CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022074Orig1s011

Trade Name:	SOMATULINE DEPOT
Generic or Proper Name:	(lanreotide)
Sponsor:	Ispen Pharma
Approval Date:	December 16, 2014
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 patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

CENTER FOR DRUG EVALUATION AND RESEARCH

022074Orig1s011

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	X
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22074/S-011

SUPPLEMENT APPROVAL

Ipsen Pharma
Attention: Steven R. Scott
Vice President, US, Global Regulatory Affairs
Ipsen Biopharmaceuticals, Inc.
106 Allen Road, 3rd Floor
Basking Ridge, NJ 07920

Dear Mr. Scott:

Please refer to your Supplemental New Drug Application (sNDA) dated June 23, 2014, received June 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for "Somatuline Depot (lanreotide) Injection."

We acknowledge receipt of your amendments dated August 4, 11, and 13; September 23; October 6, and 23; and November 14 and 25, and December 1, 3, 8 and 11, 2014; and your December 12 and 15, 2014, email communications.

This Prior Approval supplemental new drug application provides for a new indication 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.

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.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 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 includes 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 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 Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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:

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

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, call Missiratch (Mimi) Biable, Regulatory Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

PATRICIA KEEGAN
12/16/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

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
Initial U.S. Approval: 2007

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

Indications and Usage	
Gastroenteropancreatic Neuroendocrine Tumors (1.2)	12/2014
Dosage and Administration	
Gastroenteropancreatic Neuroendocrine Tumors (2.2)	12/2014
Warnings and Precautions:	
Cardiovascular Abnormalities (5.4)	12/2014

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

SOMATULINE DEPOT (lanreotide) Injection 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 patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival (1.2) [see *Clinical Studies 14.2*].

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

- Injected in the superior external quadrant of the buttock. Injection site should be alternated (2.3)

Acromegaly

- Dose range is 60 mg to 120 mg every 4 weeks. Recommended starting dose is 90 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels (2.1)
- Moderate and Severe Renal and Hepatic Impairment: Initial dose is 60 mg every 4 weeks for 3 months. Adjust thereafter based on GH and/or IGF-1 levels. (2.1, 12.3)

GEP-NET

- Recommended dose is 120 mg every 4 weeks (2.2)

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

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

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

None (4)

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

- Gallbladder: Gallstones may occur; consider periodic monitoring (5.1)
- Glucose Metabolism: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment adjusted accordingly (5.2)
- Cardiac Function: Decrease in heart rate may occur. Use with caution in at-risk patients (5.4)

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

- Acromegaly: Most common adverse reactions are diarrhea, cholelithiasis, abdominal pain, nausea and injection site reactions (6)
- GEP-NET**:** Most common adverse reactions (>10%) are abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, cholelithiasis (6)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-866-837-2422 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- Hypoglycemia agents: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment adjusted accordingly (7.1)
- Cyclosporine: Somatuline may decrease the bioavailability of cyclosporine. Cyclosporine dose may need to be adjusted (7.2)
- Drugs affecting heart rate: Somatuline may decrease heart rate. Dose adjustment of coadministered drugs may be necessary (7.3)

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

- Renal Impairment: Start dose is 60 mg for patients with acromegaly and moderate and severe renal impairment (2.1, 8.6, 12.3)
- Hepatic Impairment: Start dose is 60 mg for patients with acromegaly and moderate and severe hepatic impairment (2.1, 8.7, 12.3)

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

Revised: 12/2014

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 (lanreotide) 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.

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 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 [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

Somatuline Depot should be administered by healthcare professionals. Please see enclosed Instructions for Use Leaflet for administration of Somatuline Depot.

2.1 Acromegaly

Patients should begin treatment with SOMATULINE DEPOT 90 mg given via the deep subcutaneous route, at 4-week intervals for 3 months.

After 3 months, dosage may be adjusted as follows:

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

Thereafter, the dose 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 mg 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 dose adjustments for biochemical and clinical symptom control, as necessary, is recommended.

The starting dose in patients with moderate or severe renal impairment or moderate or severe hepatic impairment should be 60 mg via the deep subcutaneous route at 4-week intervals for 3 months followed by dose adjustment as described above [*see Clinical Pharmacology (12.3)*].

2.2 Gastroenteropancreatic Neuroendocrine Tumors

The recommended dose of SOMATULINE DEPOT is 120 mg administered every 4 weeks by deep subcutaneous injection. There is no recommended dose adjustment for mild or moderate renal impairment. There is insufficient information to recommend a dose for patients with severe renal impairment or with hepatic impairment of any severity [*see Clinical Pharmacology (12.3)*].

2.3 Administration

SOMATULINE DEPOT is provided in a single-dose, prefilled syringe affixed with an automatic needle protection system. Inject SOMATULINE DEPOT via the deep subcutaneous route in the superior external quadrant of the buttock. Alternate the injection site between the right and left sides from one injection to the next. Remove SOMATULINE DEPOT from the refrigerator 30 minutes prior to administration. Keep pouch sealed until just prior to injection.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Lanreotide 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 Thyroid Function Abnormalities

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

5.4 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) treated with SOMATULINE DEPOT in Study 3, the incidence of heart rate < 60 bpm was 23% (19/81) as compared to 16 % (15/94) of placebo treated patients; ten patients (12%) had documented heart rates < 60 bpm on more than one visit. The incidence of documented episodes of heart rate < 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.

5.5 Drug Interactions

The pharmacological gastrointestinal effects of SOMATULINE DEPOT may reduce the intestinal absorption of concomitant drugs.

Lanreotide may decrease the relative bioavailability of cyclosporine. Concomitant-administration of SOMATULINE DEPOT and cyclosporine may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels [*see Drug Interactions (7.2)*].

5.6 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 (2.1)*].

6 ADVERSE REACTIONS

The following adverse reactions to SOMATULINE DEPOT (lanreotide) Injection 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)*]
- Thyroid Function Abnormalities [*see Warnings and Precautions (5.3)*]
- Cardiovascular Abnormalities [*see Warnings and Precautions (5.4)*]

6.1 Clinical Studies 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 53.0 years of age (range 19-84 years). Fifty-four subjects (13%) were age 66-74 and eighteen subjects (4.3%) were ≥ 75 years of age. Patients were evenly matched for gender (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 < 10 ng/mL for 69% (183/265) of the patients and ≥ 10 ng/mL for 31% (82/265) of the patients.

The most commonly reported adverse-reactions reported by > 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.

<u>Adverse Reactions in Parallel Fixed-Dose Phase of Study 1:</u>
The incidence of treatment-emergent adverse reactions for SOMATULINE DEPOT 60 mg, 90 mg, 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 > 5% with Lanreotide Overall and Occurring at Higher Rate in Drug 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)** N (%)	**Lanreotide Overall (N=83)** N (%)	**Lanreotide 60 mg (N=34)** N (%)	**Lanreotide 90 mg (N=36)** N (%)	**Lanreotide 120 mg (N=37)** N (%)	**Lanreotide Overall (N=107)** 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 that occurred in 416 acromegalic patients treated with SOMATULINE DEPOT in seven studies. The analysis of safety compares adverse reaction rates of patients at baseline from the two efficacy studies, to the overall pooled data from seven studies. 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 at an Incidence > 5.0% in Overall Group 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 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 < 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, 17.4% had gallstones at baseline. New cholelithiasis was reported in 12.0% 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 (4.1%) and injection site mass (1.7%) 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 (4.8%) 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 (3.1%) was the most frequently observed heart rate and rhythm disorder. All other cardiac adverse drug reactions were observed in <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 (5.4)*].

A comparative echocardiography study of lanreotide and another somatostatin analog demonstrated no difference in the development of new or worsening valvular regurgitation between the two treatments over one 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 ≥ 6 months and 72 patients exposed for ≥ 1 year (median duration of exposure 22.1 months). Patients treated with SOMATULINE DEPOT had a median age of 64 years (range 30-83 years), 53% were men and 96% were Caucasian. Eighty-one percent of patients (83/101) in the SOMATULINE DEPOT arm and eighty-two percent 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% in patients receiving SOMATULINE DEPOT 120 mg administered every 4 weeks and reported more commonly than placebo.

Table 3: Adverse Reactions Occurring in > 5% of Somatuline Depot-Treated Patients and Occurring More Commonly Than in Placebo-Treated Patients (> 5% higher incidence) 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

6.2 Immunogenicity

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 (<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 3.7% (3 of 82) at 24 weeks, 10.4% (7 of 67) at 48 weeks, 10.5% (6 of 57) at 72 weeks, and 9.5% (8 of 84) at 96 weeks. Assessment for neutralizing antibodies was not conducted.

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 SOMATULINE DEPOT with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

As adverse reactions experienced post-approval use 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.

The profile of reported adverse reactions for SOMATULINE DEPOT was consistent with that observed for treatment-related adverse reactions in the clinical studies. Those reported most frequently being gastrointestinal disorders (abdominal pain, diarrhea, and steatorrhea), hepatobiliary disorders (cholecystitis), and general disorders and administration site conditions (injection site reactions). Occasional cases of pancreatitis have also been observed.

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 lanreotide treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

7.2 Cyclosporine

Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and, therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic levels.

7.3 Other Concomitant Drug Therapy

The pharmacological gastrointestinal effects of SOMATULINE DEPOT may reduce the intestinal absorption of concomitant drugs. Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the availability of bromocriptine.

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

Vitamin K absorption was not affected when concomitantly administered with lanreotide.

7.4 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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Lanreotide has been shown to have an embryocidal effect in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. SOMATULINE DEPOT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies 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. Studies 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.

8.3 Nursing Mothers

It is not known whether lanreotide is excreted in human milk. Many drugs are excreted in human milk. 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.

8.4 Pediatric Use

Safety and effectiveness 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. Study 3, conducted in patients with GEP-NET, 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.

Acromegaly

It is not necessary to alter the starting dose in elderly patients; lanreotide serum concentrations in the elderly are well within the range of serum concentrations safely tolerated in healthy young subjects. Similarly, it is not necessary to alter the titration or maintenance doses of SOMATULINE DEPOT, as dose selection is based on therapeutic response [*see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)*].

Gastroenteropancreatic Neuroendocrine Tumors

No dose adjustment required. [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

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)*].

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)*].

Gastroenteropancreatic Neuroendocrine Tumors

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

10 OVERDOSAGE

If overdose occurs, symptomatic management is indicated.

Up-to-date information about the treatment of overdose can often be obtained from the National Poison Control Center at phone number 1-800-222-1222.

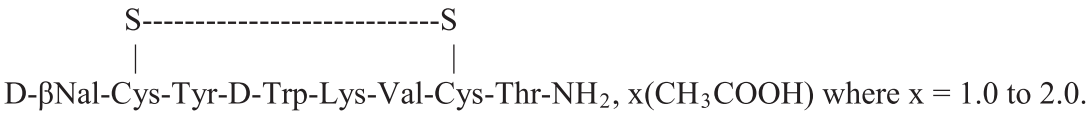
11 DESCRIPTION

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-use 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:



For appearance of the formulation, see *Dosage Forms and Strengths (3).*

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)*]. 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.

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)*].

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 20-30% 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)*].

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.

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 Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily subcutaneous doses of lanreotide acetate 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 acetate 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.

Subcutaneous dosing (30mg/kg/2 wks) before mating and continuing into gestation in rats at doses five times the human clinical exposure (120 mg every 4 weeks) based on mg/m^2 had reduced fertility. Gestation length was statistically significantly increased suggesting some delay in parturition at three times the human exposure. The reduction in fertility in non-acromegalic animals is likely related to the pharmacologic activity (decreased growth hormone secretion) of lanreotide acetate.

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 two long-term, multiple-dose, randomized, multicenter studies.

Study 1

This one-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 mg, 90 mg, 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 > 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 >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 > 50% decrease in mean GH from baseline to Week 4, including 52%, 44%, and 90% of patients in the 60 mg, 90 mg, 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 > 50%, including 68% (23/34), 64% (23/36), and 84% (31/37) of patients in the 60 mg, 90 mg, 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 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 < 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 ≤ 2.5 ng/mL (see Table 5) and 17/63 patients (27%) had both normal IGF-1 concentrations and a GH concentration of <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 30-92 years) and 95% were Caucasian. Disease progression was present in nine of 204 patients (4.4%) in the 6 months prior to enrollment and twenty-nine 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 > 25%.

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

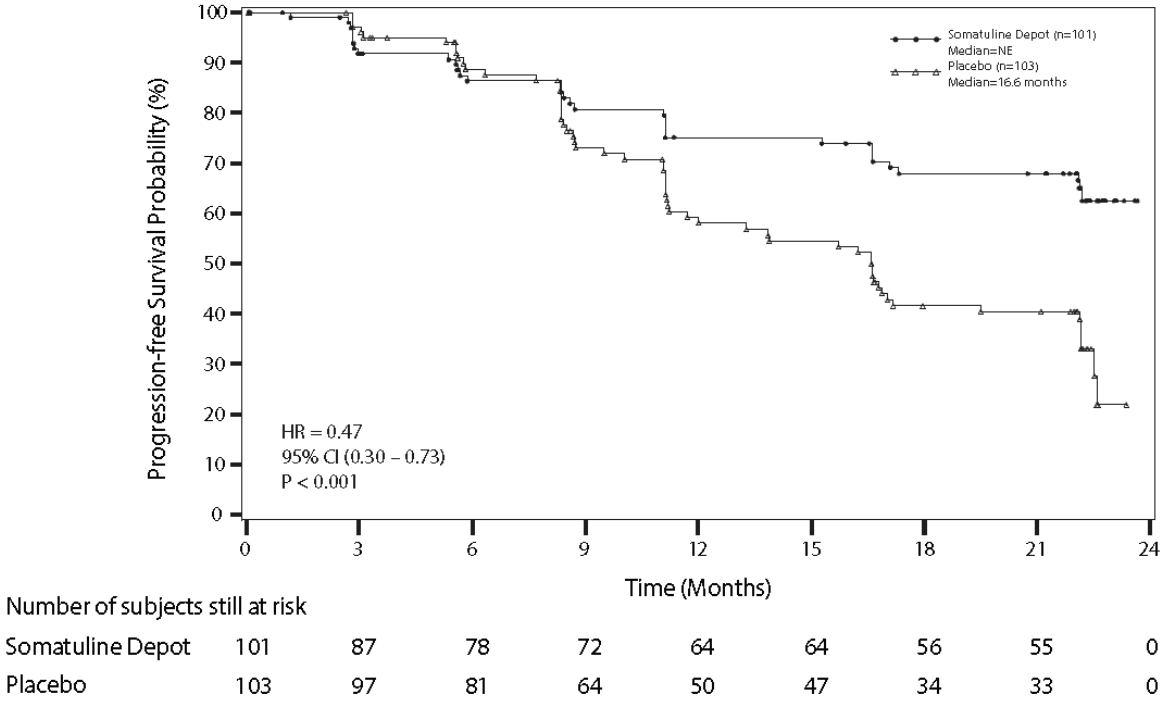
Table 6: Efficacy Results in Study 3

	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



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 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

SOMATULINE DEPOT must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package. Thirty (30) minutes prior to injection, remove sealed pouch of SOMATULINE DEPOT from refrigerator and allow it to come to room temperature. Keep pouch sealed until injection.

Each syringe is intended for single use. Do not use beyond the expiration date on the packaging.

17 PATIENT COUNSELING INFORMATION

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

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms, or if any known symptom persists or worsens.

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.

Advise patients experiencing dizziness not to drive or operate machinery.

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 professional 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 people 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

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

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

Before you receive SOMATULINE DEPOT, tell your healthcare professional if you:

- have gallbladder problems
- have diabetes
- have thyroid problems
- have heart problems
- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. SOMATULINE DEPOT may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOMATULINE DEPOT passes into your breast milk. You and your healthcare professional should decide if you will take SOMATULINE DEPOT or breastfeed. You should not do both.

Tell your healthcare professional 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 adjusted.

Especially tell your healthcare professional if you take:

- insulin or other diabetes medicines
- a cyclosporine (Gengraf, Neoral, or Sandimmune)
- a medicine called bromocriptine (Parlodel, Cycloset)
- medicines that lower your heart rate such as beta blockers

Know the medicines you take. Keep a list of them to show your healthcare professional when you get a new medicine.

How will I receive SOMATULINE DEPOT?

- You will receive a SOMATULINE DEPOT injection every 4 weeks in your doctor's office.
- Your precriber may change your dose of SOMATULINE DEPOT or the length of time between your injections. Your healthcare professional 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 professional may do certain blood tests to see if SOMATULINE DEPOT is working.

What are the possible side effects of SOMATULINE DEPOT?

SOMATULINE DEPOT may cause serious side effects, including:

- **Gallstones.** Tell your healthcare professional if you get any of these symptoms:
  - 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 professional tells you to. Your healthcare professional may change your dose of diabetes medicine especially when you first start receiving SOMATULINE DEPOT or if your dose of SOMATULINE DEPOT changes.
- **Slow heart rate**
- **High blood pressure**

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-NETs include:

- stomach area (abdominal) pain
- muscle and joint aches
- vomiting
- headache
- pain, itching, or a lump at the injection site

SOMATULINE DEPOT may cause dizziness. If this happens, do not drive a car or operate machinery.

Tell your healthcare professional if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of SOMATULINE DEPOT. For more information ask your healthcare professional.

Call your healthcare professional 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 conditions other than those listed in the patient leaflet. This Patient Information leaflet summarizes the most important information about SOMATULINE DEPOT. If you would like more information about SOMATULINE DEPOT, talk with your healthcare professional. You can ask your healthcare professional for information about SOMATULINE DEPOT that is written for health professionals.

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: 12/2014

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

SUMMARY REVIEW

Division Director Summary Review

Date	December 16, 2014
From	Patricia Keegan
Subject	Division Director Summary Review
NDA	022074/11
Applicant Name	Ipsen Pharma
Date of Submission	Received June 30, 2014
PDUFA Goal Date	December 30, 2014
Proprietary Name / Established (USAN) Name	Somatuline Depot Injection/ lanreotide
Dosage Forms / Strength	Injection supplied in sterile, single-use, prefilled syringes fitted with an automatic needle guard / 60 mg/0.2 mL, 90 mg/0.3 mL and 120 mg/0.5 mL
Proposed Indication(s)	Somatuline Depot (lanreotide) Injection 120 mg is indicated fo (b) (4) (b) (4)
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Reviews	Mona Patel & Mimi Biable
Medical Officer Review	Joohee Sul
Statistical Review	Weishi Yuan
CMC Review	Sue-Ching Lin
Clinical Pharmacology Review	Jun Yang/ Anshu Marathe
OSI	Lauren Iacono-Connors
OPDP	Carole Broadnax
Patient Labeling Team Review	Morgan Walker

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotions

Division Directory Summary Review

1. Introduction

SOMATULINE DEPOT (lanreotide) Injection is a prolonged-release formulation containing lanreotide acetate, a synthetic octapeptide that has a similar biological activity similar to human somatostatin. Lanreotide was approved in 2007 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.

This efficacy supplement is supported by a single, multicenter, international, randomized (1:1), double-blind, placebo-controlled study (Trial 2- 55-52030-726) entitled "A Phase III, Randomized, Double-Blind, Stratified, Comparative, Placebo-Controlled, Parallel Group, Multicenter Study to Assess the Effect of Deep Subcutaneous Injections of lanreotide Autogel 120 mg Administered Every 28 days on Tumor Progression Free Survival in Patients with Nonfunctioning Entero-Pancreatic Endocrine Tumor." Key eligibility requirements were unresectable locally advanced or metastatic disease, well- or moderately-differentiated histology, and non-functional tumors. Prior to randomization, patients were evaluated for evidence disease progression in the 3 months prior to study entry; disease activity during this run-in period was the basis for stratification of randomization. Randomization was stratified by tumor progression status at enrollment (present vs. absent) and whether patients had received prior therapy for their NET. Patients were randomized to receive lanreotide 120 mg deep subcutaneous injection or matching placebo every 28 days until disease progression, unacceptable toxicity, or completion of 96 weeks of study drug administration. The primary efficacy endpoint was progression-free survival (PFS) as determined by independent radiology review, defined as the time to either disease progression or death, occurring within 96 weeks after first study treatment.

The trial was analyzed after enrollment was completed and the last patient completed 96 weeks of therapy. There were 204 patients accrued across 49 clinical sites, with 101 patients allocated to lanreotide and 103 patients allocated to matching placebo. The majority of patients were enrolled in Western Europe; with 15% of the study population was enrolled at 3 clinical sites in the U.S. Disease progression was present in nine of 204 patients (4.4%) in the 6 months prior to enrollment and twenty-nine patients (14%) received prior chemotherapy Nearly all (94.6%) patients had stable disease during the 6-month period prior to randomization; 86% had received no systemic therapy for treatment of neuroendocrine tumor; 45% of patients had pancreatic neuroendocrine tumors and 55% had gastroenteropancreatic neuroendocrine tumors.

At the interim analysis, performed with 70% of the planned number of events, the trial demonstrated a significant prolongation of PFS for the lanreotide arm [0.47 (95% CI: 0.30, 0.73); $p < 0.0002$, log-rank test]. The median PFS in the in the placebo arm was 16.6 months and had not been reached in the lanreotide arm at the time of the final analysis. Overall survival data were immature with no apparent differences between treatment arms.

Safety data were evaluated in 101 patients who received at least one dose of lanreotide. The most commonly (greater than or equal to 10%) adverse reactions of lanreotide were abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, and cholelithiasis. The most common severe adverse reaction of lanreotide observed in this trial was vomiting (4%).

Specific considerations during this review were

- Whether the benefit of a 53% improvement in progression-free survival (HR 0.47), with an improvement in median PFS time of more than 6 months, outweighed the risks of lanreotide treatment in this population with relatively indolent disease;
- Whether the benefits observed in patients with non-functional neuroendocrine tumors can be extrapolated to those with functional tumors;
- Whether the results can be extrapolated to the US population; and
- Whether to include in the Indication statement of the basis for the indication, given that somatostatin analogs are used for management of the hormonal symptoms of functional neuroendocrine tumors.

2. Background

Indication Population and Available Therapy

Gasteroenteropancreatic neuroendocrine tumors are uncommon cancers arising in the pancreatic, stomach, small intestine, appendix, colon or rectum. Pancreatic neuroendocrine tumors, which originate in islet cells, account for approximately 3% to 5% of all pancreatic cancers; there are approximately 1,000 new cases of pancreatic neuroendocrine tumors per year in the United States. Five-year survival is approximately 55% for resectable, localized tumors and 15% for unresectable, metastatic pancreatic neuroendocrine tumors.[1,2] Approximately 8,000 new cases of gastrointestinal neuroendocrine tumors are diagnosed in the United States annually[3]. The demographics and natural history vary by primary site of disease.[4]. Just over one-third of cases arise in the small intestine and one-third in the rectum, with the remainder occurring (in order of decreasing incidence) in the colon, stomach, and appendix. While the overall 5-year survival ranges from 60-90%, depending on primary site, 5-year survival rates range from 40-65%, with neuroendocrine tumors arising in the appendix having the best prognosis.

Somatostatin analogs can be effective in reducing the symptoms of functional tumors, however none are approved for treatment of the cancer itself. There are no FDA-approved drugs for the

[1] Ries LAG, Young JL, Keel GE, et al., eds.: SEER Survival Monograph: Cancer Survival Among Adults: U. S. SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute, 2007. NIH Pub. No. 07-6215.

