steady state concentrations were reached after 4 to 5 injections and the mean trough serum lanreotide concentrations at steady state ranged from 5.3 to 8.6 ng/mL.

Mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment has no effect on clearance of lanreotide in patients with GEP-NET based on population PK analysis which included 106 patients with mild and 59 patients with moderate renal impairment treated with Somatuline Depot. GEP-NET patients with severe renal impairment (CLcr < 30 mL/min) were not studied.

The effect of hepatic impairment on clearance of lanreotide has not been studied in patients with GEP-NET.

Section 7.4 Drug Metabolism Interaction

The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution. Drugs metabolized by the liver may be metabolized more slowly during lanreotide treatment and dose reductions of the concomitantly administered medications should be considered."

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 120 mg every 4 weeks via deep subcutaneous injection. This is the same dosage as the regimen for the approved indication for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival.

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Updates on immunogenicity (Section 6) and pharmacodynamics biomarkers (Section 12.2) based upon the results from Study 730 were made.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

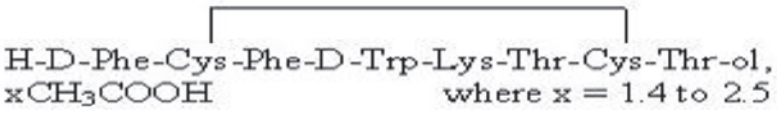
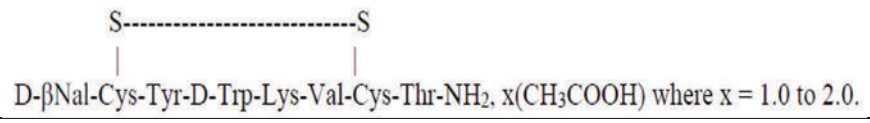
3.1 Overview of the Product and Regulatory Background

Proposed product

Lanreotide acetate is a synthetic cyclical octapeptide analog of the natural hormone, somatostatin. Lanreotide acetate (Somatuline Depot) deep subcutaneous injection product was originally approved for acromegaly on 8/30/2007 with approved dose of 60 mg and 90 mg. The new dosage form (120 mg/0.5 mL) for acromegaly was approved on 3/4/2011 (S-003). Lanreotide acetate 120 mg/0.5 mL was also approved on 12/16/2014 (S-11) for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival.

Currently approved somatostatin analog for carcinoid syndrome is octreotide. Structure difference between octreotide and lanreotide is shown in Table 1.

Table 1. Amino acid sequence of lanreotide and octreotide

	Amino acid sequence
Lanreotide	
Octreotide	

Approved therapy

Octreotide and telotristat ethyl (Xermelo) are currently approved for carcinoid syndrome.

	Octreotide	**Octreotide LAR**	**Telotristat ethyl**
Indication	Symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.	Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.	Treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy
Dosage	100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg)	20 mg every 4 weeks for 2 months following octreotide s.c. 100 – 600 mcg/day in 2 -4 divided doses for 2 weeks	250 mg p.o. tid daily for patients whose diarrhea is inadequately controlled by SSA therapy.
MOA	A cyclical octapeptide analog of natural somatostatin mimicking natural hormone somatostatin. It is a more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. It also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide		A tryptophan hydroxylase inhibitor which mediates the rate limiting step in serotonin biosynthesis

Source data: Reviewer's summary based upon the product labels.

Clinical development program and relevant regulatory background

The clinical program consisted of a pivotal placebo-controlled phase 3 study (Study 730, Figure 1), supportive uncontrolled study (Study 718), and supportive phase 3 study (Study 726). Studies 726 and 718 were completed and previously included in Efficacy Supplement 11 approved by the Division of Oncology Products 2 on December 16, 2014. Study 730, while it was still ongoing, was included in S-11 and reviewed by DOP2 as a supportive trial. At the time of submission in 2014, the 16-week double-blind phase was completed and 101 subjects (56 in treatment group and 45 in placebo group) entered the 32-week initial open label (IOL) phase. A total of 47 subjects completed the IOL phase and 31 of them entered the long-term open label extension (LTOLE) phase. Refer to Dr. Jun Yang's Clinical Pharmacology Review in DARRTS

on December 2, 2014 for details. In this submission (Table 2), additional 33 subjects completed the IOL phase and26 subjected entered the LTOE phase. Twenty-five subjects completed the LTOLE phase.

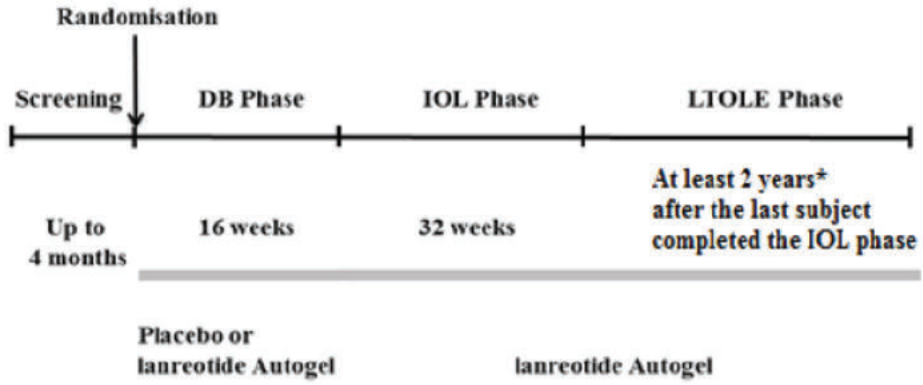
Table 2. Comparison of subject disposition in Study 730 included in S-11 (2014) and S-17 (2016)

Year when supplement submitted	2014			2016		
Treatment group	Lanreotide	Placebo	Total	Lanreotide	Placebo	Total
Completed DB phase	45	34*	79*	45	34*	79*
Early roll-over to IOL phase	11	12	23	11	12	23
Entered IOL phase	56	45	101	56	45	101
Completed IOL phase	27	20	47	43	37	80
Entered LTOLE phase	19	12	31	32	25	57
Completed LTOLE phase	--	--	--	17	8	25

*1 subject did not enter IOL phase
DB: double blind; IOL: initial open label; LTOLE: long term extension open label.

Source data: Reviewer's summary

Figure 1 Schematic drawing of Study 730.



DB=double-blind; IOL=initial open-label; LTOLE=long-term open-label extension; lanreotide Autogel=lanreotide Autogel 120 mg.
*or when marketing approval for the treatment of symptoms of carcinoid syndrome is obtained (whichever occurs first).

Source data: Figure 1, Study 730 CSR

Table 3. Clinical trials used to support the proposed indication of carcinoid syndrome associated with neuroendocrine tumors.

Type of study	Study identifier	Location of study report	Main objective(s) of the study	Study design and type of control	Test product(s); route of administration and dosage regimen;	Number of subjects	Healthy subjects or diagnosis of subjects	Duration of treatment	Study status; type of report
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication									
Efficacy and safety	2-55-52030-730	5.3.5.1	To assess the effect of lanreotide Autogel 120 mg compared to placebo on efficacy (use of rescue medication to control symptoms associated with carcinoid syndrome) and safety	Phase III/IV, double-blind, randomised, placebo controlled clinical study	Lanreotide Autogel 120 mg; deep s.c. injection every 4 weeks	Randomised: 115	History of carcinoid syndrome (symptomatic)	Double-blind phase: 16 weeks; IOL phase: 32 weeks; LTOLE phase: Maximum duration 1644 days	Full Study Report
Efficacy and safety	2-55-52030-726	5.3.5.1	To assess the effect of lanreotide Autogel 120 mg compared to placebo on efficacy (progression free survival) and safety	Phase III, randomised, double-blind, comparative, placebo controlled, parallel group, multicentre study	Lanreotide Autogel 120 mg; deep s.c. injection every 4 weeks	Randomised: 204	Well or moderately well-differentiated nonfunctioning (asymptomatic) enteropancreatic NETs	96 weeks	Full Study Report
Study Reports of Uncontrolled Clinical Studies									
Efficacy and safety	E-47-52030-718	5.3.5.2	To assess the effect of lanreotide Autogel at doses of 60 mg, 90 mg or 120 mg on efficacy (relief of clinical symptoms) and safety	Phase II/III open-label, multicentre, dose titration study	Lanreotide Autogel 60, 90 and 120 mg; deep s.c. injection every 4 weeks	Included: 71	Carcinoid NETs	Six months	Full Study Report

No additional clinical pharmacology studies were conducted for this supplement. As additional patients in Study 730 completed IOL phase and LTOLE, additional blood samples for trough concentration of lanreotide also became available. These new trough concentration samples are about 15% of the total PK samples.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 2.1.

Trough concentration of lanreotide at steady-state in patients with GEP-NETs was reported in the approved label. The simulated trough concentration was derived from a population PK analysis of pooled PK data from four clinical trials conducted in patients with GEP-NETs. The population PK model was reviewed in 2014. Refer to Dr. Jun Yang's Clinical Pharmacology Review for S-11.