[2] Exocrine and endocrine pancreas. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 241-9

[3] http://www.cancer.net/cancer-types/neuroendocrine-tumor/statistics; accessed December 13, 2014.

[4] Tsikitis VL, Wertheim BC, Guerrero MA. Trends of Incidence and Survival of Gastrointestinal Neuroendocrine Tumors in the United States: A Seer Analysis. *J Cancer* 2012; 3:292-302. doi:10.7150/jca.4502.

treatment of neuroendocrine tumors arising in the gastrointestinal tract; the following drugs are FDA-approved for pancreatic neuroendocrine tumors.

- Sutent (sunitinib) is indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. This approval was based on the results of a multi-center, international, randomized, double-blind placebo-controlled study conducted in patients with unresectable pNET. Patients were required to have documented RECIST-defined disease progression within the prior 12 months. Approximately half (49% of patients randomized to sunitinib and 52% of patients randomized to placebo) had non-functioning tumors. This trial demonstrated a statistically significant improvement in PFS (median 10.2 months versus 5.4 months), consisting of a 57% reduction in the risk of investigator-determined PFS [HR 0.43 (95% CI: 0.27 to 0.67); significant at interim analysis]..

- Afinitor (everolimus) is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (pNET) with unresectable, locally advanced or metastatic disease. This approval was based on the results of a randomized (1:1), double-blind, multi-center trial conducted in 410 patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (pNET) who had experienced disease progression within the prior 12 months. This trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), consisting of a 65% reduction in the risk of investigator-determined PFS [HR 0.35 (95% CI: 0.27 to 0.45); p<0.001].

- Zanosar (streptozocin) is indicated in the treatment of metastatic islet cell carcinoma of the pancreas. Approval is based on objective response rates, which have been reported in both functional and nonfunctional tumors.

Pre-Submission Regulatory History

July 1, 2010: Ipsen requested a Type C meeting with the Division of Gastrointestinal Drug Products to discuss the acceptability of ongoing clinical studies evaluating the safety and efficacy of Somatuline Depot in patients with non-functioning GEP-NET (b) (4) (b) (4) based on studies being conducted under IND 63239. Ipsen was advised to submit a new IND to the Office of Oncology Drug Products (now Office of Hematology and Oncology Products) and that the conduct of these ongoing studies be completed under this new IND.

November 4, 2010: A preIND meeting was held with the Division of Biologic Oncology Products (now Division of Oncology Products 2) to discuss the acceptability of the single protocol intended to support approval, Study 2-55-52030-726 (Study 726), supported by safety information obtained from the extension study, Study 2-55-52030-729 (Study 729). Key issues discussed were

- To modify the planned statistical test from the CMH to a log-rank test, either stratified or unstratified, depending on the number of patients within each stratum
- Inclusion of overall survival as a secondary endpoint,

- The requirement to demonstrate that the results could be extrapolated to the U.S. population,
- The need to minimize missing data to allow for a valid interpretation of progression-free survival (PFS) as a primary efficacy endpoint, and
- The analysis strategy for data collected from extension Study 729.

April 15, 2011: IND 109644 was submitted, containing updated versions of the ongoing Studies 726 and 729 with authorizations to cross reference IND 63239 and NDA 22074. The 30 day review period for this IND was waived.

August 25, 2011: Lanreotide acetate (Ipsen Biopharmaceuticals, Inc.) was granted orphan designation for "treatment of neuroendocrine tumors".

January 17.2014: PreNDA meeting was held to discuss the adequacy of the results of the single trial, Study 726, to provide the primary efficacy data to support filing of a supplement for the expanded labeling claim of treatment of GEP-NET, the acceptability of the proposed safety database, the acceptability of the proposed pharmacokinetic modeling approach to characterize the pharmacokinetics of lanreotide at the proposed dose and schedule for this new indication, and the content and format of the proposed NDA. Agreement was reached on all items.

3. CMC

I concur with the CMC reviewer states that there are no outstanding chemistry, controls, or manufacturing issues that preclude approval. No new CMC information was provided in this supplement and the request for categorical exclusion requested under 21 CFR 215.31(b) has been reviewed and found to be acceptable. The CMC reviewer also concurred with minor editorial changes to Sections 3, 11, and 16 of product labeling to provide the volume, as well as strength, for each presentation.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The supplement contained information from the following studies:

- pharmacokinetic, efficacy, and safety data from Study 726, a randomized, double-blind trial conducted in patients with asymptomatic GEP NETs, in which 101 patients received lanreotide 120 mg by deep subcutaneous injection (SC) every 4 weeks

- pharmacokinetic and safety data from Study 729, an open-label safety and access trial that enrolled 88 patients with asymptomatic GEP NETs who received lanreotide 120 mg SC every 4 weeks
- pharmacokinetic and immunogenicity data from a randomized, double-blind trial (Study 730 (n=11) and three open-label studies, Studies 166 (n=30), Study 216 (n=26), and Study 718 (n=71) in which patients with asymptomatic and symptomatic GEP NETs were treated with lanreotide 120 mg SC every 4 weeks

The mean steady state trough serum lanreotide concentrations ranged from 5.3 to 8.6 ng/mL and steady state was reached after 4-5 injections at 120 mg SC every 4 weeks. The Cmax and AUC are higher in patients with GEP-NETs than those with acromegaly, likely reflecting administration of higher doses administered. Based on population PK analyses, data from sparse PK sampling in Studies 726, 720 and 166, there was no evidence of clinically important impacts of weight, gender, age, or race on lanreotide pharmacokinetics. There was no significant effects of renal function on lanreotide clearance however there were no patients with Childs Pugh B or C enrolled in GEP-NET clinical trials , thus the impact of hepatic function on lanreotide clearance could not be assessed.

Pharmacokinetic, safety, and efficacy data from Study 726 were used to assess for exposure-response and exposure-toxicity relationships in exploratory analyses. There was no evidence of a correlation between exposure and efficacy, based on similar progression-free survival curves across subgroups defined by lanreotide exposure (exposure quartiles) and all quartiles appeared to provide an improvement in PFS as compared to the placebo group as a whole. There was also no evidence of an exposure-toxicity relationship in an exploratory analysis comparing the incidence of the following common adverse reactions of lanreotide by lanreotide exposure (quartiles): diarrhea, abdominal pain, vomiting, and hypertension.

Assessment of the immunogenicity of lanreotide was conducted using data from multiple clinical trials (Studies 726, 730, 718, and 166). The incidence of anti-lanreotide antibodies was variable across these studies, ranging for 0.9% in Study 730 (at 48 weeks) to 10.4% after 48 weeks in Study 726; the incidence of anti-lanreotide antibodies after 96 weeks was 11%. There was no assessment for neutralizing antibodies in Study 726. The development of anti-lanreotide antibodies did not affect the pharmacokinetics of lanreotide; there were too few patients to determine the effects of development of anti-lanreotide antibodies on efficacy.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Ipsen relied on the results of a single, randomized (1:1), double-blind, placebo-controlled, multi-center, multinational trial enrolling in 204 patients with asymptomatic, moderately- or well-differentiated, unresectable or metastatic, gastroenteropancreatic neuroendocrine tumor. The trial was initiated prior to discussion with the Office of Oncology Drug Products; while

the design was generally acceptable, the trial was modified at FDA's request to include an analysis of overall survival and to modify the analysis plan for the primary endpoint.

The trial was designed to detect a large treatment effect on progression-free survival, which has served as the basis for approval in two other drugs indicated for treatment of pancreatic neuroendocrine tumors. The study was blinded and given the modest increase (generally 10%) in adverse reactions over the background incidence in this patient population, the study blind was likely to have been maintained. However, Ipsen chose to retain a contract research organizatio (b) (4) to conduct an independent radiologic review for determination of disease progression.

During review of this efficacy supplement, bioresearch monitoring inspections were performed for the two high accruing sites and the firm conducting the independent radiologic review. Based on the inspections, the data provided were determined to be reliable.

There was no investigation for optimal dosing. The dose and schedule tested appears to be tolerable with 5% of patients discontinued treatment for adverse reactions (as compared to 3% in the placebo arm), however whether lower doses may also be effective is not known.

Trial Design

The primary objective was progression-free survival. Secondary objectives were PFS rates at 48 and at 96 weeks; time-to-progression; overall survival; assessment of effects on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)- C30 and EORTC QLQ-GI.NET21 questionnaires; effects on plasma chromogranulin A (CgA) and other tumor peptide markers with elevated level at baseline; characterization of toxicity profile of lanreotide 120 mg every 28 days; incidence anti-lanreotide antibodies; assessment of pharmacokinetic profile of lanreotide in this patient population.

Key inclusion criteria were centrally confirmed histologic diagnosis of GEP-NET; metastatic or unresectable disease; measurable disease per RECIST; absence of tumor hormone-related symptoms or gastrinoma controlled by proton-pump inhibitors; well- or moderately-differentiated tumor; Ki67 <10%; Krenning score ≥ Grade 2 per octreoscan within 6 months of study entry, and WHO PS ≤2. Patients with the following were ineligible: treatment with a somatostatin analog; treatment with radionuclide at any time or with interferon, chemoembolization or chemotherapy within 6 months prior to study entry; and a history of multiple endocrine neoplasia (MEN).

Treatment Plan: Patients were registered with tumor assessments performed at study visit 1 and again at study visit 2, 12-13 weeks later, to assessment for disease progression. Following the second visit, patients were randomized (1:1) to receive lanreotide 120 mg or matching placebo by deep subcutaneous injection every 28 days until disease progression, unacceptable toxicity, or a maximum of 24 injections (96 weeks on study). Randomization was stratified by evidence of disease progression in the preceding 12-13 weeks (yes/no) and prior therapy (yes/no).

Monitoring plan: Patients were monitored for tumor status by physical examination and CT scans at Study visit 2 /initiation of lanreotide/placebo and weeks 12, 24, 36, 48, 72, and 96

weeks post-initiation of study drug or until documentation of progressive disease by the independent radiology committee.

Analysis plan: The original analysis plan specified that172 patients (86 patients per arm) were to be enrolled and that the final analysis would be conducted after 120 PFS events, to achieve 80% power to detect an improvement in PFS (HR 0.80) at a two-sided significance level of 0.05 for the lanreotide arm compared with placebo. The primary efficacy analysis was based on determination of PFS by an independent imaging review committee.

The analysis plan was revised to include a plan for sample size re-estimation based on the assumption of a constant hazard ratio (HR) of 0.57 over time, to increase the sample size to 200 patients, and to require the final analysis after 132 events. The sample size of 200 patients (100 per arm) was required to ensure a total of 132 PFS events, which would have 90% power to detect a significant difference in at a 0.05 two-sided significance level, assuming a median PFS of 41.3 weeks in the placebo arm and 72.6 weeks in the lanreotide arm, with a constant hazard ratio of 0.57.

Key amendments:

- April 30, 2008: extension study (Study 729) opened to allow patients to continue on lanreotide after 96 weeks or to receive lanreotide if previously receiving placebo.
- March 5, 2010: Addition of sensitivity analyses for the primary efficacy analysis
- February 11, 2011: Changes to test method for the primary analysis of PFS to the log rank test instead of testing for significance according to the Cox Proportional Hazards Ratio model, based on FDA's advice; added overall survival as a secondary endpoint, per FDA's request; limited the number of sample size re-estimations to one

Results

A total of 204 patients were enrolled and randomized (101 to lanreotide and 103 to placebo) with the first patient visit on June 22, 2006, the last patient visit was April 9, 2013, closure of the trial on closed May 2013 and the database lock was April 24, 2013.

Across the entire study population, the median patient age was 63 years (range, 30-92 years) and 95% were Caucasian. Disease progression was present in nine patients (4.4%) in the 6 months prior to enrollment and twenty-nine 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 lanreotide arm and 27% of patients in the placebo arm who had hepatic involvement by tumor of > 25%. The baseline demographics and prognostic characteristics of patients enrolled in the US were similar to the study population enrolled outside the US. In addition, the diagnosis and management in the US and Western Europe (the highest accruing region) are similar.

A blinded sample size re-estimation was planned when the first 100 patient had been randomized and treated on study, died or progressed after 1 year, or after 66 events, whichever

occurred first; the analysis was performed on June 16, 2010 and the sample size was not modified based on this analysis. The analysis of PFS occurred after 92 PFS and is considered to be an interim analysis by FDA; after adjustment of the alpha level for this interim analysis, the statistical reviewer concurred that this analysis was statistically significant. The effects on PFS were consistent across exploratory subgroups defined by gender, age, primary site (pancreas vs. other), and region (US vs. Western Europe vs. Eastern Europe and India). An analysis of overall survival was performed, after 36 deaths and showed no difference between arms at this early look requested by FDA [HR 0.97 (95% CI: 0.50, 1.90)].

Efficacy results are summarized in the following table and figure, abstracted from the package insert:

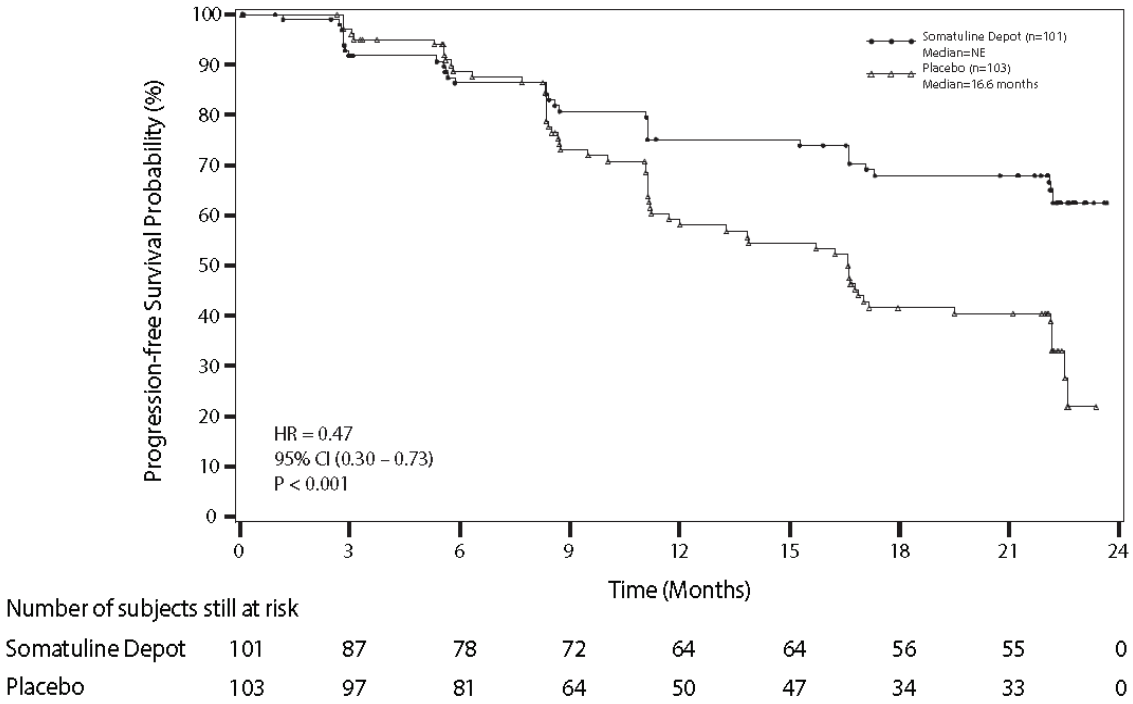
Efficacy Results in Study 726

	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 24 months

2: Hazard Ratio is derived from a Cox stratified proportional hazards model

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



8. Safety

The safety database for this supplement includes the safety information contained in the original approval of lanreotide 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 7 years of post-marketing surveillance reports, and the results of Study 726, a randomized, placebo controlled trial in which 101 patients with gastroenteropancreatic neuroendocrine tumors received lanreotide at a dose of 120 mg by deep subcutaneous injection every 4 weeks for up to 2 years (96 weeks). In Study 726, 87 patients were exposed to lanreotide for more than 6 months and 72 patients were exposed to lanreotide for more than one year. Five of the 101 (5%) patients in the lanreotide arm discontinued treatment for treatment-emergent adverse reactions.

Lanreotide is labeled for the following serious and potentially serious risks: cholelithiasis, hyperglycemia and hypoglycemia, thyroid function abnormalities, and cardiovascular abnormalities. In Study 726, an increased risk of bradycardia, hyperglycemia, and new onset cholelithiasis/gallbladder sludging were observed but did not result in serious adverse events. Among the 81 patients with baseline heart rates of $\geq$ 60 beats per minute (bpm) in the lanreotide arm, the incidence of heart rate < 60 bpm was 23% (19/81) as compared to 16 % (15/94) of placebo treated patients; ten patients (12%) had documented heart rates < 60 bpm on more than one visit. The incidence of hyperglycemia was also increased in the lanreotide arm as compared to placebo (14% vs. 5%); however there were no patients with severe hyperglycemia. Finally, there was a higher incidence of new onset cholelithiasis or sludging for lanreotide-treated patients (40% vs. 17%); based on cross-study comparisons, this may be a dose-dependent finding.

The table below, abstracted from the package insert, lists the adverse reactions reported with an incidence of >5% in patients receiving lanreotide and which occurred frequently in the lanreotide arm than in the placebo arm.

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

In Study 726, development of anti-lanreotide antibodies was assessed. the incidence of anti-lanreotide antibodies was 3.7% (3/82) at 24 weeks, 10.4% (7/of 67) at 48 weeks, 10.5% (6 of 57) at 72 weeks, and 9.5% (8 of 84) at 96 weeks in lanreotide-treated patients, as determined by using a radio-immunoprecipitation assay. Development of anti-lanreotide antibodies did not appear to have any impact on pharmacokinetics or increase the risks of adverse reactions. Assessment for neutralizing antibodies was not conducted.

- *REMS*
  There is no REMS for lanreotide for the previously approved indication, with 7 years of marketing experience. I concur with the clinical review team that a REMS is not required to ensure safe and effective use of lanreotide for the indicated population.

- *PMRs and PMCs*
  No post-marketing requirements were identified by the clinical review team based on out outstanding safety issues. A post-marketing commitment was considered to request the results of the final analysis of overall survival, as requested for sunitinib and everolimus

for approvals in a similar population. However the basis for the post-marketing requirements for sunitnib and everolimus were to ensure no long-term adverse impact on overall survival, given the serious risks of each drug. In contrast, serious adverse reactions were uncommon in Study 726 and the quality of the potentially serious adverse reactions with lanreotide as described in the Warnings and Precautions section of the approved label indicate that, as in Study 726, the described adverse reactions are not often serious (resulting in death, hospitalization, or need for medical intervention). Based on all these considerations, a post-marketing requirement was not imposed to assess for potential adverse effects on survival.

9. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee the safety profile is acceptable for treatment of neuroendocrine tumor without disease progression in the preceding 6 months, the clinical trial design is similar to that use for other products approved for this indication and the application did not raise significant safety or efficacy issues that were unexpected or unacceptable for the intended population.

10. Pediatrics

Orphan designation was granted for lanreotide for the treatment of neuroendocrine tumors on August 25, 2011, therefore this supplement was not subject to the requirements of the Pediatric Research Equity Act (PREA) for the proposed indication.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling:
  - Indications and Usage: the indication statement was modifie (b) (4) (b) (4) in order to provide clarity on the basis for use, since somatostatin analogs are used on- and off-label for control of tumor-related hormonal symptoms. In addition, the indication was revised to include both functional and non-functional tumors. Although Study 726 was conducted in patients without hormonal symptoms in order to allow for a placebo control arm, there is no scientific basis for concluding that lanreotide would not be effective in patients with functional tumors. In addition, data from Studies 718 and 730 conducted in patients with functional GEP-NETs showed that lanreotide at the to-be-recommended dose (120 mg every 28 days) can result in symptomatic relief.
  - Dosage and Administration: A new subsection corresponding to the recommended dose was included.

- Dosage Forms and Strengths: Revised to include volume as well as strength for each presentation.
- Warnings and Precautions: Revised to describe the incidence of bradycardia and recommendations, which may require clinical assessment and/or dose modification. Although the incidence of cholilithiasis and hyperglycemia were also increased for lanreotide-treated patients in Study 726, these findings would not require actions on the part of the physician that differ from current recommendations for monitoring. This information is described in Section 6.
- Adverse Reactions: Revised to include a description of the safety database for this expanded indication and to include a tabular listing of selected adverse reactions occurring at an incidence of ≥5% and which were more frequent in lanreotide-treated patients as compared to the placebo group. In addition, information on the incidence of anti-lanreotide antibody formation was also included.
- Use in Specific Populations: Described the results of population PK analyses, requiring no dose modification for renal insufficiency but for which there is inadequate data to describe recommended modifications for hepatic dysfunction.
- Clinical Pharmacology: Described the results of population PK analyses, requiring no dose modification for renal insufficiency but for which there is inadequate data to describe recommended modifications for hepatic dysfunction.
- Clinical Studies: Described the results of Study 726; edited for brevity; demonstration information described in text rather than tabular forma; remove (b) (4) (b) (4) and remove (b) (4) (b) (4)

- Carton and immediate container labels: Carton and container labeling were revised to include new NDC numbers for the presentation approved under Supplement 10, on October 2014.

- Patient labeling/Medication guide:

  - A medication guide was not required to ensure safe use of lanreotide for this expanded indication.
  - The approved Patient Labeling was modified to include information on the expanded labeling claim; additional editorial changes to limit redundancy and substitution with language at a 6th grade reading level were included.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Metastatic or unresectable, gastroenteropancreatic neuroendocrine tumors are rare cancers, with an estimated incidence of less than 20,000 new cases in the US annually, although survival varies depending on the primary site, 5-year survival ranges from 40-65%; thus patients are in need of effective therapies that prolong life or delay

symptomatic progression. Even in patients with asymptomatic disease and no evidence of disease progression within the preceding 3 months, median progression-free survival was 16.6 months for patients receiving placebo in Study 726; at which time treatment with either everolimus or sunitinib, may be indicated. Thus there is a benefit to patients to delay disease progression and need for agents with clinically important risks for 6 months or longer.

Study 726 demonstrated a clinically important increase in median progression-free survival of up to 6 months and possibly longer. In light of the low incidence of severe side effects and ability of nearly all patients (≥95%) to tolerate lanreotide for up to two years, the benefit:risk ratio is favorable. The results observed in Study 726, which are largely driven by patients enrolled in Western Europe, are considered to be relevant to patients in the US, based on similarity of patient management in the US and Western Europe and are also likely to be relevant to patients with non-functioning tumors, based on knowledge of tumor biology and results of the supportive trials, 718 and 730. All members of the review team recommended approval of this supplement..

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  A Risk Evaluation and Mitigation Strategy (REMS) is not required for safe and effective use of lanreotide for the treatment of neuroendocrine tumors.

- Recommendation for other Postmarketing Requirements and Commitments
  No post-marketing requirements have been identified as there were no new serious risks identified and there are no unaddressed safety concerns. Specifically, a post-marketing requirement was not imposed for the final analysis of overall survival, to determine whether lanreotide had any adverse effects on survival, since the incidence of serious adverse drug reactions is low (≤ 3% in Study 726) and drug-related toxicity is not expected to result in impaired survival.

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/s/

PATRICIA KEEGAN
12/16/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

OFFICER/EMPLOYEE LIST

Officer/Employee List
NDA 22074/S-11

The following officers or employees of FDA participated in the decision to approve this BLA and consented to be identified:

Ayalew, Kassa
Biable, Missiratch (Mimi)
Demko, Suzanne
Fuller, Barbara
Gwise, Thomas E
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Yuan, Weishi (Vivian) (CDER)
Zhao, Hong (CDER)
Zhao, Liang
Zhou, Liang

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022074/S-11
Priority or Standard	Priority
Submit Date(s)	June 23, 2014
Received Date(s)	June 30, 2014
PDUFA Goal Date	December 30, 2014
Division / Office	DOP2
Reviewer Name(s)	Joohee Sul
Team Leader	Suzanne Demko
Review Completion Date	November 26, 2014
Established Name	Lanreotide acetate injection
(Proposed) Trade Name	Somatuline® Depot®
Therapeutic Class	Somatostatin analog
Applicant	Ipsen Pharma
Formulation(s)	Prolonged release injection
Dosing Regimen	120 mg every 4 weeks
Indication(s)	Treatment of gastroentero-pancreatic neuroendocrine tumors (GEP-NET)
Intended Population(s)	Adults with GEP-NET

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical team recommends regular approval of this supplemental NDA for lanreotide Depot® (lanreotide) in the treatment o (b) (4)
(b) (4)

This sNDA is primarily supported by a single, multi-center, international, randomized, placebo-controlled trial, study 2-55-52030-726 (Study 726) also referred to as the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET). The recommendation for approval is based on clinical data that supports the conclusion that lanreotide prolongs progression-free survival (PFS) for patients with unresectable, well or moderately differentiated, non-functioning, locally advanced or metastatic GEP-NETs, compared to placebo.

There are limitations of relying on results from a single clinical trial to demonstrate effectiveness; however, this submission provides sufficient evidence to support approval as outlined in "FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products". This guidance document states that *"...reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible"*. It is the clinical team's assessment that the results of Study 726 meet these criteria.

1.2 Risk Benefit Assessment

This NDA includes the final study report for Study 726 that demonstrates evidence of substantially improved PFS in patients with GEP-NET. Review of the safety profile did not identify risks associated with lanreotide therapy in this patient population that would offset its demonstrated benefits; therefore, the risk/benefit assessment favors full approval of lanreotide for the treatment o (b) (4)
(b) (4)

Analysis of the primary endpoint:
GEP-NET is a rare disease and is classified by the Food and Drug Administration (FDA) as an orphan indication. One clinical study was conducted to demonstrate the efficacy and safety of lanreotide 120 mg in the treatment of patients with GEP NETs; Study 726 was a multicenter, international, placebo-controlled, randomized clinical trial with a pre-specified duration of two years. This two year duration was determined to be clinically meaningful by experts in

neuroendocrine tumors (NET) during an Applicant directed advisory board for designing the protocol.

The primary endpoint was to assess the effect of lanreotide compared to placebo on PFS in patients with well or moderately differentiated, non-functioning, locally advanced or metastatic GEP-NETs. PFS has been used as the basis for approval in other oncology indications, and an intermediate endpoint such as PFS may be suitable for rare and indolent tumors; however, the relationship between PFS and survival in GEP-NET is uncertain. In general, whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk/benefit of the treatment compared to available therapies.

A total of 101 patients were treated every 4 weeks with lanreotide 120 mg and 103 patients received placebo every 4 weeks on Study 726. Disease status was assessed by independent central radiology review (IRRC), and in the pre-specified PFS analysis patients randomized to treatment with lanreotide had a median PFS > 22 months (not yet reached) compared to 16.5 months for those receiving placebo (see section 6.1.4.1).

Analysis of risk:
The safety profile of lanreotide was consistent with the known toxicity profile of lanreotide found in current prescribing information for the treatment of patients with acromegaly. The rates of discontinuation due to adverse events (AEs) were low in both arms (5/103 and 3/101patients in the lanreotide and placebo arms, respectively). Treatment emergent serious AE (SAEs) occurred in 25 patients (25%) on the lanreotide arm and 30 patients (29%) on the placebo arm. Adverse reactions occurring more frequently in the lanreotide arm included abdominal pain, musculoskeletal pain, injection site reactions, vomiting, headache, hyperglycemia, hypertension (HTN) and cholelithiasis. Two patients on each treatment arm died during the study.

Given the variable and often indolent disease course of some GEP-NETs, the optimal timing of treatment in asymptomatic patients is unclear and the supposition that all patients, including those with stable disease or slowly progressive disease, will derive benefit from delayed disease progression is uncertain. Guidelines from the European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Society (NANETS) suggest initiation of a somatostatin analog (SSA) in patients with unresectable, asymptomatic, somatostatin-receptor positive, well-differentiated GEP-NETs and a high tumor burden, while observation is generally recommended for patients with low volume disease, with initiation of SSA therapy if there is evidence of clinically meaningful tumor progression. Disease surveillance in patients with non-functioning GEP-NET is a reasonable and well-established approach to patient management. In this clinical setting, the risk of anti-tumor therapy may be considered to outweigh the benefits of delay in radiographically detected but clinically asymptomatic disease progression. Only nine patients in Study 726 had disease progression at baseline, prior to study entry. In order to assess the risk/benefit of treatment for these patients, we endeavored to consult with experts in the field of NET; however, at the time this review, a consult is still pending. Consult recommendations and conclusions may be provided in an amendment to this review.

Conclusion:
We recommend approval of lanreotide for this rare disease based on the totality of the data. The investigator and FDA analyses revealed an improvement in median PFS with hazard ratios (HRs) ranging from 0.41 (FDA analysis) to 0.47 (Applicant analysis). The PFS improvement is consistent across subgroups and in post-hoc sensitivity analyses (see sections 6.1.4.1 and 6.1.7).

Furthermore, the trials supporting approval of available therapies for patients with GEP-NET have been largely limited to patients with pancreatic NET (pNET); therefore, there remains an unmet medical need for treatment of NETs arising from sites outside the pancreas. Fifty-five percent of patients (113/204) enrolled in Study 726 had tumors arising in the mid-gut, hind-gut, other sites or unknown primary site of disease. Based on a subgroup analysis, the treatment effects in patients with NETs outside the pancreas were consistent with the overall findings of the study (see section 6.1.7).

1.2 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional clinical post-marketing risk management activities are required for this approval indication.

1.3 Recommendations for Postmarket Requirements and Commitments

The primary endpoint for Study 726 was PFS, and overall survival (OS) was not specified as an endpoint until approximately 5 years after study initiation and is subsequently difficult to interpret due to low events and missing data. A post marketing commitment (PMC) to conduct an additional study with OS as a primary endpoint could be considered; however, given that GEP-NETs are an uncommon disease, additional randomized studies would be difficult to enroll and complete in a timely fashion to verify clinical benefit; it took approximately 7 years to complete Study 726 in a multi-national environment. In addition, further placebo-controlled trials using lanreotide may prove difficult to accrue given the evolving treatment landscape of GEP-NET.

Nonetheless, the final analysis of OS for Study 726 may be helpful to place the improvement in PFS in the context of the overall safety of lanreotide. Therefore, FDA may ask the applicant to submit the results of the final analysis of OS data from Study 726 to further characterize the safety and efficacy profile of lanreotide in treating GEP-NET tumors.

2 Introduction and Regulatory Background

Neuroendocrine tumors are a relatively rare, clinically diverse group of malignancies that originate most commonly from the gastrointestinal tract and pancreas (GEP-NETs). The annual incidence in the United States is roughly 5.25 per 100,000[1], and appears to increasing[2]. These tumors can arise in the setting of inherited genetic syndromes such as multiple endocrine

neoplasia (MEN) 1 and 2; however, most occur sporadically and are generally classified by site of origin, stage and tumor differentiation.

GEP-NETs are characterized as functional or non-functional depending on whether or not they secrete peptide hormones that result in clinical symptoms, and these tumors are named to reflect the hypersecreted hormone (e.g. insulinoma, gastrinoma, etc.) The clinical symptoms associated with functional tumors frequently lead to their diagnosis at an earlier stage compared with non-functional tumors that often present with symptoms related to mass effect or metastatic disease. The World Health Organization (WHO) classifies all GEP-NET into low-grade (G1), intermediate grade (G2), and high grade (G3) categories based upon mitotic count and proliferative index or Ki-67. The natural history of GEP-NET varies considerably and appears to be affected by the primary site of disease, degree of differentiation and presence of metastases at diagnosis.

Initial treatment of GEP-NET consists of wide surgical resection if feasible and treatment of hormone-related symptoms; the approach is determined by the rate of disease progression and presence of symptoms. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option, while SSAs are used for patients with hormone-related symptoms. Patients with progressive or metastatic disease may receive treatment with chemotherapy, targeted therapies, radiolabelled SSA, interferon or hepatic artery embolization. None of these therapies has demonstrated significant prolongation of survival. Although SSA were primarily used to manage the hormonal symptoms related to NETs, *in vitro* studies have demonstrated the potential for SSAs to exert antiproliferative activity[3] and clinical studies have demonstrated prolonged PFS in patients with NETs treated with octreotide and lanreotide [4-6].

Lanreotide first received regular approval in the US on August 30, 2007 for the following indication:

> *"Somatuline Depot (lanreotide) 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".*

The evaluation of efficacy for this indication was based on two controlled studies conducted in 171 patients with acromegaly.

2.1 Product Information

Drug Established Name:	Lanreotide
Trade Name:	Somatuline® Depot® (US)
Drug class:	Polypeptide somatostatin analog, binds to somatostatin receptors
Applicant:	Ipsen Pharma
Approved Indications:	Acromegaly
Approved Dose:	Dose range of 60 mg to 120 mg every 4 weeks
Proposed Indication:	Gastroenteropancreatic neuroendocrine tumors
Proposed Dose:	120 mg every 28 days

2.2 Tables of Currently Available Treatments for Proposed Indications

It is important to distinguish between current available therapies for GEP-NET aimed at symptomatic control and those aimed at tumor control. There are three FDA approved systemic therapies for treatment of pNET based on data supporting their antiproliferative effects:

- Streptozocin (Zanosar) is an alkylating agent approved in 1982 based on response rates observed in patients with functional and nonfunctional pancreatic islet cell tumors. It should be noted that the criteria used to define response in these trials were less rigorous than current standards; in addition to CT scans, liver-spleen scans, physical examination findings, and in some cases reduction in hormone levels were accepted as evidence of a response. Streptozocin-based combination therapy with other cytotoxic agents such as doxorubicin and 5-fluorouracil (5-FU) has been shown to result in objective tumor response.

- Sunitinib (Sutent) is a receptor tyrosine kinase inhibitor that primarily targets vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Sunitinb was approved in 2011 for the treatment of patients with progressive, locally advanced or metastatic pNET based on improved PFS.

- Everolimus (Afinitor) is a mammalian target of rapamycin (mTOR) kinase inhibitor that was also approved in 2011 for the treatment of patients with progressive, locally advanced or metastatic pNET based on improved PFS.

Octreotide acetate (Sandostatin) is a SSA approved by the FDA in 1998 for symptomatic treatment of diarrhea and flushing episodes associated with carcinoid syndrome and vasoactive intestinal peptide tumors (VIPomas). Octreotide may control disease related hormonal symptoms; however the studies were not designed to show an effect on the size, rate of growth, or progression of carcinoid tumors or VIPomas.

Table 1: FDA approved therapies for GEP-NET

DRUG	YEAR	INDICATION	BASIS FOR APPROVAL
Streptozocin (Zanosar®)	1982	Treatment of metastatic islet cell carcinoma of the pancreas limited to patients with symptomatic or progressive metastatic disease	Response rates observed in patients with functional and nonfunctional pancreatic islet cell tumors.
Octreotide (Sandostatin ® LAR Depot)	1998	Symptomatic treatment of metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.	Similar control of symptoms and degree of reduction of urinary 5-HIAA levels among 67 patients treated with sandostatin LAR and 26 patients with sandostatin injection.
Sunitinib (Sutent®)	2011	Treatment of progressive, well-differentiated pNET in patients with unresectable locally advanced or metastatic disease	Results of a randomized, double-blind, placebo-controlled study demonstrating a statistically significant improvement in PFS [median 10.2 vs 5.4 months, HR 0.43 (95% CI: 0.27, 0.67); p 0.001]
Everolimus (Afinitor®)	2011	Treatment of advanced pancreatic neuroendocrine tumors (pNET)	Results of a randomized, double-blind trial of patients with locally advanced or metastatic pNET and disease progression, demonstrating a statistically significant improvement in PFS [median 11.0 vs. 4.6 months, HR 0.35 (95% CI: 0.27, 0.45); p 0.001].

Other cytotoxic agents such as dacarbazine, temozolomide, and platinum based therapies have demonstrated activity in NETs when used in combination regimens or as single agents[7-9]. Localized therapy using chemoembolization and targeted radiotherapy using radiolabeled SSA may also be administered to patients with refractory disease[10-12].

In summary, the approved therapies for treatment of GEP-NET are largely limited to the pNET indication, although they may be used off-label for treatment of GEP-NETs arising outside the pancreas.

2.3 Availability of Proposed Active Ingredient in the United States

Lanreotide was approved in the US on August 30, 2007 for the long-term treatment of patients with acromegaly who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.

2.4 Important Safety Issues With Consideration to Related Drugs

Lanreotide is a polypeptide SSA that shares a common mechanism of action with octreotide. Adverse reactions reported with octreotide include sinus bradycardia, chest pain, fatigue, headache, malaise, fever, dizziness, hyperglycemia, diarrhea, cholelithiasis, biliary sludge, arthropathy, myalgia, dyspnea, and flu-like symptoms. Less commons side effects include hypothyroidism, depressed vitamin B12 levels, and cardiac conduction abnormalities.

Streptozocin is a cytotoxic chemotherapy that frequently causes gastrointestinal toxicity including nausea, vomiting and diarrhea. It can also induce renal and liver dysfunction, myelosuppression and hypoglycemia. Since it carries a substantial risk of renal toxicity, the product label states that therapy with this drug should be limited to patients with symptomatic or progressive metastatic disease.

Common adverse events reported with sunitinib include diarrhea, nausea/vomiting, fatigue, HTN, hand-foot syndrome, stomatitis, neutropenia, and thrombocytopenia. Hemorrhage, renal failure, hepatic toxicity, ventricular arrhythmia and cardiac failure have also been reported.

The most common adverse reactions associated with everolimus include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, cough, headache and decreased appetite. Non-infectious pneumonitis has also been associated with everolimus. Inhibitors of mTOR kinase are known to cause hypersensitivity (anaphylactic reactions), creatinine elevations and hyperglycemia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There was no Special Protocol Assessment related to this submission.

- November 2010: Type B, pre-IND meeting with Division of Biologic Oncology Products, now Division of Oncology Products 2 (DOP2)
    - Discussed the planned statistical methods for primary efficacy analysis and supportive sensitivity analyses. FDA recommended that the primary analysis be changed from the Cox proportional hazards (PHs) model to either a stratified or unstratified log rank test. FDA also recommended OS should be investigated as a secondary endpoint.
    - Discussed the requirement for the population to be representative of the US population
    - FDA emphasized the need to minimize missing data to allow for a valid interpretation of PFS as a primary efficacy endpoint, and the analysis strategy for data collected from extension Study 729
    - Discussed concerns related to the potential for unintentional unblinding

- April 2011: New IND (109644) submitted for the indication of NET to the Office of Oncology Drug Products, now Office of Hematology and Oncology Products (OHOP).

- August 2011: Lanreotide granted Orphan Drug Designation for treatment of NETs.

- January 2014: Type C, pre-sNDA meeting with DOP 2
    - The scope of the Integrated Summary of Safety (ISS) was revised based on the FDA's comments
    - FDA considered that based on the summary information provided there was sufficient evidence of efficacy obtained in an adequately designed trial to support the filing of a sNDA

- FDA did not agree with the Applicant's pla (b) (4)
(b) (4)

2.6 Other Relevant Background Information

There have been no market withdrawals or other significant issues outside the US.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall submission quality of this NDA was satisfactory. The data were well organized, and for the most part easy to navigate. There were minor difficulties with hyperlinks, but these did not interfere with the timely review of this submission. Requests for additional information were submitted to the Applicant on August 8, 2014 and November 12, 2014, and responses were prompt.

3.2 Compliance with Good Clinical Practices

According to the Applicant, Study 726 was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP). The study protocol, amendments and the informed consent document (ICD) were reviewed and approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) prior to commencement of the study in all countries where the study was conducted. Written informed consent was obtained from each participant in Study 726 before initiation of any study related procedures.

FDA CDER Office of Scientific Investigations (OSI) visited site 616005 in Poland and site 840003 in the US. Site 616005 was a site of relatively high accrual enrolling a total of 29/204 patients representing 14 % of the study population. In addition, there were forty-one patients screened at this site and twenty patients who did not enroll on study, indicating a high screen failure rate. Site 840003 enrolled fourteen patients in the US, the highest of the three US sites.

Table 2: Sites of Inspection by OSI

Site number Site Location	Site PI	Patients Screened/ Randomized	Inspection Date	Final Classification
#616005 Diagnostic Radiology Department, Central Clinical Hospital of the Ministry of Interior in Warsaw UL Woloska 137, 02-507 Warsaw, Poland	Dr. Jerzy Walecki	41/29	November 12-18, 2014	Pending Interim classification: NAI
#840003 MD Anderson Cancer Center, Gastrointestinal Medical Oncology, 1515 Holcombe Blvd Houston, TX 77030-4009, USA	Dr. Nageshwara Vijaya Arvind Dasari	24/14	October 28 – November 7, 2014	Pending Interim classification: VAI

NAI: No deviation from regulations
VAI: Deviation(s) from regulations
Pending: Preliminary classification based on information in 483 or preliminary communication with the field.

The Clinical Inspection Summary from OSI states that based on a review of preliminary inspection findings and on available information for clinical investigators (Dr. Jerzy Walecki and Dr. Nageshwara Vijaya Arvind Dasari) Study 726 data submitted in support of sNDA 22074 S-11 appear reliable. Please see Dr. Lauren Iacono-Connors Clinical Inspection Summary dated November 24, 2014 for full details.

The following are excerpted from Dr. Iacono-Connors summary:

Regarding site #616005:
"*Generally, the investigator's execution of the protocol was found to be adequate. There was no evidence of underreporting of adverse events. The records were well organized. Review of source documentation for eligibility, randomization, treatment regimens, AE reporting, and study drug administration cycles, and drug accountability found no discrepancies. The primary efficacy endpoints were supported by source documentation at the site. There were a few minor discussion points at the conclusion of this inspection. A Form FDA 483 was not issued.*"

Regarding site #840003:
"There were multiple protocol deviations for out of window protocol-specified procedures such as labs and EKGs. The site did receive a sponsor waiver for the EKG protocol deviations. These observations were discussed with the site. The site did not always obtain informed consent from each human subject prior to conducting study-related tests. A one item Form FDA 483 was issued".
"Dr. Dasari's site did not always obtain informed consent from each human subject prior to conducting study-related tests. Specifically, the study informed consent document included an option to participate in an investigational product (IP) PK substudy. Subjec (b) (6) *and* (b) (6) *did not consent to participate in the additional blood draws for IP PK analyses. However,*

the site took blood samples from Subject [redacted] an [redacted] and shipped these samples to the Sponsor's central laboratory for analysis. Based upon information and documentation found at the site, the site staff found the errors and notified the central laboratory on January 2010 and October 2011, of these errors associated with Subject [redacted] an [redacted] an [redacted] respectively, and requested they destroy the "tubes received". Therefore, these observations should not impact PK data submitted to the application."

Reviewer comment: Notwithstanding the inspection observations noted above for Dr. Dasari's site, the data from Study 726 submitted in support of this sNDA appear reliable.

3.3 Financial Disclosures

In accordance with 21 CFR § 54.4(a)(3)(i)-(iv), the Applicant provided a list of all clinical investigators with disclosable financial interest or arrangements who participated in covered clinical studies (Study 726 and 729) as defined in 21 CFR 54.2(e).

Contents of the submission include:

- Form 3454, certifying that 182 of 190 investigators for Study 726 and twenty-one of twenty-five investigators for Study 729 had no financial arrangement as defined in 21 CFR 54.2(a), had no proprietary interest in the product or significant equity interest in the covered studies as defined in 21 CFR 54.2(b) and was not the recipient of significant payments as defined in 21 CFR 54.2(f). There were no investigators who did not respond or could not be reached despite due diligence.
- Form 3455 disclosed that seven of the 190 investigators for Study 726 and four of twenty-five investigators for Study 729 had significant payments that exceeded the $25,000 threshold for significant payments of other sorts as defined in 21 CFR 54.4(a)(3).
- One investigator for Study 726 and 729 is identified a [redacted]
- All signed disclosure forms were included in the submission.

Steps taken to minimize bias include:

- The primary study in support of this supplemental NDA was a double-blind, placebo controlled, randomized, multicenter study.
- The primary efficacy endpoint of the primary study was based on a central radiological assessment by a blinded IRRC.
- The clinical trials were monitored by a Contract Research Organization (CRO) for data management and statistic [redacted] and central review of scans [redacted] according to the principles of GCP.

Reviewer comments: The steps taken to minimize bias appear sufficient. The financial disclosures do not raise questions about data integrity from Study 726 or 729.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Sue-Ching Lin's primary review from the Office of New Drug Quality Assessment (ONDQA) for details. There are no changes to the CMC section. A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b), which has been reviewed and found acceptable.

4.2 Clinical Microbiology

No new data submitted for review. Please refer to the review for NDA 22074.

4.3 Preclinical Pharmacology/Toxicology

No new data submitted for review. Please refer to the review for NDA 22074.

4.4 Clinical Pharmacology

An independent review of the clinical pharmacology data was not performed by this reviewer, and the information presented below represents a summary of the Applicant's analyses of data. Please refer to Dr. Jun Yang's clinical pharmacology review and Dr. Anshu Marathe's pharmacometrics review for additional information.

4.4.1 Mechanism of Action

SSAs are peptide hormones that regulate neurotransmission and cell proliferation through interaction with G-protein coupled somatostatin receptors (SSTRs) leading to inhibition of numerous secondary hormones. Lanreotide is a synthetic octapeptide SSA with a longer half-life ($t_{1/2}$) than the native molecule that selectively binds to somastostatin receptor 2 (SSTR2) and SSTR5. Lanreotide Depot® is a prolonged release, supersaturated solution for injection supplied as a prefilled syringe. Lanreotide 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 the sustained release is by prolonged passive diffusion. The release profile of lanreotide acetate is characterized by a limited initial burst release of approximately 8%, followed by a sustained release. The apparent terminal $t_{1/2}$ of lanreotide is 23-30 days, and is due to the slow release of lanreotide from the drug depot at the injection site, and not due to the $t_{1/2}$ of the peptide itself.

4.4.2 Pharmacodynamics

The relationship between the PD parameters tumor size and plasma chromogranin A (CgA) levels was evaluated in a non-linear, mixed effect model of data obtained in Study 726. A total

of 1296 CgA observations obtained from 200 patients were used in the PK/PD analysis. Observations were obtained over a period of 96 weeks after the start of study treatment; however, it was not possible to relate the drug effect on change in plasma CgA with lanreotide exposure using the currently available data.

A total of 1057 tumor measurements of target lesions (sum of largest diameters) obtained from 196 patients were used in the PK/PD analysis. Measurements were obtained over a period of 96 weeks after the start of study treatment. Most of the patients with an increase in tumor size from the placebo arm and patients with a decrease in tumor size were from the lanreotide arm. In the first step of PK/PD modelling the drug effect was captured; however, in a second step, it was not possible to relate the drug effect on tumor size of target lesions with lanreotide exposure using the current available data.

4.4.3 Pharmacokinetics

In patients with GEP-NETs treated with lanreotide 120 mg every 4 weeks, steady state concentrations of lanreotide 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.