Immunogenicity

The immunogenicity was first assessed in patients with GEP-NETs in S-11. The immunogenicity profile of Somatuline Depot was evaluated across studies 726, 730, and 166, and 718. A radioimmunoprecipitation assay (RIPA) was used to detect the anti-drug antibodies (ADAs) with a multitiered approach. For details, refer to Dr. Jun Yang's Clinical Pharmacology Review for S-11. The incidence of ADA in Study 730 was 1/107 (0.93%) when it was reviewed

in 2014. In this submission, one additional subject in Study 730 was found to have detectable ADA. Thus, the incidence rate is 2/108 (1.85%).

Pharmacodynamics (PD)

Urinary 5- hydroxyindoleacetic acid (5-HIAA) and plasma Chromogranin A (CgA) levels were the two exploratory endpoints measured in Study 726 (pivotal phase 3 study for GEP-NETs progression-free survival in S-11). According to the Clinical Review of S-11 by Dr. Joohee Sul, DOP2, plasma CgA is stored in the majority of well differentiated NETs and its presence in the circulation has been used as a marker of secretory activity. It has also been considered as a marker for nonfunctioning GEP-NETs which do not have other tumor markers available to follow disease status. Urinary 5-HIAA is also a tumor marker. (b) (4)

(b) (4)

For CgA and 5-HIAA changes in asymptomatic GEP-NETs (Study 726), refer to Dr. Joohee Sul's Clinical Review for S-11 in DARRTS.

In the pivotal phase 3 study for carcinoid syndrome (Study 730), the effects of lanreotide on urinary 5-HIAA and plasma CgA were studied. The sponsor proposed (b) (4)

(b) (4)

(b) (4)

Reviewer's comment (b) (4)

(b) (4) *These are not pre-specified analyses. In addition, Study 726 (Study 3 in the label) excluded patients with GEP-NET and hormone related symptoms (functioning tumors) while Study 730 (Study 4 in label) enrolled patients with hormone related symptoms.*

The newly reviewer's proposed labeling language regarding PD effect is below:

> In Study 4, patients with carcinoid syndrome treated with Somatuline Depot 120 mg every 4 weeks had reduced levels of urinary 5-hydroxyindoleacetic acid (5-HIAA).

Refer to the final approved labeling when available.

.

CgA and 5-HIAA changes in symptomatic NETs (Study 730) are summarized below.

16-week double-blind (DB) phase (Week 12)

As one of the secondary endpoints, absolute changes from baseline in plasma CgA and urinary 5-HIAA levels during the 16-week DB phase were analyzed. Plasma CgA and urinary 5-HIAA levels were measured at Week 12.

Plasma CgA Subjects treated with lanreotide or placebo both showed reductions from baseline in median values of CgA at Week 12 (Table 4).

Reviewer's comment: The sponsor reported that increases in median values were observed in the placebo group.[1] The discrepancy between reviewer's and sponsor's assessment is unclear.

However, increase in **mean** plasma CgA from baseline was observed in lanreotide treatment group while there was a decrease in mean plasma CgA from baseline in the placebo group.

Reviewer's comment: The sponsor stated that "subjects in the lanreotide Autogel group showed greater improvement (declines) in mean levels of CgA compared with the placebo group at the end of the DB phase."[2] However, based upon summary data presented in Table 4, mean CgA concentrations increased in the lanreotide group. The discrepancy between reviewer's and sponsor's assessment is unclear.

It is noteworthy that the baseline mean value of plasma CgA in the lanreotide treatment group is less than the placebo group (4092 μg/L vs 17693 μg/L, respectively). The variability of baseline CgA is large. The CV% calculated by SD/mean × 100 was 624% for plasma CgA in the placebo group and 208% in the lanreotide group. Therefore, changes in median values may be more representative than changes in mean values.

Urinary 5-HIAA

The sponsor reported that subjects treated with lanreotide showed reductions from baseline in median values of 5-HIAA at Week 12, while increases in median values were observed in the placebo group (Table 4). Similar trend was observed using mean values. A 52% reduction in the lanreotide group and ~23% increase in the placebo group were found.

It is noteworthy that the baseline mean value of urinary 5-HIAA in the lanreotide treatment group is greater than the placebo group (388 μmol/d vs 157 μmol/d, respectively). The CV% for baseline urinary 5-HIAA in the lanreotide and placebo group are 308% and 128%, respectively. Therefore, the difference of changes in urinary 5-HIAA between the treatment group and placebo group should be interpreted with caution. In addition, octreotide is known to reduce urinary 5-

[1] Pg 73 of Study 730 CSR
[2] Pg 89 of Study 730 CSR

HIAA levels (octreotide product label). The difference in urinary 5-HIAA levels between the treatment and placebo group is confounded by the fact that patients in both groups during the DB phase received octreotide as the rescue medication.

Table 4. Absolute changes from baseline in plasma CgA and urinary 5-HIAA during the double-blind, placebo controlled phase (Week 12) (Study 730)

	Lanreotide (N=59)		Placebo (N=56)	
	Value	Change from Baseline	Value	Change from Baseline
Plasma CgA [µg/L] at Baseline				
n	51		50	
Median	784.0		1078.0	
Min, max	98,48902		49,782040	
Q1, Q3	343.0, 4410.0		441.0, 2793.0	
Mean (SD)	4092.0 (8504.4)		17692.9 (110363.0)	
95% CI	(1700.1, 6483.9)		(-13671.9, 49057.7)	
Plasma CgA [µg/L] at Week 12				
n	41	41	28	28
Median	539.0	-98.0	833.0	196.0
Min, max	49,108731	-10731,78400	98,13769	-4557,6174
Q1, Q3	294.0, 1666.0	-441.0, 49.0	294.0, 2989.0	-196.0, 1641.5
Mean (SD)	4261.8 (16964.6)	1125.8 (12579.4)	2383.5 (3267.5)	801.5 (2294.0)
95% CI	(-894.7, 8841.4)	(-2844.8, 5096.4)	(1116.5, 3650.5)	(-88.0, 1691.0)
Urinary 5-HIAA [µmol/d] at Baseline				
n	39		27	
Median	73.0		44.0	
Min, max	0,7175		13,722	
Q1, Q3	19.0, 187.0		20.0, 257.0	
Mean (SD)	388.0 (1195.9)		157.1 (200.7)	
95% CI	(0.3, 775.6)		(77.7, 236.5)	
Urinary 5-HIAA [µmol/d] at Week 12				
n	39	39	27	27
Median	36.0	-7.0	68.0	8.0
Min, max	2,2088	-6314,130	1,773	-449,272
Q1, Q3	17.0, 156.0	-64.0, 7.0	18.0, 322.0	-6.0, 138.0
Mean (SD)	186.6 (406.6)	-201.4 (1009.9)	193.4 (234.1)	36.3 (142.3)
95% CI	(54.8, 318.4)	(-528.7, 126.0)	(100.7, 286.0)	(-20.0, 92.6)

Data Source: Post-hoc Table 14.2.5.6.2.1, Post-hoc Table 14.2.5.5.7.2 and Post-hoc Table 14.2.5.6.7.2.
Note: 'Week 12' consists of subjects who are still in the blinded phase.
Change from baseline=absolute change.
Baseline is defined as the last non-missing observation obtained prior to the initiation of study treatment.
Only the observed data are used in the calculation. The missing data are excluded from the analysis.
CgA= Chromogranin A; CI=confidence interval; N=total number of subjects in group; n=number of subjects taken into account for the analysis; SD=standard deviation; 5-HIAA=5-hydroxyindoleacetic acid.

Source data: Table 23, Study 730 CSR

32-week IOL phase (Week 48)

Absolute changes from baseline in plasma CgA and urinary 5-HIAA were assessed as exploratory endpoints.

Plasma CgA

The sponsor reported that the absolute reduction of median concentration from baseline was 294.0 µg/L for the group that received lanreotide during the DB phase compared with 49.0 µg/L for the group that received placebo during the DB phase. The difference in mean values between treatment groups was not statistically significant.

Urinary 5-HIAA

The sponsor reported that the absolute mean (SD) reduction from baseline was 102.0 (481.0) µmol/day for the group that had received lanreotide during the DB phase compared with 28.6 (258.2) µmol/day for the group that received placebo during the DB phase. The difference in least square means between treatment groups was not statistically significant.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Not applicable. As indicated in Section 3.1, no additional clinical pharmacology studies were conducted for this supplement.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. Only one dosing regimen was studied. Refer to Medical Officer's review for the efficacy and safety of lanreotide in patient population.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes. This has been addressed in the current approved label for the indication of GEP-NETs.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interactions

Since lanreotide is administered by deep subcutaneous injection, a food-effect study is not conducted as food-drug interactions are not anticipated or applicable.

Drug-drug interactions

Yes. This has been addressed in the current approved label for the indication of GEP-NETs. See Section 3.2.

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

Radioimmunoassays (RIAs) were used for both the quantification of serum lanreotide and for the detection of serum ADAs. These methods were used to support S-11 submission and were reviewed by Dr. Jun Yang, Clinical Pharmacology Reviewer and deemed acceptable. Refer to Clinical Pharmacology Review for S-11 for details.