In order to build a population PK model, blood samples from the measurement of serum lanreotide concentrations in patients with GEP-NETs were obtained in four studies: Study 726, 2-55-52030-730 (Study 730), A92-52030-166 (Study 166) and E47-52030-718 (Study 718) (see table 3 for description of clinical studies and patient populations).

Body weight was identified as a covariate for drug clearance and gender was identified as a covariate for bioavailability (F1). The overall change in lanreotide serum clearance of a 51 kg individual (5th percentile of weight) and a 105 kg individual (95th percentile of weight) was 23% and 30%, respectively, compared to a 74 kg individual (median weight of the population). No dose adjustment based on body weight is needed because no exposure-response relationship was identified for efficacy or safety. Although gender was identified as a covariate for F1, this did not translate into significant difference in exposure between men and women; the steady state AUC in women was increased by 13% compared to men. Age and race did not have an effect on drug exposure and were not identified as covariates.

In the pooled PK analysis, there were 166 patients with renal impairment. No effect from renal impairment was observed on lanreotide pharmacokinetics and creatinine clearance was not identified as a covariate in the model. The predicted steady state AUC increased by 1.3 fold in patients with moderate renal impairment compared to patients with normal renal function. Effects of renal impairment on GEP-NET patients with severe renal impairment were inconclusive due to a limited number of patient with severe renal impairment (n=1).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Data from six clinical trials were submitted in support of this sNDA. This included Study 726 providing the primary results in support of this application, and the additional studies described below.

Table 3: Clinical studies submitted

Study Number	Study Design	Lanreotide dose (duration)	# Patients treated with lanreotide	Patient Population	Status
2-55-52030-726	Randomized, double blind, comparative, placebo controlled, multicenter study	120 mg every 4 weeks (96 weeks)	Randomized 204	Non-functioning GEP-NET	Full study report
2-55-52030-730	Randomized, double blind, placebo controlled	120 mg every 4 weeks (48 weeks)	Randomized 115	Carcinoid syndrome	Interim report
2-55-52030-729	Nonrandomized, multicenter, open label (extension of Study 726)	120 mg every 4 weeks (maximum 8 years)	Included 88*	Patients enrolled on Study 726	Interim report
A-92-52030-166	Open label, non-comparative study	120 mg every 4 weeks (92 weeks)	Included 30	Progressive NET	Full study report
E-47-52030-718	Open label, multicenter, dose titration study	60, 90 or 120 mg every 4 weeks (7-8 months)	Included 71	Carcinoid tumors	Full study report
A-99-52030-216	Open label, randomized, crossover, multicenter study	90 or 120 mg every 4 weeks (6 months)	Included 26	NET	Full study report

**41 patients from Study 726 continued on lanreotide, 47 patients from Study 726 who received placebo were subsequently treated with lanreotide on Study 729.*

Source: Clinical Overview, page 13 and Tabular Listing of all Clinical Studies (module 5.2)

5.2 Review Strategy

The focus of the sNDA clinical review was on the efficacy and safety data from Study 726. The electronic submission, with case report forms (CRFs), clinical study reports (CSRs), amendments and other relevant portions of the trials were reviewed and analyzed. The key review materials and activities are outlined below:

- A survey of current literature on diagnosis, classification and treatment of GEP-NETs using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed;
- Review of the Applicant's description of all the trials submitted with this sNDA;
- Review of supporting tables and data listings of various parameters of the trials in order to evaluate the Applicant's data;
- Confirmation of the Applicant's findings for efficacy and safety of lanreotide in the studied patient population;
- Consultations with the biostatistics reviewer;
- Review of previous reviews completed for the original NDA approval;
- Relevant submissions in response to clinical reviewers' information requests;
- Formulation of conclusions and recommendations.

5.3 Discussion of Individual Studies/Clinical Trials

Study 2-55-52030-726 (Study 726)

Study 726 is a multinational, multi-center, randomized, double-blind, placebo controlled study comparing lanreotide versus placebo in patients with GEP-NET (including adequately controlled gastrinomas and tumors of unknown origin).

5.3.1Protocol Landmarks

Final protocol **November 22, 2005**

Study initiation **June 22, 2006**

Amendment #1 **January 3, 2007**

- Modified inclusion criteria to allow patients with gastrinomas and tumors of unknown origin; extended the window for tumor biopsy
- Removed local tolerance and disease progression from adverse events
- Clarified role of the DSMC, on study procedures, and statistical definitions and testing
- Removed the plan for a formal interim analysis of the primary efficacy variable after 50% of anticipated events has occurred (i.e., 60 out of 120 progressions or deaths)

Amendment #2 **July 30, 2007**

- Modified inclusion criteria related to tumor biopsy and imaging window
- Specified the randomization list to be provided to the independent statistician in charge of reporting for the DSMC

Amendment #3 **April 30, 2008**

- Introduced the plan for an extension study allowing patients to continue on lanreotide after 96 weeks or to receive lanreotide if previously receiving placebo

Amendment #4 **April 4, 2009**

- Change of saline solution in the U.S.
- Change of Sponsor administrative information

Amendment #5 **March 5, 2010**

- Addition of hepatic tumor load evaluation
- Removed restriction limiting study centers to recruitment of 20 patients
- Addition of sensitivity analyses for the primary efficacy analysis

Amendment #6 **February 11, 2011**

- Changes in response to FDA to use the log rank test instead of the Cox PH ratio model originally planned for the analysis of PFS.
- Added OS as a secondary endpoint
- Changed the number of sample size re-estimations to one

Amendment #7 **February 28, 2012**

- Replaced Ipsen Pharma S.A. with new laboratories to perform the PK evaluation and anti-lanreotide antibody testing

Sponsor Notification to Investigators of Study Closure: May 2013
Last Patient Visit/Data Cut-Off: April 9, 2013
Database Lock: April 24, 2013

Reviewer comment: The analysis of OS as a secondary endpoint was not included in the protocol for Study 726 until February 2011, nearly 5 years after study initiation.

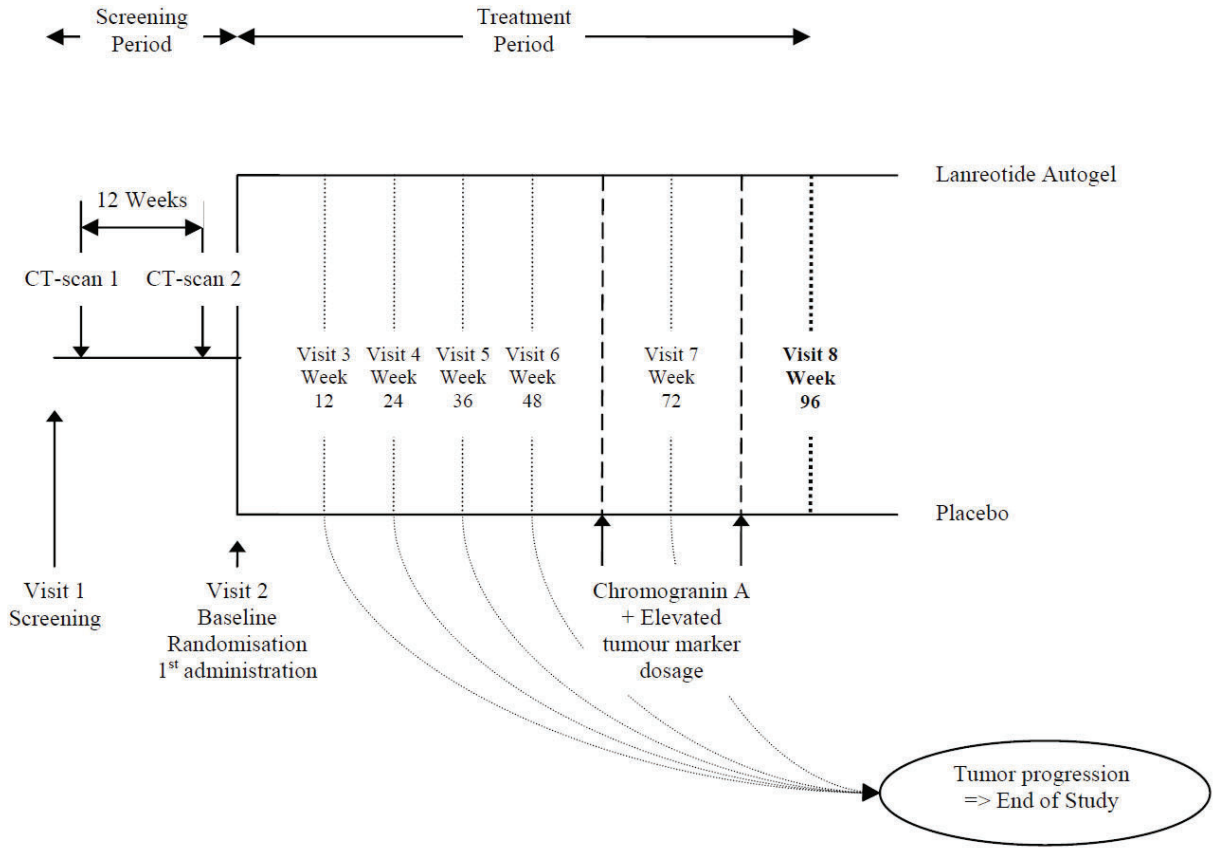
5.3.2 Study Design

The study was conducted in two parts, as summarized in Figure 1 (study schema provided by the Applicant).

- The screening period included Visit 1, followed by a period of up to 14 weeks during which two imaging studies were performed to assess tumor progression. The first CT-scan was performed as soon as possible after Visit 1, and was followed 12 weeks later by a second CT-scan. In the event that one or both of the CT-scans had already been performed within 6 months before Visit 1, and were available for central review, the screening period was shortened.
- The treatment period began with Visit 2 (baseline assessments) and was intended to take place as soon as possible after assessment for tumor progression. Patients were stratified and randomized to either the lanreotide 120 mg or the placebo arm. Injections were administered on site every 28 days for both treatment groups. Tumor assessments were planned every 12 weeks during the first study year, and every 24 weeks during the second

study year. During the second year of treatment, chromogranin A (CgA) levels were assessed at Week 60 and Week 84, and if they had increased by >50% over baseline an additional CT-scan was performed to assess possible disease progression. The study schedule is summarized in Table 5.

Figure 1: Study schema



SOURCE: Clinical Protocol, dated November 2005, page 17

Table 4: Schedule of Assessments

	Screening Period		Treatment Period																								Compl./ withd. Visit
Visit	V1		V2			V3			V4			V5			V6						V7						V8
Week	≤ 14 weeks		W1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
Lanreotide / Placebo administration			■**	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Written informed consent	X																										
Demographics & medical history	X																										
Eligibility criteria	X		X																								
WHO performance score	X																										
Octreoscan	X[a]																										
Tumour Biopsy	X[a]																										
Pregnancy test (if appropriate)	X																										
RANDOMISATION			**X**																								
CT-scan	X[b]	X[c]				X			X			X			X						X						X
Full tumour marker profile[e]			X												X												X
Chromogranin A + any elevated tumour marker(s) at baseline or visit 6						X			X			X						X			X			X			
Quality of Life			X			X			X			X			X						X						X
Physical Examination	X		X			X			X			X			X						X						X
Vital signs	X		X			X			X			X			X						X						X
Blood sample for lanreotide assay			X[d]	X		X		X[d]	X			X			X						X						X
Blood sample for antibodies to lanreotide			X						X						X						X						X
Clinical Laboratory test[f]	X		X												X												X
Gallbladder echography			X[g]												X												X*
ECG			X												X												X
Local Tolerance			◄																								►
Adverse events	◄																										►
Concomitant Medication	◄																										►

[a]: not necessary if performed within 24 weeks prior to Visit 1

[b]: Performed as soon as possible after Visit 1 if not performed within 16 weeks prior to Visit 1

[c]: Performed 12 weeks after the first CT-scan

[d]: Two additional samples will be performed after the 1st and 6th study drug administration (respectively between week 1and 4 and between week 20 and 24)

[e]: Full tumour markers profile : Chromogranin A, pancreatic polypeptide, gastrin, VIP, glucagon, somatostatin, insulin, neurotansin and urinary 5-HIAA

[f]: Clinical laboratory test: Haematology and biochemistry (to refer to section 8.2.5 for details)

[g]: not necessary if performed within 24 weeks prior to Visit 2

*: not required at a withdrawal visit

**: The patient will stay at the investigational site for 8 hours post study drug administration

Source: Clinical protocol, dated November2005, page 24

Dose selection rationale:
The Applicant states that the dose of 120 mg every 4 weeks of lanreotide was selected for development in this indication based on the rationale that inhibition of tumor growth is dependent on SSA concentrations and optimum anti-proliferative activity is seen at higher doses than those used to treat hormonal symptoms of GEP-NETs. Therefore, the highest available dose that could be administered clinically was chosen in order to maximize efficacy. There were no criteria or schema for dose reductions/modifications of lanreotide on Study 726.

Choice of control arm:
The Applicant states that placebo was chosen as the control arm in order to allow comparison of treatment effect to the natural history of these tumors. Given the relatively indolent nature of nonfunctioning GEP-NETs, it was posited that patients may have been previously treated with a range of therapeutic options throughout the course of their disease. Since none of the available therapies at the time the study began had been shown to delay progression of disease in this patient population, it was considered ethically acceptable to stipulate a 2 year placebo arm for these patients with nonfunctioning tumors.

Choice of PFS as primary endpoint:
In the CSR for Study 726, the Applicant discusses the justification for the PFS endpoint:

> *"As per the Consensus report of the National Cancer Institute neuroendocrine tumor clinical trials planning meeting, PFS is recommended as a feasible and relevant primary endpoint for both phase III and phase II studies where a delay in progression is expected in the absence of radiologic responses, because of the observed long survival after progression." (CSR, page 34)*

The FDA "Guidance on Clinical Trial Endpoints in Cancer" states that tumor assessments should be subjected to a blinded independent adjudication team to avoid systemic bias in analysis of PFS. The Applicant employed a CRO responsible for the central review of radiological imaging: (b) (4)

Objective/Endpoints:
The primary objective was to assess the effect of lanreotide 120 mg administered every 28 days compared to placebo on PFS in patients with well or moderately differentiated nonfunctioning GEP-NET.

Secondary objectives:

- To compare the proportion of patients alive and without progression between both groups at 48 and 96 weeks,
- To compare time to progression in patients with progression between both groups,
- To assess the OS in this patient population,
- To assess the effect of lanreotide 120 mg compared to placebo on European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and EORTC QLQ-GI.NET21 questionnaires,

- 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 (Visit 2),
- To assess the clinical and biological safety profile of lanreotide 120 mg,
- To assess the appearance of putative anti-lanreotide antibodies,
- To assess the PK profile of lanreotide 120 mg.

Ancillary objectives:

- Characterization of tumor somatostatin receptor profile was an optional assessment offered to all patients

Reviewer comment: The protocol specified that tumor markers (pancreatic polypeptide, gastrin, VIP, glucagon, somatostatin, insulin, neurotensin and urinary 5-hydroxyindoleacetic acid (5-HIAA) would be assessed. The kits for measuring somatostatin and neurotensin were not available so these markers were not evaluated.

Key Eligibility Criteria:

Inclusion Criteria

- An endocrine tumor confirmed by centrally assessed histological criteria
- Metastatic disease and/or locally advanced inoperable tumor, or the patient must have refused surgery (documented),
- A tumor measurable according to RECIST criteria (central assessment),
- No hormone related symptoms,
- A nonfunctioning enteropancreatic tumor of unknown origin; or with a known primary location in the pancreas, mid gut, or hind gut, or a gastrinoma adequately controlled by proton-pump inhibitors (PPIs) (four months stable prior to study entry),
- A well or moderately differentiated tumor (central assessment),
- A tumor with a proliferation index (Ki67) <10% or, in samples where the Ki67 antigen could not be reliably quantified, a mitotic index ≤2 mitosis/10 high power field (central assessment)
- A ≥ grade 2 octreoscan assessed using the Krenning scale, during the screening period or within 6 months prior to study entry (Visit 1) for the organ of target lesions
- A WHO performance score ≤2
- A biopsy performed within 6 months prior to the screening visit if the patient had a previous cancer or, if in the opinion of the Investigator, there was evidence of clinical progression.

Exclusion Criteria:

- Treatment with a SSA at any time prior to study entry (Visit 1), except if that treatment was for < 15 days (e.g., peri-operatively) was received > 6 months before study entry (Visit 1)
- Treatment with radionuclide at any time prior to study entry (Visit 1),
- Treatment with interferon, chemoembolization or chemotherapy within 6 months prior to study entry (Visit 1)

- Previous history of cancer (except basal cell carcinoma of the skin, in situ carcinoma of the cervix/uterus, or treated with curative intent and free from disease for more than 5 years)
- A history of hypersensitivity to drugs with a similar chemical structure,
- Treatment with any other unlicensed drug within the 30 days before study entry (Visit1)
- Likely to require treatment during the study with drugs that were not permitted by the study protocol
- At risk of pregnancy or was lactating. Women of childbearing potential were required to provide a negative pregnancy test at study entry (Visit 1) and use oral, double barrier or injectable contraception.
- Any mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude,
- Abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardize the safety of the patient or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study,
- Previously enrolled in this study,
- Major surgery related to the studied disease within three months prior to entering the study,
- A history of multiple endocrine neoplasia (MEN).

Randomization and Stratification:
After eligibility was confirmed at the baseline visit (Visit 2), the Investigator used the Interactive Voice Response System (IVRS) service and provided the following information to allow for stratification and randomization:

- Center number
- Patient number
- Presence/Absence of tumor progression
- Presence/Absence of previous therapy

Patients were randomized 1:1 to treatment with either lanreotide or placebo within each stratum.

Study Medications:
Arm A: lanreotide 120 mg
Arm B: placebo

Patients were to receive a maximum of 24 deep subcutaneous injections of either lanreotide or placebo in the superior external quadrant of the buttock. A window of ± 1 day was permitted for each treatment visit. Lanreotide is a mixture of lanreotide acetate and water for injection, provided in a pre-filled 0.5 mL syringe fitted with a 2 cm needle o (b) (4) nm external diameter, sealed in a laminated bag. The placebo was provided by the Applicant and consisted of sodium chloride (NaCl) solutio (b) (4) (b) (4) (b) (4)

placebo were different in color and appearance; therefore, an independent qualified person appointed by the Investigator prepared and administered the injections.

Reviewer comment: Differences in the appearance of the study treatment may have affected the quality of the blind, especially if patients were able to see the drug product during administration.

Breaking the Blind:
Two sets of individual sealed code break envelopes were prepared by an Ipsen Randomization Manager to enable code break procedures for individual patients without compromising the blind of the study. One set was provided to the investigational site and one set was provided to the Central Department of Pharmacovigilance at Ipsen. Blinding codes would be broken in an emergency situation necessitating knowledge of the patient's study drug, or in case of centrally assessed tumor progression confirmed on imaging (see Section 6.1.3.1).

Criteria for patient withdrawal from treatment:

- Tumor progression
- Any adverse event (AE) or serious AE (SAE) that could jeopardize the patient's safety
- Patient choice to withdraw from treatment
- Clinical judgment of the investigator

Statistical Methods:
Sample Size Determination:
Sample size estimation was based on the available clinical information, and the following assumptions:

- expected rate of progression in placebo group = 0.80,
- expected rate of progression in active treatment group = 0.60,
- type I error 0.05, two-sided test, 80% power

The original protocol specified that the number of patients to be randomized per group is 100, based on eighty-six patients per arm and an anticipated loss of information due to censoring in ~15% of patients. The protocol also specified that a total of 120 events of disease progression or death are required in the final analysis to demonstrate 20% improvement in time to progression (TTP) or death, from 80% in the placebo group to 60%, with 80% power using a significance level of 0.05.

With amendment #6 to the protocol (see Section 5.3.1), the Applicant revised the statistical plan to specify that the sample size estimation would also be based on the assumption of a constant hazard ratio (HR) of 0.57 over time, and that a total of 132 progression and death events would need to be observed to detect a significant treatment difference with 90% power at the 0.05 significance level, given that the PFS distributions for the two arms will be compared using the log-rank test. The number of patients to be randomized in order to observe the 132 events was estimated to be 200 (100 per arm). Eighty-six patients were planned for each arm, and the

sample size was increased to 100 patients per arm to account for 15% loss of information due to censoring

A blind sample size re-estimation was planned when the first 100 patient had been randomized and treated on study, died or progressed after 1 year, or after 66 events, whichever occurred first. The target of 100 patients was reached on June 16, 2010, and the OS estimates did not prompt a change of the planned sample size.

Reviewer comment: The original study protocol included an efficacy interim analysis after 50% of events; however, this was withdrawn with amendment #1.

Study Populations:
Screened population: All patients who underwent screening
Intent to treat (ITT) population: All randomized patients. The primary efficacy analyses were performed on the ITT population.
Per-protocol (PP) population: All patients in the ITT population, excluding patients with major protocol violations/deviations.

The PP population was determined prior to unblinding during the Blind Data Review Meeting (BDRM).

Endpoints Definitions:
Progression-free survival (PFS): The PFS was calculated as the time from randomization to either centrally assessed progressive disease (PD) or death.
PFS = [(Date of event – date of randomization) + 1] / 7 (weeks)
Progression Date: The first date at which progression could be declared

- For progression based on a new lesion, the date of the first radiological assessment when the new lesion was detected.
- For progression based on an increase in the sum of the target lesion measurements, the date of the first radiological assessment of target lesions that showed the predefined increase in the sum of the target lesion measurements (according to RECIST).

Censoring date: Censoring dates were defined in patients without a centrally assessed PD or death before end of study or withdrawal as the date of the last radiological assessment at which the target lesions were evaluated by central review.
Overall Survival: Defined as the time from randomization to death due to any cause. The protocol was amended to specify that investigators record the survival status of patients annually, from the time the patient completes (or withdraws from) study treatment, until the end of study.

Study Analyses:
The primary efficacy analysis of PFS was performed in the ITT population using the stratified log-rank test based on Kaplan-Meier (KM) estimates with the baseline stratification factors of presence/absence of tumor progression and presence/absence of prior therapy.

Five sensitivity analyses of the primary efficacy parameter were conducted:

- Sensitivity analysis 1 considered withdrawals due to PD based on the investigator's judgment (despite central assessment of stable disease) as events.
- Sensitivity analysis 2 considered all withdrawals (for disease progression or other reasons) as events.
- Sensitivity analysis 3 was similar to the primary analysis but corrected for potential bias in the follow up schedules by mapping censoring and event dates to the nominal value of the relevant scheduled radiological assessment. Any centrally assessed PDs at unscheduled radiological assessments are mapped to the next scheduled assessment.
- Sensitivity analysis 4 investigated whether the reduced frequency of CT/MRI scans in the second year could have led to bias. Events in the placebo group were analyzed as in Sensitivity analysis 3. In the lanreotide Autogel group any centrally assessed PDs at the Week 72 assessment were mapped to be at Week 60 (i.e., three months after Week 48) and all centrally assessed PDs at the Week 96 assessment were mapped to be at Week 84 (i.e., 3 months after Week 72). Any unscheduled scans resulting in PD after Week 48 were also recoded.
- Sensitivity analysis 5 was similar to the primary analysis of PFS except for the fact that PFS was calculated from the start of treatment rather than from the time of randomization. There was a delay between randomization and start of treatment in 30 patients ranging from 1 to 20 days.