Urinary 5-HIAA samples from Study 730 was measured by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The method was validated b (b) (4) In the original validation report of 2009, the standard curve ranged from 0.1 mg/L to 100 mg/L. Intra- and inter-assay precision and accuracy were both ≤ 20% at LLOQ (0.1 mg/L) and ≤ 15% throughout the remainder of the range (up to 100 mg/L). Validation summary report in 2014 and 2017 showed that these validation parameters remained the same.

Plasma CgA samples from Study 730 was assayed by the Chromogranin A radioimmunoassay diagnostic kit (Euria-Chromogranin A) a (b) (4) The method was validated b (b) (4) In the original validation report of 2008, the intra- and inter-assay precision determined at two levels of controls (low kit and high kit control) did not exceed 15% coefficient of variation. The relative accuracy was conducted by direct comparison of results with those generated by the DAKO Chromogranin A ELISA kit. A correlation coefficient of 0.987 was observed between the two methods. The analytical sensitivity was 0.20 nmol/L which was lower than manufacturer's claim of 0.4 nmol/L. Thus the analytical lab chose to report to 0.4 nmol/L. Validation summary report in 2013 and 2016 indicated that most of these parameters did not change except for the following two items: 1) inter-assay precision for low control being 26.1% in 2013 and 2) the sensitivity being 0.54 nmol/L in 2016.

For Study 730, while the analytical reports for urinary 5-HIAA and plasma CgA were all from one lab, it is unclear to the reviewer whether the assays were performed at a single lab or not.

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

/s/

ELIZABETH Y SHANG
09/01/2017

INSOOK KIM
09/01/2017

September 4, 2017

The review below needed edits. Refer to the revised review that was finalized on 9/1/2017.

APPEARS THIS WAY ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s017

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Template version: January 05, 2017

COA CONSULT TRACKING NUMBER	AT2016-293
IND/NDA/BLA NUMBER	NDA 022074 (S-017)
REFERENCED IND FOR NDA/BLA	IND 063239
ESTABLISHED NAME/TRADE NAME	lanreotide acetate/Somatuline Depot
SPONSOR/APPLICANT	Ipsen Pharma
INDICATION	lanreotide is beneficial in reducing rescue medication usag (b) (4) (b) (4)
MEETING TYPE (A/B/C/WRO)	N/A
LETTER DATE/SUBMISSION NUMBER	SDN 484
PDUFA GOAL DATE	June 15, 2017
DATE OF CONSULT REQUEST	December 5, 2016
REVIEW COMPLETION DATE	June 2, 2017
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products (DGIEP)
MEDICAL REVIEWER/TEAM LEADER (TL)	Wen-Yi Gao
REVIEW DIVISION PM	Benjamin Vali
COA REVIEWER	Wen-Hung Chen
COA TL/SECONDARY REVIEWER	
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos
INSTRUMENT(S)	Diarrhea and Flushing Symptom Daily Diary
COA TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Frequency and severity of diarrhea and flushing associated with carcinoid syndrome
INTENDED POPULATION(S)	Adults (≥18 years of age) with a histopathologically confirmed diagnosis of carcinoid tumor or carcinoid tumor of unknown location with confirmed liver metastases (with absence of tumor progression), and a history of carcinoid syndrome (flushing and/or diarrhea)
Please check all that apply:	☒Rare Disease/Orphan Designation ☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 022074. The Applicant is currently in phase 3 of their drug development program. The proposed indication is reducing rescue medication usage (b) (4) (b) (4)

The Applicant used the following patient-reported outcome (PRO) measure in their phase 3 clinical trial, Study 2-33-52030-730, in patients with histopathologically confirmed diagnosis of carcinoid tumor or carcinoid tumor of unknown location with confirmed liver metastases (with absence of tumor progression), and a history of carcinoid syndrome (flushing and/or diarrhea).

- Symptom Diary, which assesses the frequency and severity of daily diarrhea and flushing symptoms.

The Agency received an efficacy supplement (i.e., supplement-017) from Ipsen Pharma SAS (herein the Applicant) who recently developed Somatuline Depot (lanreotide acetate) for a new indication (b) (4) (b) (4) Back at the pre-sNDA meeting on September 10, 2015, the Agency stated that the Applicant needed to additionally include a thorough and careful exploratory analysis of diary data on flushing and diarrhea in order to support said primary endpoint.

In response to the Agency's request, the Application developed a post-hoc composite symptom intensity score (which incorporates diarrhea and flushing symptoms) utilizing the data from the 2-55-52030-730 study. The Division requested COA Staff input in regards to the validity of this composite symptom intensity score, and whether it provides adequate support to the pivotal trial's overall results/conclusion.

The review concludes that the post-hoc composite symptom intensity score submitted by the applicant is not appropriate to for use as endpoint to support the primary endpoint.

- It is very difficult to interpret the proposed composite symptom intensity score calculated as the product of symptom frequency and severity. Many different combinations of frequency and severity will yield the same score, but it is unlikely that all of them could be interpreted as having the same level of intensity. For example, a patient reported having one diarrhea with a severity of 3 (severe) and patient reported having three diarrheas with the severity of 1 (mild), both had the same intensity score of 3. It is arbitrary to assume that these two patients experienced the same level of intensity of diarrhea, because the sponsor has not provided evidence of patient input or other data in support of this approach to scoring. Therefore, we recommend that the frequency and severity be analyzed separately.

- The definitions of the severity ratings (i.e., mild, moderate, and severe) were not provided to the patients, therefore, the ratings were likely subjected to each patient's interpretation. This ambiguity will also affect the utility of the "composite symptom intensity score".

- Diarrhea and flushing may be more appropriately assessed by their frequency, instead of severity, as qualitative data suggested that reduction in frequency appeared to be more meaningful to the patients.

- We recommend that the Applicant submit results of the following additional post hoc analysis:

    - Responder analysis using responder definitions: 1) ≥ 50% reduction in average daily frequency; 2) with ≥ 1 reduction in average daily frequency.
    - Cumulative distribution function based on the two responder definitions above.

- An important issue regarding the sNDA submission is the large amount of missing data. We provide the following recommendations for the Applicant for strategy to minimize missing data and to consider alternative study design and endpoint for its future studies:

    - Patient reported rescue medication use can be supplemented with staff verification during study visit.
    - Training of site personnel (e.g., through site initiation visits, monthly coordinator calls, and investigator meetings) on the importance of capturing the data and ways to increase subject compliance with completing the PRO questionnaires (and other study procedures).
    - Educating subjects about the importance of completing the PRO questionnaire and providing practical ways (i.e. use of computer tablet and in-clinic completion) to make the task less burdensome.
    - Automatically sending out reminder to complete the PRO questionnaire if the patient has not responded via IVRS or IWRS after a specific time in the evening.
    - Consider alternative study design that may enhance your product's ability to demonstrate meaningful treatment benefit more clearly. For example, similar to pain palliation (Basch, 2013), a responder could be defined on the basis of symptoms as well as rescue medication use. For patients who have bothersome symptoms at baseline, a clinical treatment benefit could be defined as a patient with improvement in the symptoms of interest with no increase in rescue medication use. This definition represents a clinically meaningful endpoint, because it includes symptom improvement.
    - Consider qualitative research to better define symptoms for patients. For example, asking patients how they would define and count "diarrhea". You may also consider providing clear instructions and definition for the patients (e.g., one count

of diarrhea is defined as liquid or watery stools, such as Type 6 and 7 as illustrated in Bristol Stool Chart, in the same toilet visit)**.**

- We recommend close consultation with FDA regarding design of any future clinical studies.

B. SUGGESTED COMMENTS TO SPONSOR/APPLICANT

No questions were submitted by the Applicant. In response to the Review Division's request for review, we have the following comments:

FDA Comments on post hoc analysis of the composite symptom intensity score:

- It is difficult to interpret your proposed composite symptom intensity score calculated as the product of symptom frequency and severity. Many different combinations of frequency and severity will yield the same score, but it is unlikely that they could be interpreted as having the same intensity. For example, a patient reported one diarrhea with a severity of 3 (severe) will have the same score with a patient who had three diarrheas with the severity of 1 (mild). It is arbitrary to assume that these two patients experienced the same level of intensity of diarrhea.

- Diarrhea and flushing may be more appropriate been assessed by their frequencies as qualitative data suggested that its reduction appeared to be more meaningful to the patients. We recommend that the frequency and severity be analyzed separately.

- We recommend that the you conduct the following additional post hoc analysis:

    - Responder analysis using responder definitions: 1) ≥ 50% reduction in average daily frequency; 2) with ≥ 1 reduction in average daily frequency[1].
    - Cumulative distribution function (CDF) based on the two responder definitions above.

    <Reviewer note: Information Request of the above analyses was sent to the Applicant on February 10, 2017. The Applicant submitted responses on April 7, 2017. Selected CDF are shown in Appendix Bs. Overall, based on either responder definition, the results of the responder analyses suggested that there was no nominally statistical difference in the change of the average daily frequency of diarrhea or flushing between the lanreotide acetate and placebo arm (b) (4)

[1] Gelhorn, Heather L., Kulke, Mathew H., O'Dorisio, Thomas, et al. (2016). Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. *Clinical Therapeutics.*

(b) (4)

- We have the following recommendations for strategy to minimize missing data and for alternative study design and endpoints for your consideration for future studies

    - Patient reported rescue medication use can be supplemented with staff verification during study visit.
    - Training of site personnel (e.g., through site initiation visits, monthly coordinator calls, and investigator meetings) on the importance of capturing the data and ways to increase subject compliance with completing the PRO questionnaires (and other study procedures).
    - Educating subjects about the importance of completing the PRO questionnaire and providing practical ways (i.e. use of computer tablet and in-clinic completion) to make the task less burdensome.
    - Automatically sending out reminder to complete the PRO questionnaire if the patient has not responded via IVRS or IWRS after a specific time in the evening.
    - Consider alternative study design that may enhance your product's ability to demonstrate meaningful treatment benefit more clearly. For example, similar to pain palliation (Basch, 2013), a responder could be defined on the basis of symptoms as well as rescue medication use. For patients who have bothersome symptoms at baseline, a clinical treatment benefit could be defined as a patient with improvement in the symptoms of interest with no increase in rescue medication use. This definition represents a clinically meaningful endpoint, because it includes symptom improvement.
    - Consider qualitative research to better define symptoms for patients. For example, asking patients how they would define and count "diarrhea". You may also consider providing clear instructions and definition for the patients (e.g., one count of diarrhea is defined as liquid or watery stools, such as Type 6 and 7 as illustrated in Bristol Stool Chart, in the same toilet visit).
    - We recommend close consultation with FDA regarding design of any future clinical studies.

C. BACKGROUND

The Agency received an efficacy supplement (i.e., supplement-017) from Ipsen Pharma SAS (herein the Applicant) who recently developed Somatuline Depot (lanreotide acetate) for a new indication (b) (4) (b) (4) The original approval of this product (for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy) was made back on August 30, 2007.

A subsequent approval (i.e., supplement-003) was made for the originally approved indication, but for a higher dose, on March 4, 2011. An additional efficacy supplement (i.e., supplement-011) was approved on December 16, 2014 for another indication: the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

Back at the pre-sNDA meeting on September 10, 2015, The Agency communicated that they did not agree with the Applicant's primary endpoint from their pivotal trial (i.e., Study 2-55-52030-730), which is the basis for the new indication efficacy claim pertaining to this efficacy (b) (4) The Agency stated that the Applicant needed to additionally include a thorough and careful exploratory analysis of diary data on flushing and diarrhea in order to support said primary endpoint. The Agency also stated that additional exploratory analyses that combine endpoints of diarrhea and flushing along with severity and frequency should be submitted in the sNDA, in addition to the analysis of the individual components.

In response to the Agency's request, the Application developed a post-hoc composite symptom intensity score (which incorporates diarrhea and flushing symptoms) utilizing the data from the 2-55-52030-730 study. The Division requested COA Staff input regarding the validity of this composite symptom intensity scor (b) (4) (b) (4)

Materials reviewed:

- Previous COA Reviews: "AT 2016-106 NDA 208794, Chen, dated November 15, 2016 (DARRTS Reference ID # 4014062)"
- Meeting minutes:
  - "End-of-Phase 2 Type C Meeting, IND 063239, dated August 26, 2008 (DARRTS Reference ID # 1765912)"
  - "Pre-Efficacy Supplement Type B Meeting, IND 063239, dated September 19, 2015 (DARRTS Reference ID # 3822215)"
- Agency Advice Letter: "IND 063239, dated June 7, 2013, (DARRTS Reference ID # 3321564)"
- Brief document:
  - "Post-Hoc Derivations, Study 2-55-52030-730, Description of Post-Hoc Derivations and Analyses with Respect to Symptom Diary Data; dated July 27 2016; IPSEN."
  - IPSEN Response to Agency Information Request; dated April 7 2017; IPSEN
  - sNDA 022074, Clinical Overview

D. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

Patient population were patients ≥18 years of age with a histopathologically confirmed diagnosis of carcinoid tumor or, a carcinoid tumor of unknown location with liver metastases (documented biopsy), and a history of carcinoid syndrome (flushing and/or diarrhea); no specific level of symptoms at baseline was required for eligibility. Subjects were either naïve to Somatostatin analogue (SSTa) treatment or responsive to Sandostatin LAR® Depot or octreotide.

1.2 Clinical Trial Design

Study 2-55-52030-730 was a double blind, randomized, placebo-controlled clinical trial investigating the efficacy and safety of somatuline depot (lanreotide) injection in the treatment of carcinoid syndrome. The primary objective was to evaluate the efficacy of lanreotide Autogel injections administered every 4 weeks (± 3 days) for the control of symptoms associated with carcinoid syndrome (diarrhea and/or flushing) as compared to placebo, measured by assessing the percentage of days s.c. octreotide was used as rescue medication to control symptoms during the double-blind (DB) phase. The secondary objectives were to characterize the effect of lanreotide Autogel versus placebo on biochemical markers of tumor activity and to evaluate the safety and the pharmacokinetics (PK) of lanreotide Autogel.

Study 2-55-52030-730 consisted of a screening period (a minimum of 4 weeks), followed by a 16-week, DB, placebo-controlled phase in which subjects were randomized (1:1) to receive either lanreotide Autogel (120 mg) or placebo every 4 weeks by deep s.c. injection. The DB phase was followed by a 32-week, initial open-label (IOL) phase and a long-term, open-label extension (LTOLE) phase (at least 2 years after the last subject completed the IOL phase, or until marketing approval), in which all subjects received lanreotide Autogel.

Following instruction, daily frequency and severity of symptoms (diarrhea and flushing) and octreotide use were recorded by the subject at the end of each day using an Interactive Voice Response System (IVRS) (during screening, DB, and IOL phase).

1.3 Endpoint Hierarchy and Definition

Concept	Endpoint	Assessment
Primary Endpoint		
Use of rescue medication	The percentage of days that rescue medication (s.c.	Daily Diary

	octreotide injection) was administered for the control of symptoms during the 16-week DB phase.	
Secondary Endpoint		
Frequency of diarrhea	Average daily frequency of diarrhea events during the DB phase	Daily Diary
Frequency of flushing	Average daily frequency of flushing events during the DB phase	Daily Diary

1.4 Labeling or promotional claim(s) based on the COA

The Application proposed the following promotional claim (b) (4)

(b) (4)

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest were the frequency and severity of the diarrhea and flushing associated with carcinoid syndrome.

Items	Domain	General Concept
1. Did you have diarrhea today?	Diarrhea	Frequency and Severity of Symptoms Associated with Carcinoid Syndrome
2. Please enter the number of times you had diarrhea (allowable entry is 1–50)		
3. Overall, how would you rate your diarrhea? (1-Mild, 2-Moderate, 3-Severe)		
4. Did you have any flushing events? (1-Yes or 0-No)	Flushing	
5. Please enter the number of flushing events you had (allowable entry is 1–50)		
6. Overall, how would you rate your flushing events? (1-Mild, 2-Moderate, 3-Severe)		

3 CLINICAL OUTCOME ASSESSMENTS

On each day subjects completed the following questions with regard to symptoms.

Diarrhea:
1. Did you have diarrhea today? (1-Yes or 0-No)
2. Please enter the number of times you had diarrhea (allowable entry is 1–50)
3. Overall, how would you rate your diarrhea? (1-Mild, 2-Moderate, 3-Severe)

Flushing:
1. Did you have any flushing events? (1-Yes or 0-No)
2. Please enter the number of flushing events you had (allowable entry is 1‑50)
3. Overall, how would you rate your flushing events? (1-Mild, 2-Moderate, 3-Severe)

4 CONTENT VALIDITY

This submission does not include document regarding content validity for review.

<Reviewer note: frequency of diarrhea was considered an important symptom for patients with carcinoid syndrome and has been accepted by the Division as a study endpoin (b) (4) (b) (4) *However, the Applicant's proposed* (b) (4) (b) (4) *is considered inadequate* (b) (4) (b) (4) (b) (4) (b) (4) *Specifically, it is necessary for the Applicant to demonstrate* (b) (4) *that it is equally important to reduce the level of severity and the number of frequency. It is also unclear how the severity levels were interpreted by patients.>*

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

This submission does not include document regarding psychometric properties for review.

<Reviewer note: Freqauency of diarrhea has been accepted by the Division as a study endpoint (b) (4) *However, the Applicant's proposed* (b) (4) (b) (4) *is considered inadequate. See comments above.>*

6 INTERPRETATION OF SCORES

This submission does not include document regarding interpretation of scores for review.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

This submission does not include document regarding language translation or cultural adaption for review.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

This submission does not include a user manual for review.