The analyses for the primary efficacy endpoint (including KM plots with the stratified log-rank test and the KM summary table and the Cox PH model) were repeated for these five sensitivity analyses.

Reviewer Comments:
1. The primary endpoint is defined in the protocol as "the time to either disease progression (measured using RECIST criteria) or death, occurring within 96 weeks after first study treatment". This was clarified in the reporting and analysis plan (RAP) with PFS defined as "the time from randomization to the first occurrence of a documented progression or death". Sensitivity analysis 5 calculated PFS from start of treatment as originally specified in the protocol.

2. Sensitivity analyses 3, 4, and 5 were not specified in the original statistical analysis plan and were added to the RAP before breaking the blind of the study.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is fo [redacted]

6.1.1 Methods

The primary efficacy analysis is based on Study 726, a multi-center, multi-national, randomized, placebo-controlled trial of 204 patients with locally advanced or metastatic nonfunctioning GEP-NET.

Statistical analyses were performed by an external CRO [redacted] A RAP describing the planned statistical analysis in detail, including table, figure and listing (TFLs) templates, was developed as a separate document (dated June 6, 2013). Statistical evaluation was performed using Statistical Analysis System (SAS)® version 9.3. The bioanalysis (lanreotide serum levels) was performed independently b [redacted] Analysis of putative antibodies was undertaken by the Applican [redacted] an [redacted]

Tumor assessments:
An independent central imaging company [redacted] assessed disease status and results of the review were provided to the investigators s [redacted] he imaging tests were evaluated to enable patients to continue on study or withdraw due to PD. The local radiological assessments of tumor progression were not recorded. The independent central imaging company had each CT/MRI scan read by two independent radiologists, and by a third radiologist in cases where adjudication was required. The radiologists were experienced in RECIST assessment and oncology studies but had no special expertise in neuroendocrine tumors.

Censoring for Study 726:
Censoring dates were defined for patients without centrally assessed PD or death before end of study or withdrawal. In these patients, the censoring date was defined as the last date at which disease progression status was "adequately" assessed (i.e., the date of the last radiological assessment at which the target lesions were evaluated by central review).

6.1.2 Demographics

A total of 264 patients were screened at 48 sites in 14 countries, and 204 patients were randomized to treatment with lanreotide 120 mg or placebo every 28 days.

The study initiation date was June 22, 2006, and the study completion date (last patient visit date) was April 9, 2013. As depicted in Table 6, a total of 41 centers across 3 regions enrolled patients in this study. The majority of patients were recruited from Europe, primarily France followed by Poland. There were thirty (30) patients enrolled from the US.

Table 5: Patient enrollment by country

COUNTRY	Lanreotide (n=101)	Placebo (n=103)	Total (n=204)	Regional Totals
Austria	6	8	14	Western Europe n=120 (59%)
Belgium	0	4	4	
Netherlands	6	8	14	
Denmark	0	1	1	
Spain	7	3	10	
France	18	23	41	
Great Britain	12	17	29	
Italy	4	2	6	
Sweden	0	1	1	
Czech Republic	9	5	14	Eastern Europe + India n=54 (26%)
India	0	4	4	
Poland	17	13	30	
Slovakia	6	0	6	
USA	16	14	30	USA n= 30 (15%)

Source: adsl.xpt

Baseline patient characteristics are presented in Table 7. The treatment arms were similar with respect to age, gender and race.

Table 6: Baseline patient characteristics

	Lanreotide (n=101)	Placebo (n=103)
Gender, n (%)		
Men	53 (52%)	54 (52%)
Women	48 (48%)	49 (48%)
Median Age (Range)	64 (30-83)	63 (31-92)
< 65 years	53 (53%)	58 (56%)
≥ 65 years	48 (48%)	45 (44%)
Race, n (%)		
White	97 (96%)	96 (93%)
Asian	2 (2%)	5 (5%)
Black or African American	2 (2%)	2 (2%)
Baseline ECOG, n (%)		
0	84 (83%)	84 (82%)
1	17 (17%)	17 (16%)
2	0	2 (2%)

Source: dm.xpt, adsl.xpt

Reviewer comment: The high number of PS 0 patients may indicate a population which does not necessarily require immediate therapy for locally advanced or metastatic GEP-NET.

Table 8 includes baseline patient characteristics of the US population compared with the ex-US population enrolled on Study 726.

Table 7: Baseline patient characteristics, US population compared with ex-US population

	Lanreotide (n=16)	Placebo (n=14)	Lanreotide (n=85)	Placebo (n=89)
	USA		EX-US	
Gender, n (%)				
Men	8 (50%)	8 (57%)	45 (53%)	46 (52%)
Women	8 (50%)	6 (43%)	40 (47%)	43 (48%)
Median Age (Range)	57.5 (43-82)	65.5 (50-92)	65 (30-83)	63 (31-85)
< 65 years	11 (69%)	7 (50%)	42 (49%)	51 (57%)
≥ 65 years	5 (31%)	7 (50%)	43 (51%)	38 (43%)
Race, n (%)				
White	14 (88%)	12 (86%)	83 (98%)	84 (94%)
Asian	0	0	2 (2%)	5 (6%)
Black or African American	2 (12%)	2 (14%)	0	0
Baseline ECOG, n (%)				
0	14 (88%)	11 (79%)	70 (82%)	73 (82%)
1	2 (12%)	2 (14%)	15 (18%)	15 (17%)
2	0	1 (7%)	0	1 (1%)

Source: dm.xpt, adsl.xpt

Reviewer comment: The patient characteristics appear to define a population that is representative of the US population.

Table 9 summarizes the baseline tumor characteristics by treatment arm. Fifty-five percent of patients included in Study 726 had a primary tumor site outside the pancreas, and 69% of patients were determined to have WHO grade 1 tumors. Eighty-three percent of patients had some degree of disease in the liver (85/101 and 85/103 patients in the lanreotide and placebo arms, respectively).

Table 8: Baseline tumor characteristics

	Lanreotide (n=101)		Placebo (n=103)	
Primary Tumor Type				
Pancreas	42	42	49	49
Mid-gut	32		40	
Hind-gut	11	59	3	54
Other/Unknown	16		11	
Tumor Grade				
Grade 1	69		72	
Grade 2	32		29	
Missing	0		2	
Time to Diagnosis				
≤ 5 years	85		87	
> 5 years	16		16	
Median (years)	1.1		1.1	
Previous surgery				
Yes	40		39	
No	61		64	
Prior chemo				
Yes	14		15	
No	87		88	
Baseline CgA				
Elevated (>1 to 2 ULN)	25		18	
High Elevated (> 2ULN)	41		48	
Not Elevated (≤ULN)	33		34	
Missing	2		3	
Tumor Hepatic Load				
0%	16		18	
> 0% and ≤ 10%	33		40	
> 10% and ≤ 25%	13		17	
> 25% and ≤ 50%	23		12	
> 50%	16		16	
Progression at baseline				
Yes	4		5	
No	97		96	
Previous Therapy				
Yes	16		16	
No	85		87	

Source: adsl.xpt

Reviewer comment:
-There is an imbalance in the tumor hepatic load between the two arms: 39% of patients in the lanreotide arm had >25% tumor hepatic load compared with 28% in the placebo arm, potentially favoring the placebo arm. Metastatic disease to the liver is a recognized cause of significant morbidity and mortality in patients with GEP-NET, and is associated with worse prognosis.

-Pyrimidine analogs and platinum compounds were the most commonly used prior chemotherapies in both arms (i.e., ≥ 5% of patients).

6.1.3 Subject Disposition

Table 10 summarizes patient disposition. There were 70 sites open for Study 726, and 48 of these sites in 14 countries actively screened patients. There were 60 patients who were screened but did not meet criteria for enrollment on Study 726. The most common reason for screen failure was patient ineligibility based on the following inclusion criteria:

1. has Ki67 <10 (n=19)
2. has tumor measurable according to RECIST (n=18)
3. has grade 2 octreoscan (n=14)
4. centrally confirmed diagnosis of GEP-NET (n=12)

Table 9: Patient disposition

POPULATIONS	Lanreotide	Placebo	Total
Screened population			264
Planned randomization	100	100	200
Actual randomization (ITT)	101	103	204
Per protocol (PP)	96	101	197
Completed study	56	34	90
Patients withdrawn	45	69	114
PD	27	49	76
Adverse event (Death)	5(2)	3(2)	8
Investigator decision or PD not centrally confirmed	8	9	17
Protocol violation	2	2	4
Other	3	6	9

Source: adsl.xpt and adie.xpt

Reviewer comment: The Applicant identified three patients on each treatment arm who were withdrawn from study due to adverse events. FDA review of the data identified an additional two patients on the lanreotide arm: patien (b) (6) was withdrawn for "Consent withdrawn: very uncomfortable with side effect; eye burning" and patien (b) (6) was withdrawn for "Other: sponsor decision due to AE04" (bronchial carcinoma). In addition, patien (b) (6) on the placebo arm discontinued treatment due to the AE tuberculosis; therefore, this withdrawal could be considered related to an AE.

There were two patients withdrawn from each treatment arm for protocol violations. On the lanreotide arm, patien (b) (6) was withdrawn for a negative octreoscan at screening, and patien (b) (6) was withdrawn for treatment with an SSA (Sandostatin). On the placebo arm, patien (b) (6) did not receive treatment for > 4 months (due to AE, tuberculosis), and patien (b) (6) received prior treatment with a SSA.

6.1.3.1 Protocol Deviations

The Applicant states that the data were reviewed prior to unblinding in order to identify patients with major protocol violations for possible exclusion. Seven patients were excluded (5 and 2 in the lanreotide and placebo arms, respectively) from the PP population; reasons for exclusion are described in Table 11. The most common reason for exclusion was failure to satisfy the eligibility criterion *"no previous treatment with radionuclide"*. In addition, one patient on the lanreotide arm had a missing treatment label at two consecutive visits and one placebo patient received one dose of open label extension investigation medicinal product (IMP) at the baseline visit.

Table 10: Reasons for exclusion from the PP population

	Lanreotide Autogel 120 mg (N=101)	Placebo (N=103)	Total (N=204)
	n (%)		
Number of subjects excluded from the PP population	5 (5.0)	2 (1.9)	7 (3.4)
Reason for exclusion			
Krenning scale <2	1 (1.0)	0	1 (0.5)
Previous treatment with radionuclide	3 (3.0)	0	3 (1.5)
Previous treatment with an SSTa	0	1 (1.0)	1 0.5)
Randomisation pack number different across the study[a]	1 (1.0)	0	1 (0.5)
Study treatment administration of open-label extension IMP[b]	0	1 (1.0)	1 (0.5)

Data Source: Table 14.1.2.3, Listing 16.2.3.1 and Listing 16.2.5.1.1.
PP=per protocol; ITT=intent to treat; N=total number of subjects in group; n=number of subjects with event; SSTa=somatostatin analogue; IMP=investigational medicinal product.
a Subjec (b) (6) had no treatment label available at two successive visits (Week 60 and Week 64). This deviation was considered as relevant.
b Subjec (b) (6) received open label treatment from Study 2-55-52030-729 in error on one occasion (at the baseline visit).

Source: CSR, page 59

After database lock, an audit of a study center in France (site # 250001) revealed that one patient randomized to placebo had two hospitalizations for the SAE of confusional state (considered unrelated); however, only one hospitalization had been reported. This was deemed to be a breach of GCP.

Unblinding during study

In accordance with protocol amendment # 3 (see Section 5.3.1) sixty-three patients (63) had their treatment allocation unblinded due to centrally assessed PD. An additional two patients in the placebo group had treatment allocation unblinded due to investigator determined radiographic progression or clinical progression.

Four patients had their treatment allocation unblinded by the Applicant due to suspected unexpected serious adverse reactions (SUSARs); two patients in each treatment arm. Table 12 describes the SUSARs leading to unblinding of treatment allocation.

Table 11: SUSARs leading to unblinding of treatment allocation

Treatment Arm	Patient ID	SUSAR
Lanreotide	(b) (6)	biliary fistula, cholelithiasis
		liver failure, sepsis
Placebo		metastases to liver
		bile duct stenosis

Source: CSR, page 59 and adae.xpt

The SUSARs for patien (b) (6) on the lanreotide arm and patie (b) (6) on the placebo arm were later reassessed as not related to study treatment.

Treatment Compliance

The protocol specified that study treatment injections were to be made every 28 days ±1 day; however, the majority of patients received injections within 28 days ±7 days of the previous injection. Thirteen patients in the lanreotide arm (13%) and eighteen patients in the placebo arm (17%) did not receive injections of study treatment at 28 days ±7 days. Of these patients, the injections were delayed due to AEs in four patients in the lanreotide arm and three patients in the placebo arm.

Table 12: Dose delays on Study 726

Treatment Arm	Patient ID	Dose delay (days)	Cause
Lanreotide	(b) (6)	63	SAE, UTI
		43	Dizziness/Nausea
		35	Bereavement, severe
		56	SAE liver abscess
Placebo		35	SAE, UTI
		40	SAE, coronary artery disease
		39	SAE, humerus fracture

Study treatment was interrupted due to AEs for three patients in the placebo group (patient ID (b) (6) an (b) (6) There were no treatment interruptions due to AEs for any patients in the lanre hough one patient in this group did have 2 consecutive missed injections prior to withdrawal from study. No study treatment compliance violations were recorded as major protocol deviations.

6.1.4 Analysis of Primary Endpoint: Progression-Free Survival (PFS)

Centrally determined PFS:
The primary endpoint was centrally determined PFS calculated at the end of Study 726 and defined as the time to PD, measured using RECIST 1.0, within 96 weeks after randomization. In the ITT population, thirty-two events were observed in the lanreotide arm compared with sixty events in the placebo arm.

6.1.4.1 Applicant Analysis of PFS

Lanreotide was shown to prolong PFS compared to placebo ($p = 0.0002$). The median PFS was not yet reached but > 22 months (96 weeks) in the lanreotide arm and 16.5 months (72 weeks) in the placebo arm. The estimated HR was 0.47 with 95% CI (0.3, 0.73). The Applicant PFS results (KM estimates and log-rank test) in the ITT population are presented in Table 14 and Figure 2.

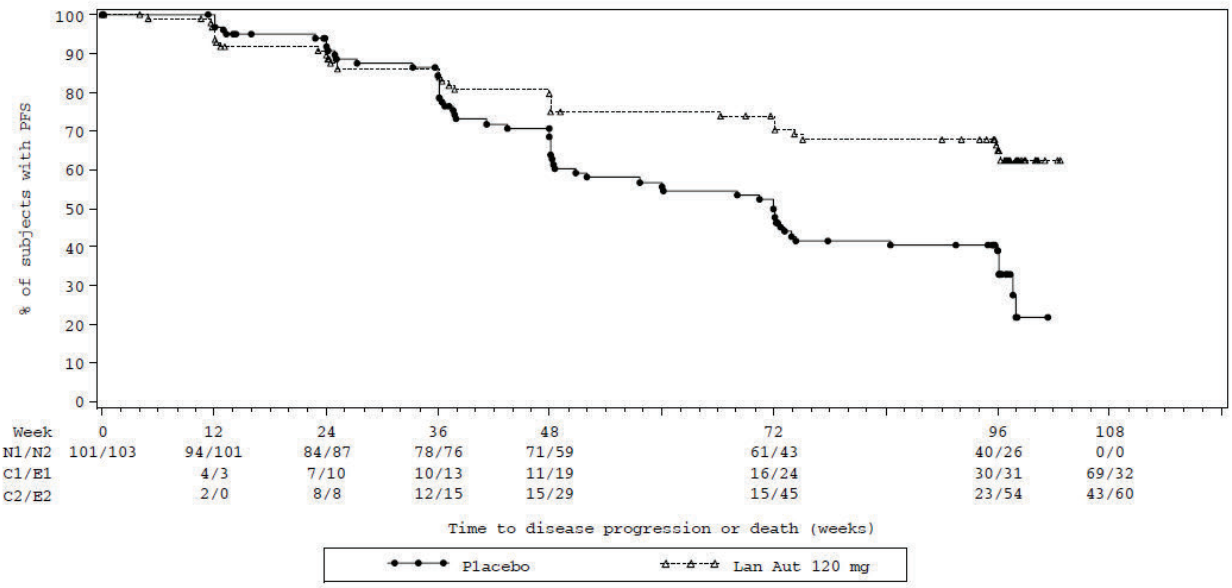
Table 13: Applicant PFS results

Lanreotide Autogel 120 mg (N=101)					Placebo (N=103)				
Survival time*	**No. events**	**No. censored**	**No. at risk**	**Survival estimate**	**Survival time**	**No. events**	**No. censored**	**No. at risk**	**Survival estimate**
0 weeks	0	0	101	1.0000	0 weeks	0	0	103	1.0000
12 weeks	3	4	94	0.9692	12 weeks	0	2	101	1.0000
24 weeks	10	7	84	0.8959	24 weeks	8	8	87	0.9191
36 weeks	13	10	78	0.8631	36 weeks	15	12	76	0.8429
48 weeks	19	11	71	0.7962	48 weeks	29	15	59	0.6846
72 weeks	24	16	61	0.7396	72 weeks	45	15	43	0.4990
96 weeks	31	30	40	0.6506	96 weeks	54	23	26	0.3899
103 weeks	32	69	0	0.6246	102 weeks	60	43	0	0.2199
Median (95% CI): Not reached					Median (95% CI): 72.0 weeks (48.6, 96.0)				
p-value†: 0.0002									
p-value††: 0.0002									

Data Source: Table 14.2.1.1.1 and Table 14.2.1.1.3.
PFS=progression-free survival; KM=Kaplan-Meier; ITT=intent to treat; CI=confidence interval; N=number of subjects in specific group; HR=hazard ratio; PH=proportional hazard; NET= neuroendocrine tumour.
Note: This analysis of PFS considers as events centrally assessed disease progressions (using RECIST criteria) and any deaths reported during the study.
* Survival times are based on the PFS, i.e., [(event date or censoring date) – randomisation date + 1]/ 7, rather than the scheduled radiological assessment. The timepoints presented were selected to be indicative of the scheduled scan times (the complete table of KM estimates is provided in the Statistical Appendix – Section 16.1.9). Estimation of median based on the KM method.
† p-value of the stratified logrank test comparing lanreotide Autogel with placebo, stratified according to progression status at baseline and previous therapy for nonfunctioning enteropancreatic NET at entry (primary analysis).
†† p-value of the unstratified logrank test comparing lanreotide Autogel with placebo (supportive analysis).
HR=0.47; 95% CI:0.30, 0.73 (supportive analysis from Cox PH model: Table 14.2.1.2.1).

Source: CSR, page 73

Figure 2: Applicant KM curves PFS (ITT population)



Data Source: Figure 1.2.1.
PFS=progression-free survival; KM=Kaplan-Meier; ITT=intent to treat; N1/N2=subjects at risk in treatment group lanreotide Autogel/Placebo;
C1/E1=cumulative number of censored observations/cumulative number of events in treatment group lanreotide Autogel;
C2/E2=cumulative number of censored observations/cumulative number of events in treatment group placebo.
Note: This analysis of PFS considered as centrally assessed disease progression and any deaths reported during the study.

Source: CSR, page 74

Reviewer comment: The original protocol specified that approximately 132 events were required to conduct the final PFS analysis; however, the study was stopped and the final PFS analysis was conducted after 96 events. Therefore, the result of the PFS analysis is considered an interim analysis of PFS. The observed p-value is 0.0002; therefore, the study result is still considered statistically significant based on the O'Brien-Fleming boundary and fraction of information. The Applicant proposes that Study 726 was designed as a fixed-time duration study (2 years); therefore, the study was considered completed after the last patient received 2 years of study treatment (Module 5.3.5.1, Study 726 protocol, Section 4.1.3). For further discussion, see Dr. Weishi Yuan's biostatistics review.

Event and censoring times did not occur exactly at the scheduled assessment times as planned in the protocol for several reasons:

- PFS was calculated relative to the time of randomization rather than the actual start of treatment. These dates were different in 30 patients (14 in the lanreotide and 16 in the placebo arm);
- Imaging was sometimes early or late, or unscheduled CT/MRI scans were sometimes performed;
- Death events almost always occurred at times other than the scheduled visits

The first two factors were seen as potential sources of bias in the analysis, and separate sensitivity analyses were performed for these variables.

An overview of the results for the primary analysis of PFS and the five sensitivity analyses of PFS is provided by the applicant in Table 15.

Table 14: Results of primary and sensitivity analyses in the ITT population

Analysis of PFS	Treatment	N	Median PFS in weeks (95% CI)	Logrank p-value[a]	HR (95% CI)
Primary analysis (centrally assessed PD)	Lanreotide Autogel	101	Not reached	0.0002	0.47 (0.30,0.73)
	Placebo	103	72.0 (48.6, 96.0)		
Sensitivity analysis 1 (+ withdrawals due to Investigator judgment of PD despite central assessment of stable disease)	Lanreotide Autogel	101	Not reached	0.0001	0.50 (0.33,0.74)
	Placebo	103	60.1 (48.1,73.1)		
Sensitivity analysis 2 (+ all withdrawals)	Lanreotide Autogel	101	Not reached	0.0007	0.56 (0.39,0.82)
	Placebo	103	52.0 (48.0,72.1)		
Sensitivity analysis 3 (assessments mapped to nominal values)	Lanreotide Autogel	101	Not reached	0.0001	0.47 (0.30,0.73)
	Placebo	103	72.1 (48.1,96.1)		
Sensitivity analysis 4 (assessments mapped to nominal values with 3-month schedule in Yr 2 for Lanreotide Autogel	Lanreotide Autogel	101	Not reached	0.0002	0.48 (0.31,0.74)
	Placebo	103	72.1 (48.1,96.1)		
Sensitivity analysis 5 (PFS calculated from start of treatment)	Lanreotide Autogel	101	Not reached	0.0002	0.47 (0.30,0.73)
	Placebo	103	72.0 (48.4,96.0)		

Data Source: Table 14.2.1.1.9, Table 14.2.1.1.10, Table 14.2.1.1.11, Table 14.2.1.1.12, Table 14.2.1.1.13 and for HR data Table 14.2.1.2.3, Table 14.2.1.2.4, Table 14.2.1.2.5, Table 14.2.1.2.6 and Table 14.2.1.2.6.1.
ITT=intent to treat; N=number of subjects; PFS=progression-free survival; CI=confidence interval; HR=hazard ratio; Yr=year; KM=Kaplan-Meier; NET=neuroendocrine tumour.
Note: These analyses of PFS are described in the RAP (Appendix 16.1.9). Estimation of median based on the KM method. The HR is the relative hazard for lanreotide Autogel vs. placebo (i.e., HRs <1 favour treatment with lanreotide Autogel).
a p-value of the stratified logrank test comparing lanreotide Autogel with placebo, stratified according to progression status at baseline and previous therapy for nonfunctioning enteropancreatic NET at entry.

Source: CSR, p. 97

Reviewer comment: FDA statistical review determined the sensitivity analysis results were consistent with those of the primary analysis.

6.1.4.2 FDA PFS analysis

FDA conducted an analysis of PFS using a different modeling approach. The results were similar to the analysis of PFS from the Applicant. Please see Dr. Yuan's review for additional details.

Table 15: FDA PFS Analysis

	Lanreotide (n=101)	Placebo (n=103)
Number of events (%)	32 (31.7%)	60 (58.3%)
Median PFS, months (95% CI)	NE (NE,NE)	16.6 (11.2, 22.1)
Hazard Ratio (95% CI) **p-value (unstratified)**	0.41 (0.26, 0.64) 0.0002	

Source: modified, from FDA statistical review *NE: not evaluable

Reviewer comment: The HR estimates differ from the Applicant's due to alternate options used in the SAS program.