10 KEY REFERENCES FOR COA

Basch, E., Trentacosti, A. M., Burke, L. B., Kwitkowski, V., Kane, R. C., Autio, K. A., Papadopoulos, E., Stansbury, J. P., Kluetz, P. G., Smith, H., Justice, R. and Pazdur, R. (2014), Pain palliation measurement in cancer clinical trials: The US Food and Drug Administration perspective. Cancer, 120: 761–767.

Gelhorn, Heather L., Kulke, Mathew H., O'Dorisio, Thomas, et al. (2016). Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. *Clinical Therapeutics.*

E. APPENDICES

Appendix A. Daily assessment of symptoms

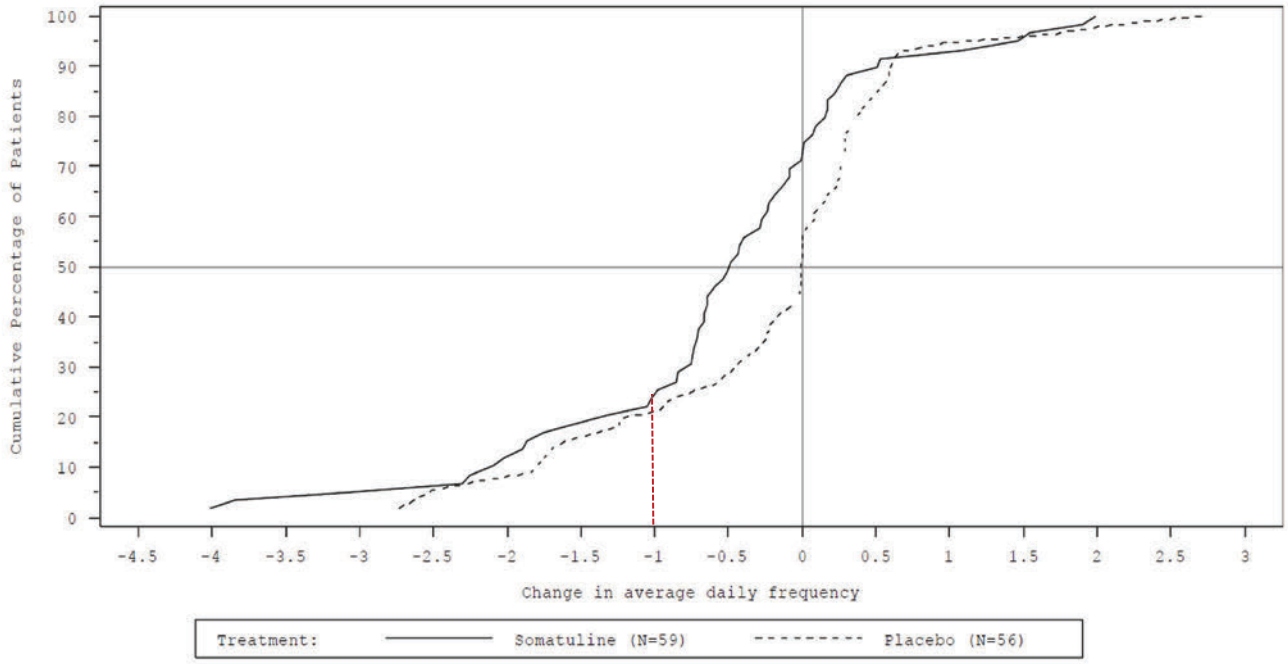
Diarrhoea:

1. Did you have diarrhea today? (1-Yes or 0-No)
2. Please enter the number of times you had diarrhea (allowable entry is 1‑50)
3. Overall, how would you rate your diarrhea? (1-Mild, 2-Moderate, 3-Severe)

Flushing:

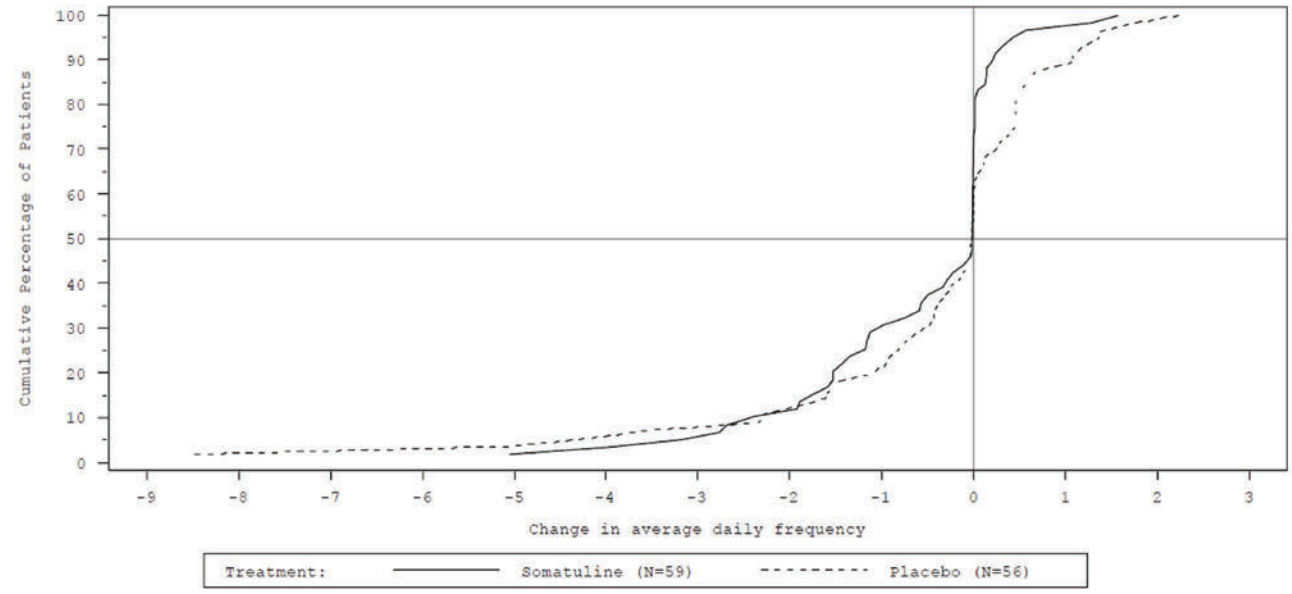
1. Did you have any flushing events? (1-Yes or 0-No)
2. Please enter the number of flushing events you had (allowable entry is 1‑50)
3. Overall, how would you rate your flushing events? (1-Mild, 2-Moderate, 3-Severe)

Appendix B-1. Cumulative distribution function of the change in the average daily frequency of diarrhea from baseline during the double-blind phase by treatment arm



Source Data Listing: 16.2.6.2.2.1 Analysis dataset: ADXD.SAS7BDAT 15MAR2016 05:38
Notes: Days without any diarrhea are considered with frequency = 0.
Negative values present a decrease in the average daily frequency of diarrhea compared to baseline, whereby positive values present an increase.

Appendix B-2. Cumulative distribution function of the change in the average daily frequency of flushing from baseline during the double-blind phase by treatment arm



Source Data Listing: 16.2.6.2.3.1 Analysis dataset: ADXD.SAS7BDAT 15MAR2016 05:38
Notes: Days without any flushing are considered with frequency = 0.
Negative values present a decrease in the average daily frequency of flushing compared to baseline, whereby positive values present an increase.

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/s/

WEN-HUNG CHEN
06/07/2017

ELEKTRA J PAPADOPOULOS
06/08/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 18, 2017
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SOMATULINE DEPOT (lanreotide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 022074
Supplement Number:	S-017
Applicant:	Ipsen Biopharmaceuticals, Inc., Authorized U.S. Agent for Ipsen Pharma

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 17, 2017

To: Benjamin Vali
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 022074/S-17
OPDP Comments for draft SOMATULIN DEPOT (lanreotide) injection, for subcutaneous use, PI and PPI

OPDP has reviewed the proposed draft PI for SOMATULIN DEPOT (lanreotide) injection, for subcutaneous use and have the following additional comments. Comments on the draft PPI will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI and PPI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/17/2017

1 INTRODUCTION

On August 15, 2016, Ipsen Biopharmaceuticals, Inc., Authorized U.S. Agent for Ipsen Pharma, submitted for the Agency's review a Prior Approval Supplement to their New Drug Application (NDA) 022074/S-017 for SOMATULINE DEPOT (lanreotide) injection. This efficacy supplement provides for the new indication for (b) (4) (b) (4) with the 120 mg dose of SOMATULINE DEPOT (lanreotide) injection. SOMATULINE DEPOT (lanreotide) injection was originally approved on August 30, 2007 and is indicated for the:

- long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.
- treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on January 6, 2017, and December 6, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SOMATULINE DEPOT (lanreotide) injection.

2 MATERIAL REVIEWED

- Draft SOMATULINE DEPOT (lanreotide) injection PPI received on August 15, 2016 and received by DMPP and OPDP on August 9, 2017.
- Draft SOMATULINE DEPOT (lanreotide) injection Prescribing Information (PI) received on August 15, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 9, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
08/18/2017

MEETA N PATEL
08/18/2017

MARCIA B WILLIAMS
08/18/2017

LASHAWN M GRIFFITHS
08/18/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 3/28/17 **Date consulted:** 12/5/2016

From: Catherine Roca, M.D. Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGEIP)

Drug: SOMATULINE DEPOT (lanreotide acetate)

NDA: 022074/S-017

Applicant: Ipsen Pharma SAS (U.S. Authorized Agent – Ipsen Biopharmaceuticals, Inc)

Subject: Pregnancy and Lactation Labeling

Current Indications: 1) long-term treatment of acromegalic patients who have had an inadequate response or cannot be treated with surgery and/or radiation
2) treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival

Proposed Indication: (b) (4)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 022074
- DPMH consult request dated 12/5/2016
- DPMH review of SANDOSTATIN LAR, NDA 21008/S-036. Jane Liedtka M.D., Medical Officer. August 22, 2016. DARRTS Reference ID 3974934
- DPMH review of SIGNIFOR LAR, NDA 203255 S02, Jane Liedtka M.D., Medical Officer. September 12, 2016.
- DPMH review of XERMELO, BLA 208794, Christos Mastroyannis, M.D., Medical Officer. August 20, 2016. DAARTS Reference ID 3994274.

Consult Question: "This submission contains a Physician's Labeling Rule (PLR) that has now (for the first time) additionally converted Section 8 of the PI to be compliant with the Pregnancy and Lactation Labeling Rule (PLLR). The DPMH maternal health review team is needed to assess this PLLR conversion for appropriateness/correctness."

INTRODUCTION

On December 5, 2016, the Division of Gastroenterology and Inborn Errors Products (DGEIP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy and lactation section of SOMATULINE DEPOT labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On August 15, 2016, the applicant submitted an efficacy supplement for a new indication: the (b) (4)

(b) (4) SOMATULINE DEPOT was approved for use in the U.S. on August 30, 2007 for the treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. On December 16, 2014, SOMATULINE DEPOT was approved for an additional indication: the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced, or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

BACKGROUND

Drug Characteristics[1]

SOMATULINE DEPOT (lanreotide) injection is a prolonged release formulation of lanreotide acetate, a synthetic octopeptide with biological activity similar to naturally occurring somatostatin. Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5, which is believed to be the primary mechanism responsible for growth hormone (GH) inhibition. Lanreotide has a molecular weight of 1096.34 Daltons, a half-life of 23 to 30 days, and mean bioavailability of 73-78%. Serious adverse events from clinical trials include gallstones, hypo- or hyperglycemia, and bradycardia.

Acromegaly and Pregnancy

Acromegaly is usually caused by a growth hormone (GH)-secreting pituitary macroadenoma. Although fertility is frequently impaired[2], pregnancy is apparently becoming more common due

[1] SOMATULINE DEPOT package insert, Drugs@FDA, accessed 1/26/2017

to improvement in acromegaly treatment as well as infertility therapies. As both acromegaly and pregnancy are associated with hypertension and diabetes, in uncontrolled acromegalic patients, pregnancy is reported to increase the prevalence of those comorbidities[3] and potentially complicate obstetrical/ fetal outcomes. In 2015, Laway, *et al*.,[4] reviewed the literature on pregnancies in acromegalic patients and noted the following:

> "In the majority of patients with acromegaly, pregnancy does not have an adverse effect on mother or fetus and pituitary mass does not increase in size. The level of IGF-1 usually remains stable because of the effect of estrogen causing a growth hormone resistant state. In patients with pituitary macroadenoma, the possibility of an increase in size of the pituitary mass needs to be kept in mind and more frequent monitoring is required. In case of tumor enlargement, pituitary surgery can be considered in the mid trimester. Experience with the use of medical treatment for acromegaly during pregnancy is increasing. Dopamine agonists, somatostatin analogs, or growth hormone receptor antagonists have been used without any adverse consequences on mother or fetus. At present, it is advisable to stop any medical treatment after confirmation of pregnancy until more data are available on the safety of these drugs."

Carcinoid Syndrome in pregnancy

Well-differentiated neuroendocrine tumors (NETs), formerly known as carcinoid tumor, are relatively rare tumor types that arise from cells of the neuroendocrine system.[5,6] One reference reported that only 40 cases of carcinoid tumors had been reported during pregnancy during the past 30 years.[7] Carcinoid tumors are a type of neuroendocrine tumors often found in the gastrointestinal (GI) tract or in the lungs. Carcinoid tumors are rare and often slow growing, and can lead to various symptoms, called carcinoid syndrome. Carcinoid syndrome (CS) occurs when well-differentiated NETs secrete large amounts of serotonin and other vasoactive products into the systemic circulation. Symptoms associated with CS include cutaneous flushing, diarrhea, wheezing, abdominal pain, and valvular heart disease (shortness of breath, fibrosis (scarring) of heart valves, high blood pressure, heart murmur, and fatigue). The prevalence of carcinoid tumor is approximately 50,000 cases in any 1 year in the United States.[8] A detailed analysis based on Surveillance, Epidemiology, and End Results Program (SEER Database 2007)[5] estimates the prevalence of NETs to be 103,312 cases. It has been estimated that 10% of all

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[2] Grynberg M et al. Female gonadal function before and after treatment of acromegaly. Journal of Clinical Endocrinology and Metabolism 2010 95 4518–4525.

[3] Caron P et al. Acromegaly and pregnancy: a retrospective multicenter study of 59 pregnancies in 46 women. Journal of Clinical Endocrinology and Metabolism. 2010; 95: 4680–4687.

[4] Laway B. Pregnancy in Acromegaly. Ther Adv Endocrinol Metab. 2015, Vol. 6(6) 267–272.

[5] Turaga KK, et al. Recent progress in the Understanding, Diagnosis, and Treatment of Gastroenteropancreatic Neuroendocrine Tumors. CA Cancer J Clin. 2011. 61:113-32.

[6] Yao et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,925 cases in the United States. J Clin Oncol. 2008. 26:3063-72.

[7] Kevat D, et al. A case of pulmonary carcinoid in pregnancy and review of carcinoid tumours in pregnancy. BJOG. 2015. 122 SUPPL 2.

[8] Vinik AI et al. Neuroendocrine Tumors. A comprehensive guide to diagnosis and management. Inter Science Institute GI Council. 2009. P9. Accessed at: http://www.interscienceinstitute.com/docs/Neuroendocrine-Tumors-4th-Edition.pdf accessed 2/10/2017.

patients with carcinoid tumors will develop carcinoid syndrome.[9] Therefore, the prevalence estimate of carcinoid syndrome is about 5,166 cases. About 75% of carcinoid syndrome patients will experience diarrhea,[10] which results in an estimated prevalence of 3,874 cases of carcinoid syndrome associated with diarrhea.

Current State of the Labeling[11]
Current labeling for SOMATULINE DEPOT was approved on December 16, 2014 and is in the Physician's Labeling Rule format but is not in PLLR format. SOMATULINE DEPOT is listed as Pregnancy Category C. The current pregnancy labeling describes animal reproduction studies, but notes that "There are no adequate and well-controlled studies in pregnant women… [and] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

The Nursing Mother's section does not report human data but notes that "as a result of serious adverse reactions from SOMATULINE DEPOT in animals… a decision should be made whether to discontinue nursing or discontinue the drug."

There are no boxed warnings in the labeling, no pregnancy testing or contraception recommendations and no drug interactions with hormonal contraceptives.

Pregnancy and Lactation Labeling
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[12] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[13] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW
PREGNANCY
Nonclinical Experience
In animal reproduction studies in pregnant rats given subcutaneous lanreotide every 2 weeks during organogenesis at doses five times the human dose, based on body surface area

[9] Horton KM, et al. Carcinoid tumors of the small bowel: a multi-technique imaging approach. A, J. Roentgenol. 2004. 182:559-67.
[10] Khan, AN, et al. Gastrointestinal Carcinoid Imaging. May 12, 2015. Accessed at http://emedicine.medscape.com/article/364581-overview 2/10/17
[11] SOMATULINE DEPOT approved package insert, Drugs@FDA
[12] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[13] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

comparisons, there was a decrease in embryo/fetal survival. In reproduction studies in pregnant rabbits given subcutaneous lanreotide during organogenesis at doses two times the human therapeutic exposures at the maximum recommended dose of 120 mg, based on comparisons of relative body surface area, there was demonstrated decreased fetal survival and increased fetal skeletal/soft tissue abnormalities. The reader is referred to the full Pharmacology/Toxicology review by Sushanta Chakder, Ph.D.

Applicant's Review of Literature

The applicant reported that a literature search of Medline, Adis and Embase was done on SOMATULINE DEPOT and the following terms, "normal pregnancy conditions and outcomes", "congenital, familial and genetic disorders"; "fetal disorders", " neonatal disorders", "termination of pregnancy and risk of abortion"; "pregnancy, labour and delivery complications and risk factors," " functional lactation disorders", "neonatal exposures via breast milk" and "paternal exposure." No published references were cited. The applicant did report that they located some case reports in the literature that they integrated into their Global Safety Database. Those cases were incorporated and reported on in the applicant's pharmacovigilance review. No references were provided.