Consistency of results across strata

The primary analysis of PFS was performed in the ITT population using the stratified log-rank test, and strata were defined by disease status and previous therapy prior to study entry (see Section 5.3.2). There were only nine patients with PD at baseline; therefore, patients with PD at baseline and with and without a history of prior therapy were included in one stratum resulting in the following randomization stratification factors:

1. Progression of disease with or without prior therapy
2. Stable disease with prior therapy
3. Stable disease without prior therapy

The PFS results for each stratum are presented in Table 17.

Table 16: PFS by analysis stratum

Analysis stratum	Treatment	N	No. events n (%)	Median PFS in weeks (95% CI)	HR (95% CI)
PD at baseline	Lanreotide Autogel	4	3 (75.0%)	12.4 (11.9, 12.7)	2.69 (0.43,16.71)
	Placebo	5	3 (60.0%)	24.9 (12.1, NC)	
No PD at baseline and PT at entry	Lanreotide Autogel	14	5 (35.7%)	Not reached	0.57 (0.19,1.77)
	Placebo	16	8 (50.0%)	57.6 (13.3, NC)	
No PD at baseline and No PT at entry	Lanreotide Autogel	83	24 (28.9%)	Not reached	0.38 (0.23,0.61)
	Placebo	82	49 (59.8%)	72.1 (50.7, 96.1)	

Data Source: Table 14.2.1.1.1 and Statistical Appendix (Appendix 16.1.9).
PFS=progression-free survival; ITT=intent to treat; N=number of subjects in specific subgroup; HR=hazard ratio; CI=confidence interval; PD=disease progression (centrally assessed using RECIST); NET=neuroendocrine tumour; PT=previous therapy for nonfunctioning enteropancreatic NET; NC=not calculable; KM=Kaplan-Meier.
Note: This analysis of PFS considers as events any centrally assessed disease progressions and any deaths reported during the study. Estimation of median based on the KM method. The HR is the relative hazard for lanreotide Autogel vs. placebo (i.e., HRs<1 favour treatment with lanreotide Autogel). The HRs are derived from a Cox PH model within each stratum including a single term for treatment.

Source: CSR, page 75

The majority of patients (81%) are included in one stratum (patients with neither PD nor prior therapy) subsequently; interpretation of results within the other strata is difficult due to limited sample size.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints in Study 726 included PFS at weeks 48 and 96, TTP in patients with progression, OS, quality of life (QoL), effect on plasma CgA and other tumor peptide markers, safety, evaluation for anti-lanreotide antibodies and PK profile of lanreotide Autogel 120 mg.

Reviewer comment: The RAP does not propose a multiplicity adjustment; therefore, the secondary endpoints were considered as exploratory.

PFS at weeks 48 and 96

The proportion of patients alive and without centrally assessed disease progression at weeks 48 and 96 were compared between treatment groups using the baseline stratification factors (presence/absence of progression at baseline and presence/absence of prior therapy) as covariates. The applicant states that at week 48 and 96, the proportion of patients who were alive and progression-free was higher in the lanreotide group compared to the placebo group. A summary of the PFS at weeks 48 and 96 is presented in Table 18.

Table 17: PFS at weeks 48 and 96 in the ITT population

Patients alive and progression-free	Lanreotide (n=101)	Placebo (n=103)
Week 48		
Yes	67 (66.3%)	50 (48.5%)
No	34 (33.7%)	53 (51.5%)
Week 96		
Yes	53 (52.5%)	26 (25.2%)
No	48 (47.5%)	77 (74.8%)

Source: modified, from FDA statistical review

Time to Disease Progression

The TTP for patients who had progression (either centrally assessed or investigator assessed) were reported for each treatment group using KM estimates and the log-rank test. Since there were only two deaths on each treatment arm, the results are similar to the results of the primary endpoint, PFS.

Table 18: FDA analysis of TTP

	Lanreotide (n=101)	Placebo (n=103)
Number of Events (%)	30 (29.7%)	58 (56.3%)
Median TTP, months (95% CI)	NE (NE, NE)	16.6 (11.7, 22.1)
HR (95% CI)	0.40 (0.25, 0.63)	

Source: modified, from FDA statistical review

Overall Survival

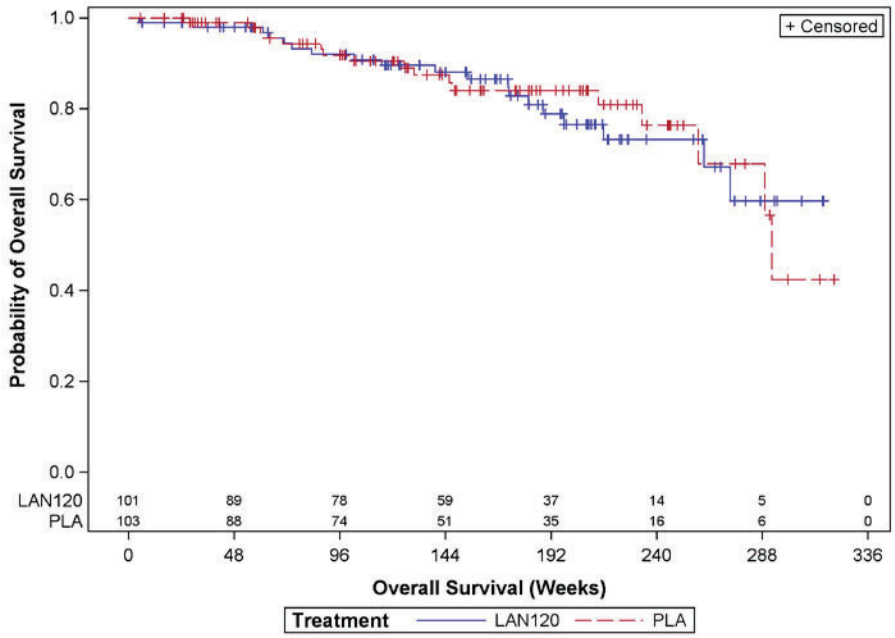
Any deaths reported as part of the post-study follow up for OS were not considered as PFS events. In the protocol and RAP the study was not powered to evaluate OS; however, OS was added as a secondary efficacy endpoint in February 2011, following discussion with the FDA. At that time, some patients had left the study and some had not signed the informed consent allowing participation for post-study follow-up for OS. Seventy-nine percent (161/204) of randomized patients had at least one follow-up assessment for OS. The investigators recorded survival status annually, on the anniversary of the first dose of study treatment. Survival status, date of death (if applicable) and whether death was related to disease (if known) were captured. A review of the limited survival data reveals nineteen deaths in the lanreotide arm compared to seventeen deaths in the placebo group. Four deaths (two in each treatment group), occurred during the study and none were considered related to treatment. The remaining thirty-two deaths occurred during the post-study follow up period. Interpretation of survival data is confounded by challenges encountered in collecting OS data, crossover to other therapies after completion of the study or its open-label extension, and the low incidence of deaths observed, which was as expected given the indolent nature of the disease. The primary results for OS are provided in Table 20 and Figure 3.

Table 19: Analysis of OS

	Lanreotide (n=101)	Placebo (n=103)
Deaths on Study 726	2	2
Deaths after week 96 or withdrawal	17	15
Total number of Deaths (%)	19 (18.8%)	17 (16.5%)
Median OS, months (95% CI)	NE (60.1, NE)	67.2 (59.5, NE)
HR (95% CI)	0.97 (0.50, 1.90)	

Source: modified, from FDA statistical review

Figure 3: FDA KM curves for analysis of OS



Source: FDA statistical review

QoL

Patient reported outcomes (PROs) were assessed using the EORTC QLQ-C30 (general survey for cancer patients) and EORTC QLQ-GI.NET21 (specifically designed for patients with NET of the gastrointestinal tract) questionnaires. These questionnaires were completed during the visit at the investigational site before any other clinical assessments. The change in the transformed subscores between baseline and weeks 12, 24, 36, 48, 60, 72, 84, 96 and last value (LV) was analyzed with an analysis of covariance (ANCOVA) model that included treatment group, respective transformed baseline value and baseline stratification factors. The LV assessment of global health status domain from the EORTC QLQ-C30 was identified *a priori* as the primary assessment.

The results for the change from baseline to LV in transformed scores for the EORTC QLQ-C30 questionnaire are presented in Table 20. There were no significant differences between the two arms in transformed scores for global health status or any of the function/symptom scores from baseline to LV.

Table 20: Change from baseline in transformed scores for EORTC QLQ-C30 QoL

	Lanreotide Autogel 120 mg (N=101)			Placebo (N=103)			p-value
	n	LSMean change	SE LSMean change	n	LSMean change	SE LSMean change	
Global health status/QoL	95	-5.18	3.73	98	-4.87	3.70	0.9088
Physical functioning	94	-3.32	2.90	98	-3.80	2.86	0.8193
Role functioning	94	-4.83	4.29	98	-6.23	4.23	0.6560
Emotional functioning	95	-0.40	3.70	98	-1.31	3.65	0.7377
Cognitive functioning	95	-2.63	3.51	98	2.43	3.47	0.0502
Social functioning	95	-1.45	4.09	98	-2.73	4.04	0.6692
Fatigue	94	-0.38	3.91	98	2.44	3.85	0.3243
Nausea and vomiting	95	5.19	2.78	98	6.39	2.75	0.5562
Pain	95	3.37	3.54	98	4.04	3.49	0.7954
Dyspnoea	93	0.82	3.85	96	-0.80	3.85	0.5554
Insomnia	94	-5.41	4.81	97	-6.03	4.72	0.8586
Appetite loss	93	-1.15	4.34	98	2.04	4.28	0.3154
Constipation	94	-2.80	4.03	98	-3.41	4.00	0.8377
Diarrhoea	95	2.70	4.73	98	4.27	4.67	0.6475
Financial difficulties	95	4.25	4.28	98	2.33	4.22	0.5392

Data Source: Table 14.2.3.4.
QoL=Quality of Life; ITT=intent to treat; N=total number of subjects in group; n=number of subjects with assessment; LSMean=mean change from baseline, adjusted for covariates; SE=standard error; NET=neuroendocrine tumour.
Note: All transformed scores range from 0 to 100. A high transformed score represents a higher response level, i.e. a high transformed score for the global health status/QoL represents a high QoL, a high transformed score for a functional scale represents a high/healthy level of functioning, but a high transformed score for a symptom scale/item represents a high level of symptomatology / problems.
LSMeans, standard errors of LSMeans and p-values to compare the treatments are derived from an ANCOVA model including fixed effect terms for treatment group, progression at baseline (yes/no), previous therapy at entry (yes/no) and the covariate transformed score at baseline (Week 1).
Progression at baseline=centrally assessed disease progression; Previous therapy at entry=Previous medication given for the nonfunctioning enteropancreatic NET prior to study start.

Source: CSR, page 116

Tumor markers

Chromogranin A

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. CgA has also been considered a marker for non-functioning GEP-NETs which do not have other tumor markers available to follow disease status. The Applicant reports that more patients in the lanreotide arm had a ≥50% decrease in CgA at last available follow-up compared to patients in the placebo arm (42.2% and 4.7% in the lanreotide and placebo arms, respectively, confirmed by reviewer). This was based on a post-

hoc analysis of patients who had elevated CgA levels at baseline (excluding patients with gastrinoma).

Urinary 5-hydroxyindoleacetic acid (5-HIAA)

There were forty-three (43) patients treated with lanreotide and thirty-six (36) patients treated with placebo who had elevated 5-HIAA at baseline. Fifty-three percent of patients on lanreotide (23/43) had ≥ 50% decrease in 5-HIAA at last available follow-up compared with 6% on placebo (2/36).

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The Applicant repeated the primary analysis of PFS for the following pre-specified subgroup variables: progression at baseline, previous therapy, primary tumor location, and US vs. ex-US. Additional exploratory analyses of baseline covariates on the primary efficacy variables were also conducted. FDA analysis of subgroups is presented in Tables 22 and 23.

Table 21: FDA subgroup analysis of PFS based on demographics

Subgroups	Events/N		Median PFS (months)		HR (95% CI)
	Lanreotide	Placebo	Lanreotide	Placebo	
Gender					
Men	18/53	34/54	NE	16.6	0.38 (0.21, 0.71)
Women	14/48	26/49	NE	13.8	0.31 (0.15, 0.63)
Age					
≤65 years	19/55	34/60	NE	16.6	0.44 (0.25, 0.80)
> 65 years	13/46	26/43	NE	11.1	0.39 (0.20, 0.76)
Region					
US	4/16	9/14	NE	8.6	0.10 (0.01, 0.82)
Western EU	17/53	40/67	NE	16.6	0.45 (0.26, 0.80)
Eastern EU + India	11/32	11/22	NE	16.6	0.66 (0.28, 1.58)

Source: modified, from FDA statistical review

Table 22: FDA subgroup analysis of PFS based on baseline characteristics

Subgroups	Events/N		Median PFS (months)		HR (95% CI)
	Lanreotide	Placebo	Lanreotide	Placebo	
Performance status					
ECOG = 0	28/84	51/84	NE	16.6	0.40 (0.25, 0.65)
ECOG ≥ 1	4/17	9/19	NE	16.6	0.50 (0.15, 1.66)
Krenning scale					
grade 2	8/15	5/15	16.6	NE	1.79 (0.58, 5.49)
grade 3	14/53	32/51	NE	16.6	0.32 (0.17, 0.62)
grade 4	10/33	23/37	NE	11.2	0.25 (0.11, 0.58)
Primary tumor					
pancreatic	18/42	31/49	NE	11.2	0.53 (0.28, 0.97)
non-pancreatic	14/59	29/54	NE	17.0	0.35 (0.18, 0.66)
Tumor Grade					
G1	19/69	40/72	NE	16.8	0.43 (0.25, 0.75)
G2	13/32	19/29	NE	11.2	0.40 (0.19, 0.85)
Hepatic tumor load					
0%	5/16	11/18	NE	22.1	0.52 (0.18, 1.51)
> 0% and ≤ 10%	5/33	19/40	NE	17.1	0.17 (0.06, 0.51)
> 10% and ≤ 25%	4/13	11/17	NE	16.2	0.51 (0.16, 1.62)
> 25% and ≤ 50%	10/23	10/12	NE	8.6	0.37 (0.14, 0.96)
> 50%	8/16	9/16	17.0	8.3	0.28 (0.09, 0.87)
Ki67					
≤2%	13/52	27/51	NE	19.5	0.42 (0.21, 0.82)
>2% and ≤ 5%	12/24	13/19	22.1	13.8	0.56 (0.25, 1.26)
>5% and < 10%	1/7	6/10	NE	11.1	NE
Ki67 unknown	6/18	14/23	NE	16.6	0.51 (0.19, 1.35)

Source: modified, from FDA statistical review

Reviewer comment: The analysis results for subgroups of PFS were consistent with the primary analysis defined in the protocol. For patients with Krenning scale grade 2 octreoscans, the reported HR point estimate was greater than 1; however the sample size for this subgroup is small.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The safety analysis of lanreotide on Study 726 revealed a toxicity profile consistent with the known safety profile of this drug as prescribed for treatment of acromegaly. Common AEs include: abdominal pain, musculoskeletal pain, injection site reactions, vomiting, headache, hyperglycemia, hypertension (HTN) and cholelithiasis. There were two patients on the lanreotide arm who died during the study.

7.1 Methods

The safety review consisted of reviewing datasets submitted in this NDA, CSRs and relevant CRFs. To identify any errors or discrepancies in FDA analysis and that of the Applicant, all narratives were reviewed. Overall, the methods for evaluating the safety of patients in Study 726 were adequate.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The focus of the safety review will be the evaluation of data from Study 726.

7.1.2 Categorization of Adverse Events

In Study 726, all AEs from the time of informed consent up until the end of the study were recorded on the CRFs. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0) preferred term (PT) and system organ class (SOC). The safety profile was characterized by treatment-emergent AEs (TEAEs) defined as any AE that occurred during the study if it was not present prior to receiving the first dose of study treatment or it was present prior to receiving the first dose of study treatment but the intensity increased during the study. Any AE which started on the day of dosing was considered a TEAE. A TEAE was categorized as leading to withdrawal if the action taken with study treatment was documented as "Drug Withdrawn". Patients who had treatment withdrawn due to a TEAE were also withdrawn from the study.

The following analyses of AEs (after coding) were performed by the Applicant:

- Listings are presented and sorted by treatment group, patient ID, onset of AEs, primary SOC, PT and verbatim terms for all AEs recorded during the study.
- Listings of all AEs/SAEs, AEs leading to withdrawal and AEs leading to death are presented.

Pre-existing conditions that worsened during the study were reported as AEs. Any deaths that occurred within 28 days after last administration of study treatment were included; however deaths that occurred during the follow up collection of survival data were reported in the post study survival status CRF and were not reported as SAEs.

AEs were classified as mild, moderate or severe according to the following criteria:

- Mild: Symptoms do not alter the patient's normal functioning;
- Moderate: Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient;
- Severe: Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

The relationship of an AE to the study treatment was classified according to the following:

- Related: Reports include good reasons and sufficient information (e.g., plausible time sequence, dose response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the study treatment that it is plausible, conceivable or likely;
- Not related: Reports include good reasons and sufficient information (e.g., implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the study treatment.

Reviewer comment: The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is typically used for oncology trials conducted in the US; consequently, the toxicity assessment scale used by the Applicant may be unfamiliar to clinicians in the US.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

The safety assessments for Study 726 appear acceptable; particular attention was paid to the evaluation of gallbladder toxicity due to the known hepatobiliary effects of SSAs. A review of the CRFs verified adequate characterization of AEs.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose of lanreotide in Study 726 was 120 mg every 28 days. Data describing exposure is provided in Table 24.

Table 23: Summary of Exposure

	Lanreotide (n=101)	Placebo (n=103)
Mean duration (months)	16.3	14.4
Median (months)	22.1	13.8

Source: adsl.xpt

7.2.2 Explorations for Dose Response

Not performed.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Patients were evaluated by physical examinations, vital signs, ECOG performance status, CBC, blood chemistries, gallbladder echography, and ECG (see Table 4 for Schedule of Assessments).

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolism, clearance and drug-drug interactions were reviewed previously in NDA 022074.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The label for octreotide, an approved SSA, carries a "Warning" for new biliary abnormalities including gallstones, cholelithiasis, sludge and dilatation.

7.3 Major Safety Results

Safety results are summarized in Table 25. There were 101 lanreotide-treated patients and 103 placebo-treated patients evaluable for AEs. The data in Table 25 were confirmed by the reviewer, with the exception that FDA review revealed that an additional two patients on the lanreotide arm were withdrawn for TEAE (see section 6.1.3).

Table 24: Applicant overview of adverse events

	Lanreotide Autogel 120 mg (N=101)	Placebo (N=103)
	n (%)	
Any AE	**90 (89.1)**	**94 (91.3)**
Any TEAEs	**89 (88.1)**	**93 (90.3)**
Maximum intensity of TEAEs		
Severe	26 (25.7)	32 (31.1)
Missing	2 (2.0)	0
Moderate	44 (43.6)	44 (42.7)
Mild	17 (16.8)	17 (16.5)
Most serious causality of TEAEs		
Related	50 (49.5)	29 (28.2)
Not Related	39 (38.6)	64 (62.1)
Causality and Intensity of TEAEs		
Related and severe	4 (4.0)	2 (1.9)
Related and missing	1 (1.0)	0
Related and moderate	27 (26.7)	14 (13.6)
Related and mild	18 (17.8)	13 (12.6)
Unrelated and severe	8 (7.9)	14 (13.6)
Unrelated and moderate	21 (20.8)	35 (34.0)
Unrelated and mild	10 (9.9)	15 (14.6)
SAEs	**25 (24.8)**	**32 (31.1)**
Related SAEs	**3 (3.0)**	**1 (1.0)**
TEAEs leading to withdrawal	**3 (3.0)**	**3 (2.9)**
TEAEs leading to death	**2 (2.0)**	**2 (1.9)**
Deaths[a]	**2 (2.0)**	**2 (1.9)**

Data Source: Table 14.3.1.1 and Listing 16.2.7.2.
N=total number of subjects in group; n=number of subjects with event; AE=adverse event; TEAE=treatment emergent adverse event; SAE=serious adverse event.
Note: In the event of multiple adverse events being reported by the same subject, the most related causality (related > not related) and the maximum intensity (severe > missing > moderate > mild) were counted. For the cross classification of causality and intensity, a subject was summarised under the maximum intensity within the most related causality.
Adverse events with missing relationship are imputed as related.
Calculation of percentages based on N.
a All deaths reported during the study including deaths due to non-TEAEs, TEAEs and deaths due to disease progression and other.

Source: CSR, page 131

7.3.1 Deaths

As of the study termination date (April 9, 2013), nineteen patients (19%) randomized to lanreotide have died, and seventeen (17%) patients initially randomized to placebo have died. On study deaths were defined as those deaths that occurred after the first dose of study drug and within 28 days of the last administration of study drug. Table 26 provides summary information of four on-study deaths that occurred.

Table 25: Summary of deaths on-study

Treatment Arm	Patient ID	Cause of Death	Timing of Death
Lanreotide	(b) (6)	AE: Sepsis, Hepatic Failure	28 day follow-up
		AE: Intestinal Obstruction	28 day follow-up
Placebo		AE: Circulatory Collapse	During treatment
		AE: Gastrointestinal Hemorrhage (ZE syndrome)	28 day follow-up

Source: adae.xpt and CRFs

The following are brief narratives of the two patients who died on-study in the lanreotide arm:

Patien (b) (6) This 57 year old man was diagnosed with a nonfunctioning pNET on (b) (6) and enrolled on Study 726 o (b) (6) Relevant past surgical history includes splenectomy, cholecystectomy and duodenopancreatectomy in (b) (6) (related to the diagnosis of pNET). The patient started study treatment on (b) (6) and received his last injection of study treatment o (b) (6) # 18).

The patient experienced several AEs on study including a hyperglycemia SAE (blood glucose 487 mg/dl) o (b) (6) for which he was hospitalized and diagnosed with new onset diabetes mellitus. During this hospitalization, the patient had elevated brain natriuretic peptide (274 pg/mL) accompanied by lower extremity edema and minimal ascites thought to be related to obstruction of the inferior vena cava (IVC). An echocardiograph revealed mild-moderate reduction of left ventricular function. Also reported were new diagnoses of Sicca syndrome and hypothyroidism (*hypothyreosis*). The patient was discharged o (b) (6) with improvement in glucose levels.

O (b) (6) the patient developed liver failure and Klebsiella sepsis (18 days after the last study treatment), and was hospitalized. It is unknown what treatments he received for these events. The patient died o (b) (6), due to sepsis and hepatic failure. No autopsy was performed. It was reported that the liver failure was related to suspected clinical tumor progression.

Reviewer Comments:

- The patient's diagnosis of hypothyroidism and Sicca syndrome were not captured as AEs. Upon review of the CRFs, it appears the patient had a history of hypothyroidism prior to enrollment on study, and this was not a new AE. There are no additional details available on the diagnosis of Sicca syndrome and no description of related symptoms; therefore there is insufficient information to assess this AE.

-IVC syndrome with ascites and mild-moderate reduction of left ventricular function was not captured as an AE, and additional follow-up details related to this event are not available. This collection of symptoms may have indicated clinical progression, although no imaging results related to this event are reported. In addition, this event may have prolonged hospitalization in which case it would have been captured as an SAE.