DPMH review of literature

DPMH conducted a review of the literature using PUBMED, Embase, and Reprotox using the search terms, "lanreotide acetate and pregnancy", "lanreotide acetate and pregnant women", "lanreotide acetate and pregnancy and birth defects", "lanreotide acetate and pregnancy and fetal malformations", "lanreotide acetate and pregnancy and still birth", "lanreotide acetate and spontaneous abortion", and "lanreotide acetate and miscarriage." The search revealed the following reports:

- A case of a woman in her early thirties treated with slow release lanreotide who became pregnant. Lanreotide was discontinued during the first trimester (fetus had a month exposure). The pregnancy was normal, and she delivered a healthy infant.[14]
- A case of a 26-year-old woman with acromegaly treated with lanreotide who became pregnant. The lanreotide was stopped once pregnancy was diagnosed. She carried the pregnancy to term and delivered a healthy baby.[15]
- A woman with acromegaly continued lanreotide throughout her first pregnancy and through the first four months of her second pregnancy. She delivered two healthy infants without congenital anomalies.[16]

TERIS[17] states, "the magnitude of teratogenic risk to the child born after exposure during gestation is undetermined."

Review of Pharmacovigilance Database

According to the applicant:

[14] De Menis E, et al. Uneventful pregnancy in an acromegalic patient treated with slow-release lanreotide: a case report. J Clin Endocrinol Metab. 1999. 84(4):1489.
[15] Ben Salem HL, et al. Management of acromegaly in pregnant woman. Ann Endocrinol (Paris). 2010. 71(1):60-3.
[16] Khan Y and Raghuwanshi MP. Lanreotide acetate (somatuline) found safe in pregnancy: a case report and 10 years follow up. Endocrinol Rev. 2013. 34:3. Suppl 1.
[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 2/10/2017

> "The Standardized MedDRA Queries (SMQs) used to search the IPSEN safety database were: Normal pregnancy conditions and outcomes; Congenital, familial and genetic disorders; Foetal disorders; Neonatal disorders; Termination of pregnancy and risk of abortion; Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth); Functional lactation disorders, Neonatal exposures via breast milk and paternal exposure.
>
> Safety information is included (from all sources including serious adverse events from the sponsor's clinical studies; serious and non-serious adverse events from spontaneous reports e.g. from healthcare professionals, health authorities, literature articles and consumers; and serious and non-serious adverse events from other solicited sources e.g. patient support programs, investigator-initiated studies) from the first commercial launch of SOMATULINE DEPOT on 16 May 1994 in France."

The applicant reported that this search yielded 68 cases of exposure to lanreotide during pregnancy. Of these 68 cases, 26 cases were reported to have a normal outcome, and 22 cases had an unknown outcome. Of the remaining, there were three cases of preterm birth, including a case due to Hemolysis Elevated Liver enzymes Low Platelet count (HELLP)[18] syndrome and a set of twins delivered at 28 weeks with one twin dying after birth. Four patients had "voluntary abortions," and one patient had two reported miscarriages. There were eight reported adverse neonatal outcomes (one broken clavicle, one infant with hypoglycemia and thrombocytopenia, one infant with low Apgar scores and respiratory distress, four infants reported small for gestational age (SGA) (there was no discussion on the size of the infant and no information regarding follow-up). One infant developed elevated liver enzymes and thrombocytopenia (mother with HELLP syndrome- this is the same case noted earlier with the infant reported as preterm). There were also ten reported maternal adverse events affecting seven women (including diabetes, increased IGF-1 levels, preeclampsia, headache, tumor progression, HELLP syndrome [same case noted with the preterm infant], and thrombocytopenia).

The applicant concluded that, "The available human data for pregnancy exposure with SOMATULINE comprise individual case safety reports from the Ipsen Global Patient Safety Database (ARIS) and do not establish the presence of a drug-associated risk."

Summary

The most common adverse event was SGA infants, but prevalence in the applicant's small sample was not greater than the estimated 8.1% prevalence rate of SGA in the U.S. population.[19] There was also one case of HELLP syndrome, which is a relatively rare complication occurring in 0.5-0.9% of pregnancies.[20] Overall, the cases available in the published literature and in the applicant's database do not indicate a pattern of maternal or fetal adverse outcomes. However, the number of reported exposed cases is limited. Current Endocrine Society Clinical Practice

[18] There was only one case of HELLP syndrome that is reported on several times under 1) preterm birth, 2) SGA infant with elevated LFTs and thrombocytopenia and 3) maternal adverse events.
[19] Hamilton BE, et al. Annual summary of vital statistics: 2010-2011. Pediatrics. 2013. 131:548-558.
[20] Haram K, et al. The HELLP syndrome: Clinical issues and management. A review. BMC Pregnancy and Childbirth. 2009. 9(8):1-15.

Guidelines recommend that acromegaly therapy be withheld throughout pregnancy and administered only for tumor and headache control.[21]

LACTATION

Nonclinical Experience

Available data in animals have shown excretion of lanreotide acetate in milk. After a single subcutaneous dose of 2 mg/kg to lactating rats, the transfer of radioactivity into milk was observed. Total radioactivity in plasma reached the highest levels at 6 hours (h) and 24 h post-dose, with mean values of 0.700 and 0.79 µg equiv/ml, respectively. The highest concentration of total radioactivity in milk was noted at 6 h post-dose with a mean value of 3.402 µg equiv/ml. Radioactivity was still measurable at 72 h post-dose in both plasma and milk with mean values of 0.318 and 0.213 µg equiv/ml, respectively. The mean milk: plasma concentration ratios were 0.7, 4.9, 1.3 and 0.7 at 1, 6, 24 and 72 h, respectively. For further details, the reader is referred to the Nonclinical Review by Dylan Yao, Ph.D.

Applicant's Review of Literature

According to the applicant, "Lactation studies have not been conducted to assess the presence of SOMATULINE DEPOT in human milk, the effects on the breastfed infant, or the effects on milk production. As a result of serious adverse reactions from SOMATULINE DEPOT in animals and, potentially in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, after taking into account the importance of the drug to the mother." No references were found regarding the use of lanreotide acetate and lactation or breastfeeding.

DPMH Review of Literature:

DPMH conducted a search of *Medications and Mother's Milk*[22], the Drugs and Lactation Database (LactMed),[23] Micromedex[24], and of published literature in PubMed and Embase using the search terms "lanreotide acetate and lactation" and "lanreotide acetate and breastfeeding." No reports of adequate and well-controlled studies of lanreotide acetate use in lactating women were found.

Lanreotide acetate is not referenced in LactMed[23] or in *Medications and Mother's Milk* [22] by Thomas Hale.

Micromedex[17] notes the following; "Infant risk cannot be ruled out," and "It is not known if lanreotide is excreted in human milk."

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[21] Katznelson L, et al. Acromegaly: An Endocrine Society Clinical Practice Guideline. JCEM. 2014. 99(11):3933-3952.

[22] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.

[23] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[24] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/1/16.

Review of Pharmacovigilance Database
The applicant's search of the pharmacovigilance database yielded one case of infant exposure via breastmilk. The patient report occurred because the mother developed joint pains while on SOMATULINE DEPOT therapy. At the time of the report, she was breastfeeding her two month old infant. Data on the infant were not reported.

Summary
Available data in rats have shown excretion of lanreotide acetate into rat milk with a maximum M/P ratio of 4.9 at six hours. There are no data on the presence of lanreotide acetate in human milk. No specific data on lanreotide acetate and breastfeeding were found either in the published literature or in the applicant's pharmacovigilance database. Despite the high molecular weight of lanreotide acetate (molecular weight >1096.34 Daltons), lanreotide has a half-life of 23-30 days and animal data that has demonstrated an M/P ratio >1. Given the potential for lanreotide to accumulate in human milk and lanreotide's effect on GH inhibition, DPMH recommends that the following risk benefit statement is included in section 8.2 of labeling:

> Because of the potential for serious adverse reactions in breastfed infants from SOMATULINE DEPOT, including effects on glucose metabolism and bradycardia, advise women not to breastfeed during treatment with SOMATULINE DEPOT and for six months (6 half-lives) following the last dose.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
In the fertility and early embryonic development study in rats, there was a significant decrease in the number of implantation and the number of conceptions in females at lanreotide doses that were 10-fold the plasma exposure at the maximum recommended human dose (MRHD) of 120mg. However, there was also a decreased body weight gain (up to 79%) in the female animals. The reversibility of the effects was not studied in rats. Fertility in male rats was not affected by lanreotide treatment at exposures of 11-fold the plasma exposure at the MRHD. The reduction in fertility in non-acromegalic animals is likely related to the pharmacologic activity (decreased growth hormone secretion) of lanreotide acetate.

Review of Literature
The applicant did not submit a literature search related to lanreotide acetate and fertility.

DPMH review of literature:
DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "lanreotide acetate and fertility", "lanreotide acetate and contraception", "lanreotide acetate and oral contraceptives" and "lanreotide acetate and infertility."