-Agree that the likely cause of death is sepsis. The patient's history of splenectomy places him at increased risk for infections from encapsulated organisms such as Klebsiella.

Patien (b) (6) This 82 year old man was diagnosed with a GEP-NET, primary site of tumor unknown, o (b) (6) The patient was enrolled on Study 726 o (b) (6) and received his first and last injection of study treatment o (b) (6) On (b) (6) (b) (6) the patient presented with peritoneal carcinomatosis and intestinal obstruction, confirmed by abdominal x-ray (date not specified). The patient was reportedly medically managed and surgery was not indicated. Treatments included morphine, haloperidol and diet restrictions. On (b) (6) the patient died due to intestinal obstruction. No autopsy was performed. In the opinion of the reporting investigator, the event of intestinal obstruction was not related to the study treatment but was related to the patient's underlying disease.

Reviewer Comment: Agree that the likely cause of death is intestinal obstruction due to disease progression. There are no radiographic data provided to confirm a diagnosis of peritoneal carcinomatosis; however, the history presented is plausibly consistent with the course of this disease. Therefore, the cause of death is more correctly identified as progression of disease.

7.3.2 Nonfatal Serious Adverse Events

There were treatment emergent SAEs reported in 25 of 101patients (25%) treated with lanreotide and 30 of 103 (30%) of patients treated with placebo. This was verified by FDA review of the adae.xpt dataset; however, as noted above, the AE of IVC syndrome with ascites and mild-moderate reduction of left ventricular function was not recorded for patien (b) (6) The Applicant's analysis of SAEs is provided in Table 27 below.

Table 26: SAEs occurring in > 1% of patients in any treatment group by SOC or PT (confirmed by reviewer)

SOC PT	Lanreotide Autogel 120 mg (N=101)		Placebo (N=103)	
	n (%)	E	n (%)	E
Any SAE	**25 (24.8)**	**54**	**32 (31.1)**	**68**
Gastrointestinal disorders	**11 (10.9)**	**16**	**9 (8.7)**	**20**
Vomiting	4 (4.0)	4	2 (1.9)	3
Abdominal pain upper	2 (2.0)	2	0	
Intestinal obstruction	2 (2.0)	2	1 (1.0)	1
Nausea	1 (1.0)	1	2 (1.9)	3
Gastrointestinal haemorrhage	1 (1.0)	2	2 (1.9)	2
Diarrhoea	0		2 (1.9)	3
Infections and infestations	**8 (7.9)**	**11**	**4 (3.9)**	**8**
Urinary tract infection	3 (3.0)	3	1 (1.0)	4
Liver abscess	2 (2.0)	2	0	
Pneumonia	2 (2.0)	2	0	
Sepsis	2 (2.0)	2	0	
Gastroenteritis	0		2 (1.9)	2
Hepatobiliary disorders	**5 (5.0)**	**7**	**3 (2.9)**	**4**
Hepatic failure	2 (2.0)	2	0	
Metabolism and nutrition disorders	**5 (5.0)**	**6**	**4 (3.9)**	**5**
Hyperglycaemia	2 (2.0)	2	0	
Hypoglycaemia	0		2 (1.9)	2
Blood and lymphatic system disorders	**3 (3.0)**	**3**	**0**	
Anaemia	3 (3.0)	3	0	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**2 (2.0)**	**2**	**3 (2.9)**	**3**
Renal and urinary disorders	**2 (2.0)**	**3**	**1 (1.0)**	**1**
Respiratory, thoracic and mediastinal disorders	**2 (2.0)**	**2**	**2 (1.9)**	**2**
Vascular disorders	**2 (2.0)**	**2**	**2 (1.9)**	**2**
Musculoskeletal and connective tissue disorders	**1 (1.0)**	**1**	**2 (1.9)**	**2**
Cardiac disorders	**0**		**5 (4.9)**	**6**
Coronary artery disease	0		2 (1.9)	2
General disorders and administration site conditions	**0**		**2 (1.9)**	**2**
Injury, poisoning and procedural complications	**0**		**2 (1.9)**	**4**
Nervous system disorders	**0**		**2 (1.9)**	**2**
Psychiatric disorders	**0**		**3 (2.9)**	**3**
Confusional state	0		3 (2.9)	3

Data Source: Table 14.3.1.3.1 and Listing 16.2.7.3.
SAE=serious adverse event; N=total number of subjects in group; n=number of subjects with event; E=number of events; PT=preferred term; SOC=system organ class.
When calculating n, subjects with more than one PT within the SOC were only counted once for the SOC.
Calculation of percentages based on N.
Dictionary Name: MedDRA Version: 16.0.

Source: CSR, page 138

7.3.3 Dropouts and/or Discontinuations

Table 28 summarizes reasons for withdrawals, dropouts or discontinuation by treatment arm

Table 27: Withdrawals, dropouts or discontinuations by treatment arm

Reason	Lanreotide (n=101)	Placebo (n=103)
Consent Withdrawn	2	5
Locally assessed disease progression	6	9
Other	3	1
Protocol violation	2	2
Adverse event	5	3

7.3.4 Significant Adverse Events

Vomiting:
There were four SAEs for vomiting reported in the lanreotide arm, and three were TEAEs. Only one event was considered related to lanreotide, described below.

Patien (b) (6)
This 57 year old man with a GEP-NET of unknown primary site diagnosed o (b) (6) (b) (6) was enrolled on Study 726 o (b) (6). O (b) (6) the patient had his first and last dose of lanreotide. Following administration of study treatment, the patient experienced the events of severe abdominal pain and moderate nausea/vomiting and was hospitalized. He was treated with IV fluids, an oral antiemetic (cyclizine) and paracetamol (acetaminophen) and discharged o (b) (6) The events of abdominal pain and vomiting are reported as resolved o (b) (6) and nausea resolved o (b) (6) He withdrew consent to continue in the study o (b) (6)

Reviewer comment: Although this patient's withdrawal from study was not captured as related to an AE, the temporal description raises the possibility that the patient may have withdrawn from study due to the symptoms reported.

Valvular abnormalities:
SSAs have a potential class effect of cardiac valvular disease. On Study 726, there were more cardiac valve disorder AEs in the placebo arm (n=6) than the lanreotide arm (n=2). Although there were no SAEs reported for cardiac valve disorders, one patient on the lanreotide arm had both mitral and tricuspid valve incompetence in the setting of the SAEs "toxic nodular goiter" and "circulatory collapse", described below.

Patien (b) (6)

This 54 year old woman with pNET diagnose (b) (6) was enrolled on Study 726 on (b) (6) Her past medical history was notable for nodular thyroid goite (b) (6) (b) (6) and metastatic NET to the neck lymph nodes (fine needle aspirate biopsy (b) (6) She began study treatment on (b) (6) received her 24th and last injection of study treatment on September 21, 2010 and completed the study on (b) (6)

O (b) (6) the subject received her 14th injection of study treatment, 4 days before the events of toxic nodular goiter and circulatory collapse. On (b) (6) the patient experienced an irregular heart rate and was admitted to the clinic. An ECG revealed atrial (afib) with a frequency of about 130 beats per minute (bpm) and without signs of myocardial ischemia. On the same day, the patient's thyroid stimulating hormone (TSH) was 0.005 µU/mL (normal range: 0.27 to 4.20 µU/mL) and free T3 (fT3) was 15.5 pmol/L (normal range: 3.1 to 6.6 pmol/L). The patient was diagnosed with hyperthyroidism due to toxic nodular goiter which was thought to have been induced by contrast medium used in a previous CT scan (Jod-Basedow phenomenon). The last documented CT before the onset of afib wa (b) (6) The hyperthyroidism was implicated as the cause of afib.

Treatment for the hyperthyroidism included oral Thyrosol (dietary supplement containing vitamins) propranolol and thyrozol (thiamazol) 2.5 mg once every three days. The patient was discharged from the clinic o (b) (6) on her own request (b) (6) the patient's TSH was 0.005 µU/mL, fT3 11.06 pmol/L and free T4 (fT4) 4 range: 0.93 to 1.70 ng/dL) (b) (6) labs revealed TSH of 0.005 µU/mL, fT3 6.48 pmol/L and fT4 was 4.13 ng/dL.

O (b) (6) a thyroid biopsy showed metastases of the patient's NET and o (b) (6) (b) (6) the patient's thyroid hormone was within the normal range (no values reported). On (b) (6), following a cardiology consult, an ECG and an echocardiogram, the patient was diagnosed with "circulation failure" with mitral valve and tricuspid valve incompetence. It was concluded that the patient's cardiac problems had been present prior to entry into the study but had been asymptomatic until the hyperthyroid event occurred i (b) (6) She was treated with once daily oral acenocoumarol (warfarin) 3 mg and acetylsalicylic acid (aspirin) 150 mg. The study treatment was not altered in response to these events.

Reviewer comment: Although it is plausible that the patient's hyperthyroidism may have initiated the atrial fibrillation AE, it is not clear that the cardiac valvular disease is also related to the thyroid disease. Atrial fibrillation can cause dilatation of mitral and tricuspid annuli; however, this might be expected to occur over a longer period of time. The original NDA review for lanreotide determined that minor changes in valvular regurgitation reported in patients treated with lanreotide and octreotide most likely represented both the variability in the degree of valvular regurgitation over time and measurement variability.

7.3.5 Submission Specific Primary Safety Concerns

Cholelithiasis: Gallbladder abnormalities are a common AE reported with SSA use. Forty-one patients on the lanreotide arm (41%) and thirty-six patients on the placebo arm (36%) had undergone prior cholecystectomy. There were thirty-eight patients in the lanreotide arm who were evaluable for new onset of lithiasis or sludge, and thirty-two patients in the placebo arm (i.e., patients with intact gallbladders, data available at baseline and post-baseline, and excluding those who had abnormalities at baseline). Forty percent (14/35) of patients in the lanreotide developed new onset of lithiasis or sludge compared with 17% percent of patients (5/30) in the placebo arm.

Table 28: Analysis of gallbladder ultrasound data

	Lanreotide (n=101)	**Placebo (n=103)**
Patients without prior cholecystectomy	60	67
Patients with BL and follow-up data	38	32
Pts with baseline lithias or sludge	3/35 (9%)	1/32 (3%)
Evaluable patients*	35	30
Pts with new onset lithiasis or sludge	14/35 (40%)	5/30 (17%)

*patients with data available at baseline and post-baseline, and excluding those who had abnormalities at baseline
Source: adgb.xpt, admh.xpt and Table 14.3.3.3 (module 5.3.5.1)

Reviewer comment: According to the NDA review for lanreotide, the incidence of new onset of lithiasis and sludge by end of study E28-52030-717 (Study 717) was approximately 31% in evaluable patients treated with lanreotide. Study 717 was a placebo-controlled, double-blind trial evaluating the efficacy and safety of lanreotide subcutaneous injection in 108 patients with acromegaly. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide (≤ 10%). This raises the question of whether development of gallbladder abnormalities may be a dose dependent adverse event.

Anemia: Anemia is described as an effect associated with SSA use. On Study 726, anemia was reported as an AE in six patients (mild-moderate) on the lanreotide arm and 1 patient on the placebo arm (severe). In addition, on the placebo arm one patient was reported to have anemia of chronic disease and another patient was reported to have vitamin B12 deficiency associated anemia.

FDA analysis of anemia as determined by laboratory values is presented in section 7.4.2.

Thyroid Dysfunction: Both clinical hypothyroidism and decrease thyroid function tests (TFTs) have been reported with lanreotide use. On Study 726, TFTs were not evaluated. There were three patients on the lanreotide arm reported to have thyroid related TEAEs (goiter, toxic nodular goiter, and hyperthyroidism). One patient on the placebo arm was reported to hypothyroidism.

Reviewer comment: Decrease in TFTs is listed in the product label under "Warnings and Precautions", as it pertains to patients with acromegaly.

Cardiovascular:
Bradycardia and HTN have been reported with SSA use, including lanreotide. On Study 726, bradycardia was reported in one patient treated with lanreotide (mild) and two patients treated with placebo (mild). There were fourteen patients treated with lanreotide on Study 726 with HTN or hypertensive crisis compared with one patient on placebo.

FDA analysis of bradycardia and HTN as determined by vital signs is presented in section 7.4.2.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant's assessment of the most common TEAEs occurring in ≥ 5% of patients in either treatment arm are presented in Table 30.

FDA review of the safety data included categorization of AEs occurring in > 5% of patients treated with lanreotide, by pooled preferred terms (PT) is summarized in Table 31. The majority of TEAEs were graded as mild or moderate and twenty-six (26) patients on the lanreotide arm and thirty-two (32) patients on the placebo arm experienced severe TEAEs. Table 32 provides FDA's summary of the most common severe TEAEs by system organ class (SOC) and PTs.

Table 29: Most common TEAEs occurring in ≥ 5% of patients in either arm (confirmed by reviewer)

SOC PT	Lanreotide Autogel 120 mg (N=101)		Placebo (N=103)	
	n (%)	E	n (%)	E
Any TEAE	**89 (88.1)**	**858**	**93 (90.3)**	**815**
Gastrointestinal disorders	**68 (67.3)**	**239**	**65 (63.1)**	**281**
Diarrhoea	35 (34.7)	57	36 (35.0)	76
Abdominal pain	24 (23.8)	32	17 (16.5)	32
Vomiting	19 (18.8)	24	9 (8.7)	27
Nausea	14 (13.9)	28	14 (13.6)	23
Constipation	12 (11.9)	14	13 (12.6)	15
Flatulence	12 (11.9)	13	9 (8.7)	12
Abdominal pain upper	8 (7.9)	8	8 (7.8)	14
Abdominal discomfort	5 (5.0)	8	3 (2.9)	4
Dyspepsia	3 (3.0)	3	6 (5.8)	9
Infections and infestations	**41 (40.6)**	**76**	**46 (44.7)**	**83**
Nasopharyngitis	9 (8.9)	9	16 (15.5)	22
Urinary tract infection	9 (8.9)	15	9 (8.7)	15
Upper respiratory tract infection	2 (2.0)	4	6 (5.8)	6
General disorders and administration site conditions	**36 (35.6)**	**94**	**43 (41.7)**	**88**
Fatigue	10 (9.9)	14	15 (14.6)	17
Asthenia	8 (7.9)	8	5 (4.9)	5
Injection site pain	8 (7.9)	30	4 (3.9)	10
Oedema peripheral	5 (5.0)	5	7 (6.8)	12
Pyrexia	4 (4.0)	6	6 (5.8)	7
Musculoskeletal and connective tissue disorders	**34 (33.7)**	**79**	**24 (23.3)**	**52**
Back pain	12 (11.9)	13	11 (10.7)	11
Arthralgia	10 (9.9)	15	9 (8.7)	10
Musculoskeletal pain	7 (6.9)	8	3 (2.9)	6
Muscle spasms	5 (5.0)	5	4 (3.9)	4
Metabolism and nutrition disorders	**32 (31.7)**	**54**	**19 (18.4)**	**29**
Decreased appetite	10 (9.9)	11	9 (8.7)	11
Diabetes mellitus	7 (6.9)	8	4 (3.9)	4
Hyperglycaemia	6 (5.9)	6	0	
Dehydration	5 (5.0)	7	1 (1.0)	1
Nervous system disorders	**32 (31.7)**	**69**	**19 (18.4)**	**37**
Headache	16 (15.8)	19	11 (10.7)	18
Dizziness	9 (8.9)	12	2 (1.9)	2
Lethargy	5 (5.0)	13	4 (3.9)	4
Vascular disorders	**24 (23.8)**	**29**	**18 (17.5)**	**22**
Hypertension	13 (12.9)	16	5 (4.9)	5
Flushing	4 (4.0)	4	6 (5.8)	6
Skin and subcutaneous tissue disorders	**22 (21.8)**	**36**	**21 (20.4)**	**47**
Pruritus	5 (5.0)	5	5 (4.9)	17
Alopecia	5 (5.0)	5	4 (3.9)	4
Rash	5 (5.0)	6	3 (2.9)	3
Hepatobiliary disorders	**20 (19.8)**	**25**	**10 (9.7)**	**12**
Cholelithiasis	14 (13.9)	15	7 (6.8)	7
Investigations	**18 (17.8)**	**32**	**14 (13.6)**	**24**
Weight decreased	8 (7.9)	8	9 (8.7)	10
Pancreatic enzymes decreased	6 (5.9)	7	0	
Respiratory, thoracic and mediastinal disorders	**17 (16.8)**	**28**	**15 (14.6)**	**29**

Table 30 (continued)

SOC PT	Lanreotide Autogel 120 mg (N=101)		Placebo (N=103)	
	n (%)	E	n (%)	E
Dyspnoea	6 (5.9)	7	1 (1.0)	2
Cough	5 (5.0)	5	3 (2.9)	8
Oropharyngeal pain	5 (5.0)	5	3 (2.9)	4
Psychiatric disorders	**14 (13.9)**	**20**	**8 (7.8)**	**11**
Blood and lymphatic system disorders	**8 (7.9)**	**14**	**7 (6.8)**	**7**
Anaemia	6 (5.9)	6	1 (1.0)	1
Eye disorders	**8 (7.9)**	**8**	**11 (10.7)**	**12**
Injury, poisoning and procedural complications	**8 (7.9)**	**12**	**16 (15.5)**	**30**
Renal and urinary disorders	**8 (7.9)**	**9**	**5 (4.9)**	**7**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**6 (5.9)**	**10**	**8 (7.8)**	**8**
Cardiac disorders	**6 (5.9)**	**9**	**7 (6.8)**	**24**

Data Source: Table 14.3.1.2.
TEAEs=treatment emergent adverse event; PT=preferred term; SOC=system organ class; N=total number of subjects in group; n=number of subjects with event; E=number of events.
When calculating n, subjects with more than one PT within the SOC were only counted once for the SOC. Calculation of percentages based on N.
Dictionary Name: MedDRA Version: 16.0

Source: CSR, pages 132-133

Table 30: FDA review of AEs occurring in > 5% of patients treated with lanreotide, and by pooled by PTs

Adverse Reaction	Lanreotide (n=101)		Placebo (n=103)	
	All Grades	Severe	All Grades	Severe
Any Adverse Reactions	**88**	**26**	**90**	**31**
Abdominal pain[1]	34*	6	24*	4
Musculoskeletal pain[2]	19	2	13	2
Injection site reaction[3]	15	0	7	0
Vomiting	19*	2	9*	2
Headache	16	0	11	1
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

Includes preferred terms:
1.abdominal pain, abdominal pain upper/lower, abdominal discomfort
2.myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain
3.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.diabetes mellitus (DM), glucose tolerance impaired, hyperglycemia, type 2 DM
5.hypertension, hypertensive crisis
6.depression, depressed mood
* Includes serious adverse events (SAEs)

Source: adae.xpt

Reviewer comment:
-Pooling of PTs did not reveal any additional toxicity signals, with the exception of slightly increased incidence of depression in patients treated with lanreotide. The clinical significance of this is unclear. SSAs have been considered for use in treating patients with depression.

-The Applicant included anemia as an AE occurring more frequently in the lanreotide arm (i.e., n=6 vs. n=1 in the lanreotide and placebo arms, respectively) however, a review of the laboratory data did not support this finding. Please see section 7.4.2.

Table 31: Severe TEAEs occurring in > 1% of patients on the lanreotide arm

SOC PT	Lanreotide (n=101)	Placebo (n=101)
Gastrointestinal disorders		
Abdominal pain upper	3	1
Abdominal discomfort	1	0
Abdominal pain	2	4
Abdominal pain lower	1	0
Diarrhea	2	8
Intestinal obstruction	2	1
Vomiting	2	2
Hepatobiliary disorders		
Hepatic failure	3	0
Infections and infestations		
Urinary tract infection	3	1
Infections and infestations		
Liver abscess	2	0
Pneumonia	2	0

Source: adae.xpt

7.4.2 Laboratory Findings

Hemoglobin: On Study 726, the normal range for Hgb was reported as 130-170 g/dL in men and 116-154 g/dL in women. FDA analysis of hemoglobin (Hgb) levels was conducted by gender. Patients with baseline and at least one follow-up value for Hgb were included in the analysis (evaluable patients).

There were seventy-four (74) patients on the lanreotide arm (35 men, 39 women) and seventy-two (72) patients on the placebo arm (39 men, 33 women) with normal baseline Hgb. Of these patients, fifteen on the lanreotide arm (20%) had a ≥ 10 point drop in Hgb by the end of treatment compared with twenty-one patients (29%) on the placebo arm. There does not appear to be a significant increase in anemia (as determined by Hgb levels) in patients treated with lanreotide compared with patients treated with placebo.

Table 32: FDA analysis of Hgb levels

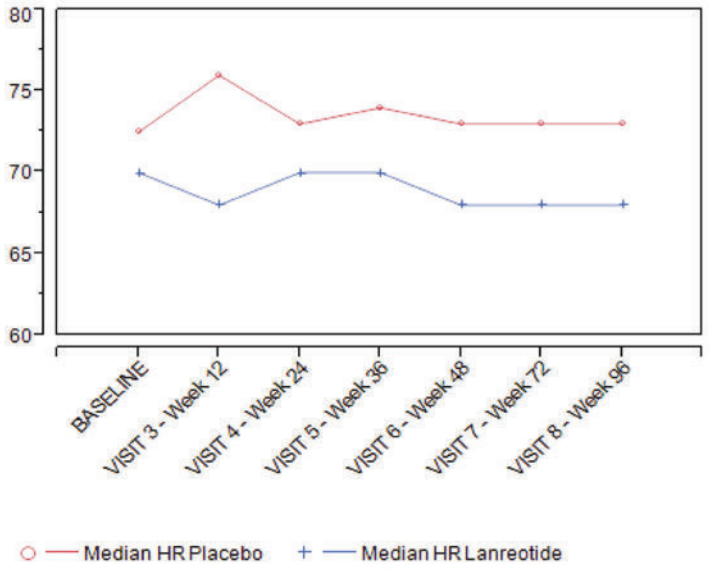
	Lanreotide (n=101)		Placebo (n=103)	
	Men (n=53)	**Women (n=48)**	**Men (n=54)**	**Women (n=49)**
Evaluable patients	46	44	45	40
Patients with baseline Hgb < LLN* AND with decreased Hgb ≥ 10 g/dL	11 (24%) 4/11 (36%)	5 (11%) 2/5 (40%)	6 (13%) 2/6 (33%)	7 (18%) 0
Patients with baseline normal Hgb AND with decreased Hgb ≥ 10 g/dL	35 (76%) 9/25 (26%)	39 (89%) 6/39 (15%)	39 (87%) 15/39 (38%)	33 (83%) 6/33 (18%)

Source: advs.xpt **LLN: lower limit of normal*

7.4.3 Vital Signs

Bradycardia: FDA analysis determined that in eighty-two patients with baseline normal heart rate (≥ 60 bpm) treated with lanreotide on Study 726, the incidence of bradycardia (HR < 60 bpm) was 23% (19/82) compared to 16 % in placebo treated patients (15/95). Ten patients (12%) had documented heart rates < 60 bpm on more than one visit. There are no documented clinical symptoms correlating with these episodes of bradycardia. Figure 4 depicts the median heart rate of patients on Study 726

Figure 4: Median heart rate (bpm) on Study 726

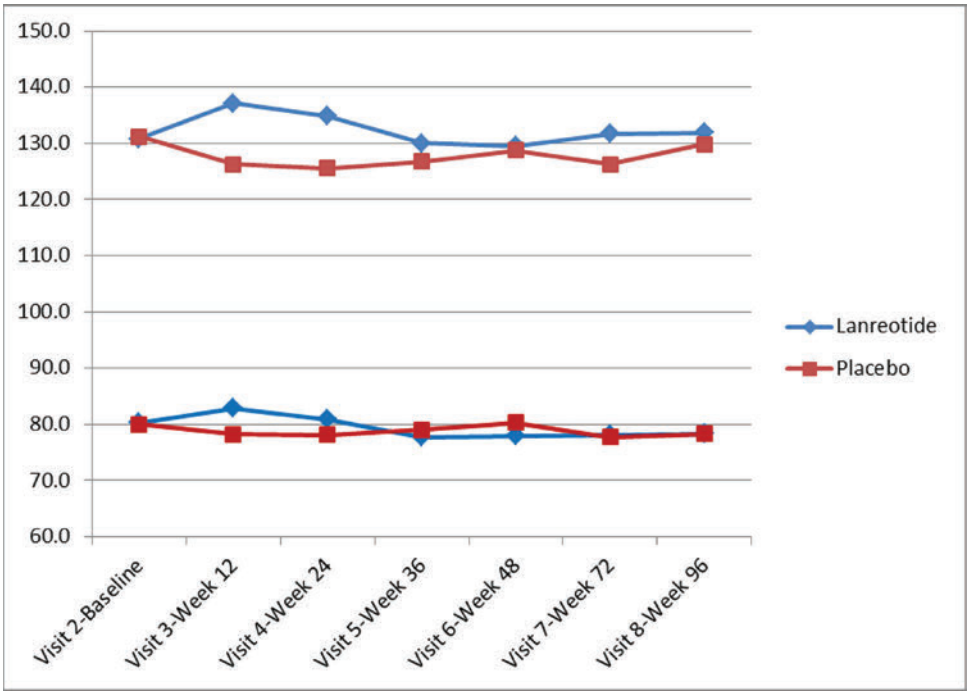


Source: advs.xpt

Reviewer comment: Bradycardia is listed under "warnings and precautions" of the label for lanreotide use in patients with acromegaly.