Micromedex states the following:

> *Male reproduction*
> *Male fertility was normal at a lanreotide dose level up to 10 mg/animal (rat) every 2 weeks. Adult toxicity was apparent at this dose level.*[25]

[25] FDA Pharmacology review part 3 for Somatuline Depot (lanreotide) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022074s00

Female reproduction
Subcutaneous injection of rats with 5 times the human dose level of lanreotide every 2 weeks decreased the number of corpora lutea and implantation sites in females.[25] *Adult toxicity was apparent at this dose level. Somatostatin also appeared to suppress the pituitary-ovarian axis. This suppression was shown in the pig as inhibition of the normal follicular cAMP response to gonadotropins.*[26] *In women, somatostatin decreased the release of LH but not FSH after gonadotropin releasing hormone was administered.*[27] *The use of lanreotide in the therapy of uterine myomas has been described.*[28] *In case reports of normal pregnancies conceived on somatostatin analogs, the authors suggested an improvement in ovulation permitting spontaneous pregnancy as a result of drug treatment.*[29]

A search of the published literature yielded one article that indicated that short-term growth hormone and IGF-1 suppression after lanreotide therapy significantly increase testosterone and improved sperm number and motility in acromegalic men.[30] No articles were found on female infertility or interactions with lanreotide on hormonal contraception.

Review of Pharmacovigilance Database
The applicant did not provide specific information related to fertility and SOMATULINE DEPOT.

Summary
Animal data suggest reduced fertility in female but not male rats. Data in humans are limited. Given the concern for infertility in females of reproductive potential, DPMH proposes the following language for section 8.3

> Based on results from animal studies conducted in female rats SOMATULINE DEPOT may reduce fertility in females of reproductive potential. The reversibility of the effects was not studied in rats *[see Nonclinical Toxicology (13.1)]*.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of SOMATULINE DEPOT labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.

[26] Rajkumar K, Kerr DE, Kirkwood RN, Laarveld B. Inhibitory action of somatostatin-14 on hormone-stimulated cyclic adenosine monophosphate production in porcine granulosa and luteal cells. J Endocrinol 1992;134:297-306.
[27] Chiodera P, Volpi R, d'Amato L, Fatone M, Cigarini C, Fava A, Caiazza A, Rossi G, Coiro V. Inhibition by somatostatin of LH-RH-induced LH release in normal menstruating women. Gynecol Obstet Invest 1986;22:17-21.
[28] De Leo V, la Marca A, Morgante G, Severi FM, Petraglia F: Administration of somatostatin analogue reduces uterine and myoma volume in women with uterine leiomyomata. Fertil Steril 2001;75:632-3.
[29] Persechini ML, Gennero I, Grunenwald S, Vezzosi D, Bennet A, Caron P. Acromegalie et grossesse: six nouvelles observations. J Gynecol Obstet Biol Reprod (Paris). 2014 Nov;43(9):704-12.
[30] Colao A, et al. Short-term suppression of GH and IFG-1 levels improves gonadal function and sperm parameters in men with acromegaly. J Clin Endocrinol Metab. 2002. 87(9):4193-7.

- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," section.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection of SOMATULINE DEPOT labeling was formatted in the PLLR format to include information about the potential for infertility in females of reproductive potential.
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.3 of labeling.

LABELING RECOMMENDATIONS
DPMH revised sections 8.1, 8.2, 8.3 and 17 of SOMATULINE DEPOT labeling for compliance with the PLLR (see below). See Appendix A for the applicant's proposed pregnancy and lactation labeling. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling- SOMATULINE DEPOT (lanreotide acetate)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited available data based on postmarketing case reports with SOMATULINE DEPOT use in pregnant women are not sufficient to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, decreased embryo/fetal survival was observed in pregnant rats and rabbits doses 5- and 2-times the maximum recommended human dose (MRHD) of 120mg *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
Reproductiv (b) (4) in pregnant rats given 30 mg/kg by subcutaneous injection every 2 weeks (five times the human dose, based on body surface area comparisons) resulted in decreased embryo/fetal survival (b) (4) in pregnant rabbits given subcutaneous injections of 0.45 mg/kg/day (two times the human therapeutic exposures at the maximum recommended dose of 120 mg, based on comparisons of relative body surface area) shows decreased fetal survival and increased fetal skeletal/soft tissue abnormalities.

8.2 Lactation
Risk Summary
There is no information available on the presence of lanreotide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Studies show that

lanreotide acetate administered subcutaneously passes into the milk of lactating rats; however, due to specifies-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Because of the potential for serious adverse reactions in breastfed infants from SOMATULINE DEPOT, including effects on glucose metabolism and bradycardia, advise women not to breastfeed during treatment with SOMATULINE DEPOT and for six months (6 half-lives) following the last dose.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on results from animal studies conducted in female rats, SOMATULINE DEPOT may reduce fertility in females of reproductive potential (b) (4) (b) (4) *[see Nonclinical Toxicology (13.1)]*.

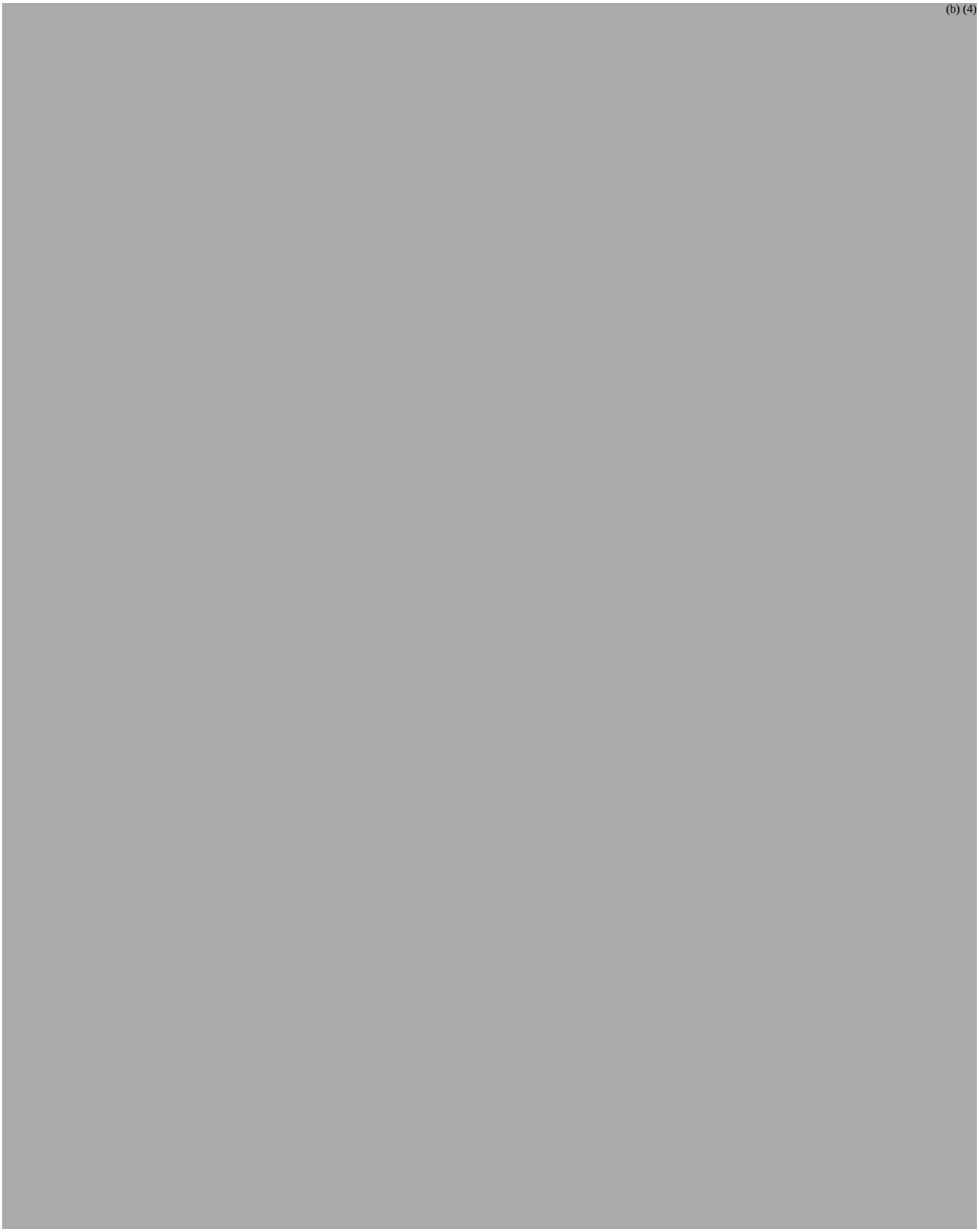
17 PATIENT COUNSELING INFORMATION

Infertility

Advise females of reproductive potential of the potential for reduced fertility from SOMATULINE DEPOT *[see Use in Specific Populations (8.3)]*.

APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

(b) (4)

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/s/

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03/28/2017

JANE E LIEDTKA
03/29/2017

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