Hypertension:
Figure 5 summarizes the mean change in blood pressure (BP) from baseline by treatment arm. On the lanreotide arm, the most significant change in BP occurred between visit 2 (baseline) and visit 3. There was a mean increase of 6.3 mmHg in systolic BP (130.8 to 137.1) and a mean increase of 2.6 mmHg in the diastolic BP (80.3 to 82.9) from baseline to week 12. These changes are not clinically significant.

Figure 5: Absolute median change in systolic and diastolic BP (mmHg) between baseline and week 96



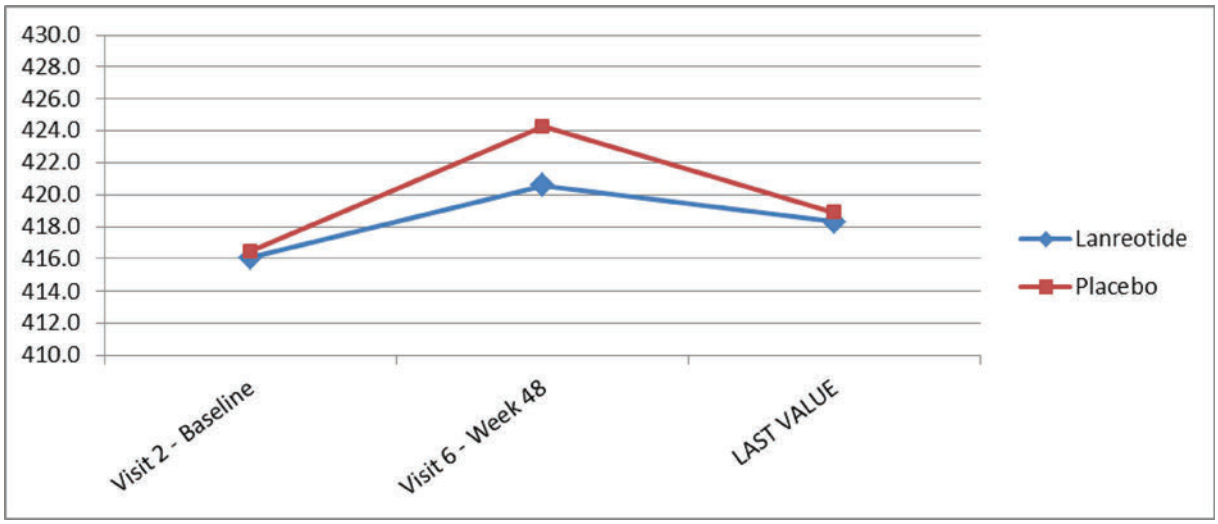
Source: advs.xpt

7.4.4 Electrocardiograms (ECGs)

According to the Applicant, one patient on the lanreotide arm had an abnormal ECG reading at early withdrawal and left ventricular hypertrophy (patien [redacted] (b) (6) and the ECG abnormality was reported as a TEAE. One patient in the placebo group had afib at baseline and week 48, and Wolff-Parkinson-White syndrome at week 96. None of the events were serious or considered by the Investigator to be related to study treatment.

The absolute mean change in QTc interval (msec) between baseline and last follow-up value was similar in both arms: 2.2 msec for the lanreotide treated patients and 2.5 msec for the placebo treated patients.

Figure 6: Mean change in QTc (msec) between baseline and last visit



Source: adeg.xpt

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies submitted for this review.

7.4.6 Immunogenicity

Please see Dr. Jun Yang's clinical pharmacology review for a complete discussion of immunogenicity.

Analysis of anti-lanreotide antibodies was based on a radioimmunoprecipitation analysis (RIPA). Lanreotide putative antibodies determination of serum samples collected in clinical study 726 were first conducted by Ipsen Pharma S.A. Due to the closure of Ipsen Pharma Barcelona site in December 2011, the method to determine putative antibodies against Lanreotide was validated at (b) (4) Ipsen study code TR-001148) and the analysis of the remaining samples from study 2-55-52030-726 was transferred (b) (4) (b) (4) with a new bioanalytical protoco (b) (4) Ipsen study code TR-001216).

The incidence of anti-drug antibodies (ADAs) to lanreotide in studies 726, 730, 718 and 166 were variable and ranged from 0.93% after 48 weeks of treatment in Study 730 to 11% after 72 weeks of treatment on Study 726. On Study 726, 3 of 82 patients remaining on study after 24

weeks were positive of ADA, 7 of 67 patients after 48 weeks on treatment, 6 of 57 after 72 weeks on treatment, and 8 of 84 patients after 96 weeks on treatment. Assessment for neutralizing antibodies was not conducted. The impact of immunogenicity on duration of treatment could not be determined due to the relatively small number of patients who developed ADAs on Study 726.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A single lanreotide dose regimen was administered to patients on this study. In general, the adverse event profile of lanreotide 120 mg every 4 weeks appears similar to the adverse event profile for lanreotide dosing for patients with acromegaly. Dosing for acromegaly is not continuous, and varies based on laboratory measurements of growth hormone (GH) and insulin-like growth factor (IGF); therefore, no definite conclusions can be made.

7.5.2 Time Dependency for Adverse Events

According to the Applicant, the percentage of patients reporting TEAEs was highest in the first 12 weeks of treatment in the lanreotide arm (61.4%) compared to the placebo arm (50.5%). The percentage of patients reporting TEAEs in the placebo group was highest between 12 and 24 weeks post initiation of treatment (62.0%, compared to 53.7% in the lanreotide group). A summary of TEAEs by timepoint of onset is presented in Table 33 (confirmed by reviewer).

Table 33: Summary of TEAEs by timepoint of onset

Timepoint	Lanreotide Autogel 120 mg			Placebo		
	N	n (%)	E	N	n (%)	E
Any TEAE reported:						
Within 12 weeks	101	62 (61.4)	246	103	52 (50.5)	168
>12 to 24 weeks	95	51 (53.7)	142	100	62 (62.0)	147
>24 to 36 weeks	84	34 (40.5)	85	92	43 (46.7)	110
>36 to 48 weeks	79	31 (39.2)	71	79	29 (36.7)	85
>48 to 72 weeks	72	42 (58.3)	129	63	32 (50.8)	131
>72 to 96 weeks	62	36 (58.1)	121	47	28 (59.6)	113
>96 weeks	23	6 (26.1)	8	14	3 (21.4)	4
Exact onset unknown	101	29 (28.7)	56	103	25 (24.3)	57

Data Source: Table 14.3.1.7, Listing 16.2.7.2 and Statistical Appendix (16.1.9).
TEAE=treatment emergent adverse event; N=number of subjects still exposed to treatment at the start of each time interval; n=number of subjects with event; E=number of events.
Calculation of percentages based on N.
Timepoint of onset of the TEAE is calculated as: (TEAE start date - date of start of study treatment + 1)/7.
Dictionary Name: MedDRA Version: 16.0.

7.5.3 Drug-Demographic Interactions

In the efficacy analysis of subgroups, the HR for demographic factors of age and gender did not differ significantly. Table 35 summarizes the incidence of TEAEs by age group and Table 36 summarizes by gender.

Table 34: Incidence of TEAEs occurring in ≥ 5% of patients treated with lanreotide by PT and by age group

	Lanreotide (n=101)		Placebo (n=103)	
SOC PT	**Age < 65 (n=53)**	**Age ≥ 65 (n=48)**	**Age < 65 (n=58)**	**Age ≥ 65 (n=45)**
Gastrointestinal disorders				
Diarrhea	19	16	19	17
Abdominal pain	12	12	8	9
Vomiting	9	10	5	4
Constipation	4	8	5	8
Flatulence	8	4	6	3
Abdominal pain upper	1	7	6	2
Nausea	7	7	8	6
Abdominal discomfort	4	1	3	0
Hepatobiliary disorders				
Cholelithiasis	11	3	5	2
Vascular disorders				
Hypertension	5	8	4	1
Musculoskeletal and connective tissue disorders				
Back pain	6	6	8	3
Arthralgia	8	2	6	3
Musculoskeletal pain	5	2	2	1
General disorders and administration site conditions				
Fatigue	5	5	6	9
Asthenia	6	2	4	1
Injection site pain	6	2	2	2
Edema peripheral	2	3	2	4
Metabolism and nutrition disorders				
Diabetes mellitus	6	1	2	2
Hyperglycemia	5	1	0	0
Dehydration	2	3	1	0
Decreased appetite	3	7	4	5
Infections and infestations				
Nasopharyngitis	3	6	11	5
Urinary tract infection	7	2	4	5

	Lanreotide (n=101)		Placebo (n=103)	
SOC PT	**Age < 65 (n=53)**	**Age ≥ 65 (n=48)**	**Age < 65 (n=58)**	**Age ≥ 65 (n=45)**
Nervous system disorders				
Headache	10	6	6	5
Dizziness	5	4	2	0
Lethargy	4	1	3	1
Investigations				
Weight decreased	3	5	4	5
Respiratory, thoracic and mediastinal disorders				
Dyspnea	3	3	1	0
Oropharyngeal pain	2	3	2	1
Cough	4	1	1	2
Skin and subcutaneous tissue disorders				
Alopecia	3	2	1	3
Pruritus	3	2	3	2
Rash	3	2	2	1

Source: adae.xpt

The incidence of specific AEs was similar between the age groups in most cases. Exceptions include headache, cholelithiasis and diabetes which appear to occur more frequently in patients < 65 in the lanreotide arm.

Table 35: Incidence of TEAEs occurring in ≥ 5% of patients treated with lanreotide by PT and by gender

	Lanreotide (n=101)		Placebo (n=103)	
SOC PT	**Women (n=48)**	**Men (n=53)**	**Women (n=49)**	**Men (n=54)**
Gastrointestinal disorders				
Diarrhea	15	20	17	19
Abdominal pain	13	11	9	8
Vomiting	8	11	3	6
Constipation	7	5	7	6
Flatulence	3	9	3	6
Abdominal pain upper	5	3	4	4
Nausea	8	6	5	9
Abdominal discomfort	4	1	1	2
Hepatobiliary disorders				
Cholelithiasis	7	7	3	4
Vascular disorders				
Hypertension	6	7	1	4

	Lanreotide (n=101)		Placebo (n=103)	
SOC PT	**Women (n=48)**	**Men (n=53)**	**Women (n=49)**	**Men (n=54)**
Musculoskeletal and connective tissue disorders				
Back pain	3	9	6	5
Arthralgia	4	6	6	3
Musculoskeletal pain	2	5	1	2
General disorders and administration site conditions				
Fatigue	5	5	5	10
Asthenia	5	3	4	1
Injection site pain	3	5	3	1
Edema peripheral	2	3	3	3
Metabolism and nutrition disorders				
Diabetes mellitus	2	5	0	4
Hyperglycemia	3	3	0	0
Dehydration	1	4	1	0
Decreased appetite	3	7	2	7
Infections and infestations				
Nasopharyngitis	6	3	6	10
Urinary tract infection	4	5	6	3
Nervous system disorders				
Headache	7	9	7	4
Dizziness	4	5	1	1
Lethargy	1	4	2	2
Investigations				
Weight decreased	1	7	2	7
Respiratory, thoracic and mediastinal disorders				
Dyspnea	5	1	0	1
Oropharyngeal pain	2	3	2	1
Cough	3	2	1	2
Skin and subcutaneous tissue disorders				
Alopecia	5	0	2	2
Pruritus	1	4	4	1
Rash	3	2	1	2

Source: adae.xpt

In general, the incidence of specific AEs was similar between the women and men.

7.5.4 Drug-Disease Interactions

None known.

7.5.5 Drug-Drug Interactions

There are no new drug-drug interactions. The following is excerpted from the current label:

"Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is altered and antidiabetic treatment should be adjusted accordingly."

"Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and, therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic levels."

"The pharmacological gastrointestinal effects of Somatuline Depot may reduce the intestinal absorption of concomitant drugs. Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the availability of bromocriptine. Concomitant administration of bradycardia inducing drugs (e.g. beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dose adjustments of concomitant medication may be necessary. Vitamin K absorption was not affected when concomitantly administered with lanreotide."

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no human carcinogenicity studies submitted with this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to the review for NDA 22074. Lanreotide has been shown to cause embryo lethality in rats and decreased fetal survival and increased fetal skeletal/soft tissue abnormalities in rabbits. There are no adequate and well-controlled studies in pregnant women. The current label advises that lanreotide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no pediatric studies submitted with this sNDA. GEP-NETs are primarily an adult malignancy and lanreotide was granted orphan-drug designation for the treatment of neuroendocrine tumors on August 25, 2011; therefore, the indication for this supplement is exempt from the requirements to the Pediatric Research Equity Act (PREA).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reports of overdose on Study 726. Lanreotide does not appear to have drug abuse potential, withdrawal, or rebound effects.

7.7 Additional Submissions / Safety Issues

Study 729

Patients on Study 726 with either stable disease at end of study (irrespective of treatment received) or PD during treatment with placebo were eligible to participate in study 2-55-52030-729 (Study 729) an ongoing, open-label extension of Study 726. Some investigational sites elected not to participate in this extension study; therefore, not all eligible patients on Study 726 were able to enroll on Study 729. The primary objective of Study 729 was to assess the long term safety of administration of lanreotide 120 mg every 28 days in patients with nonfunctioning GEP-NET. One interim analysis of Study 729 has been conducted as planned.

A total of eighty-eight patients enrolled on Study 729 (41 patients from Study 726 continued on lanreotide, 47 patients who had received placebo). Table 37 summarizes the most common AEs occurring on Study 729, by SOC and PT.

Table 36: AEs occurring in ≥5% of patients on Study 729

SOC PT	Lanreotide (n=88)
	n (%)
Gastrointestinal disorders	
Diarrhea	24 (27)
Abdominal pain	12 (14)
Abdominal pain upper	12(14)
Nausea	8 (9)
Vomiting	8 (9)
Abdominal distension	7 (8)
Flatulence	7 (8)
Constipation	6 (7)
Abdominal discomfort	5 (6)
Dyspepsia	5 (6)
Steatorrhoea	4 (5)
Vascular disorders	
Hypertension	12 (14)
Hepatobiliary disorders	
Cholelithiasis	11 (13)
General disorders and administration site conditions	
Fatigue	9 (10)
Asthenia	6 (7)
Injection site pain	4 (5)
Edema peripheral	4 (5)
Metabolism and nutrition disorders	
Decreased appetite	9 (10)
Diabetes mellitus	4 (5)
Musculoskeletal and connective tissue disorders	
Arthralgia	8 (9)
Back pain	6 (7)
Nervous system disorders	
Headache	8 (9)
Dizziness	6 (7)
Infections and infestations	
Bronchitis	6 (7)
Urinary tract infection	5 (6)
Nasopharyngitis	4 (5)
Viral infection	4 (5)
Investigations	
Weight decreased	6 (7)

SOC PT	Lanreotide (n=88)
	n (%)
Psychiatric disorders	
Insomnia	5 (6)
Skin and subcutaneous tissue disorders	
Dry skin	5 (6)
Rash	5 (6)
Respiratory, thoracic and mediastinal disorders	
Cough	4 (5)
Oropharyngeal pain	4 (5)

Reviewer comment: The toxicity profile appears similar for patients treated on Study 729 compared with Study 726.

Safety update

The Applicant submitted a 120-Day safety update as a supplement to the application on October 27, 2014. The safety update includes separate analysis for new data since the cutoff date for the safety summary included in the efficacy supplement, and cumulative data (i.e., all data available up to the 120-Day safety update cut-off date). The updated data relevant to the proposed indication of treatment of GEP-NETs are from two on-going supportive studies: Study 729 and Study 730. Overall, the data included in the 120-Day safety update did not reveal any new safety findings, and did not substantially change the analyses included in this supplement.

8 Postmarket Experience

The most recent periodic safety update report (PSUR) submitted for lanreotide encompasses the period from June 1, 2013 to May 31, 2014. During this reporting period, 3 signals of allergic reactions, hypothyroidism and impaired renal function/acute renal failure were evaluated. Based on an evaluation of these toxicity signals, the Applicant has included events of allergic reactions including angioedema, anaphylaxis and hypersensitivity as Undesirable Effects in the post-marketing safety data section of the lanreotide Company Core Safety Information (CCSI). The MAH concluded that no association could be identified between hypothyroidism or impaired renal function/acute renal failure following treatment with lanreotide to justify the inclusion of these events in the CCSI.

In addition, on June 19, 2014, the Applicant submitted a labeling supplement to NDA 22074 to include allergic reactions in the current label under POSTMARKETING EXPERIENCE section and to include the statement that lanreotide should not be prescribed to patients with hypersensitivity to somatostatins or related peptides under the CONTRAINDICATIONS section.

9 Appendices

9.1 Labeling Recommendations

The Applicant has submitted labelling changes to include data from Study 726. As of the completion of this review, labeling negotiations are ongoing and nearing completion.

9.2 Advisory Committee Meeting

This application did not warrant an oncology drug advisory committee (ODAC) meeting as there were no significant safety or efficacy concerns with the design, conduct or outcome of Study 726. Please see Section 1.2 for discussion of risk/benefit, and the addendum to this review discussing recommendations from experts in the field of NETs.

9.3 Literature Review/References

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/s/

JOOHEE SUL
11/26/2014

SUZANNE G DEMKO
11/26/2014
I have read this review and discussed the contents with the reviewer. I agree with the findings and conclusions contained herein.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

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 Serial Number:	22074/ S11
Drug Name:	SOMATULINE® DEPOT (Lanreotide)
Indication(s):	Gastroenteropancreatic Neuroendocrine tumors (GEP-NET)
Applicant:	Ipsen Pharma
Submission Date:	06/23/2014
PDUFA Date:	12/23/2014
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Weishi Yuan
Concurring Reviewers:	Kun He, Team Leader Thomas Gwise, Deputy Division Director
Medical Division:	Oncology Products 2
Clinical Team:	Joohee Sul, Clinical Reviewer Suzanne Demko, Team Leader Patricia Keegan, Division Director
Project Manager:	Missiratch Biable
Keywords:	Log-rank Test, Hazard ratio, Progression-Free Survival, GEP-NET

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The applicant submitted data and final study reports of a randomized study to support approval for lanreotide as the treatment of patient (b) (4) (b) (4) (b) (4) Lanreotide was previously approved as a long-term treatment of acromegalic patients.

This application was based on a single randomized study, Study 2-55-52030-726 (Study 726), titled "Phase III, randomized, double blind, stratified comparative, placebo controlled, parallel group, multi-center study to assess the effect of deep subcutaneous injections of lanreotide autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning entero pancreatic endocrine tumor." The primary endpoint was progression free survival (PFS) assessed by central review. Secondary endpoints included proportion of patients alive and without progression at 48 and 96 weeks and time to progression (TTP). The study planned to enroll 200 patients.

A total of 204 patients were randomized in a 1:1 allocation with 101 in the lanreotide arm and 103 in the placebo arm. Randomization was stratified by progression at baseline (yes/no) and previous therapy at entry (yes/no). Lanreotide was shown to prolong PFS compared with placebo with p-value = 0.0002 based on a stratified log-rank test. The median PFS was not reached in the lanreotide arm and 72 weeks in the placebo arm. The estimated HR was 0.41 with 95% CI (0.26, 0.64) based on a stratified Cox model.

Based on the data and analyses, lanreotide showed a statistically significant improvement in PFS compared with placebo. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will defer to the clinical review team.

2. INTRODUCTION

The applicant submitted data and final study report of a pivotal study to seek regular approval for a new indication for lanreotide. This application was based on Study 2-55-52030-726 (Study 726), a Phase 3, randomized, double blind, placebo controlled, parallel group, multi-center study to assess the effect of deep subcutaneous injections of lanreotide autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning entero pancreatic endocrine tumor.

2.1 Overview

2.1.1. Class and Indication

Lanreotide is a synthetic octapeptide analogue of somatostatin with a longer half life than the native molecule. Somatostatin analogues are the treatment of choice for hormone related syndromes associated with neuroendocrine tumors (NETs). Lanreotide autogel is a prolonged release, pharmaceutical form of lanreotide. The formulation is a supersaturated solution for injection supplied as a prefilled polypropylene syringe with (b) (4) needle.

2.1.2. Regulatory History

Lanreotide Injection was approved for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy on August 30, 2007.

In November 2010, FDA and the applicant held a Type B, pre-IND meeting to discuss the study design for Study 726 including the planned statistical methods for primary efficacy analysis and supportive sensitivity analyses. FDA recommended that the primary analysis be changed from the Cox proportional hazards model to either a stratified or unstratified log rank test, and overall survival (OS) be a secondary endpoint. FDA emphasized the need to minimize missing data to allow for a valid interpretation of progression free survival (PFS) as a primary efficacy endpoint.

In April 2011, IND109644 was submitted for the indication of NET. In August 2011, lanreotide acetate was granted Orphan Drug Designation for the treatment of neuroendocrine tumors.

In January 2014, FDA and the applicant held a Type C, pre-sNDA meeting to discuss the adequacy of the efficacy data obtained from Study 726 to support the filing of a sNDA. FDA did not agree with the applicant's plan (b) (4)

(b) (4)

The sNDA was submitted on June 23, 2014.

2.1.3. Study Reviewed

Study 2-55-52030-726 (Study 726) was a Phase 3, randomized, double blind, placebo controlled, parallel group, multi-center study to assess the effect of deep subcutaneous injections of lanreotide autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning entero pancreatic endocrine tumor.

The study consisted of two periods: the screening period and the treatment period. The screening period consisted of the screening visit and followed by a period of maximum 14 weeks during which two CT-scans were to be performed in order to assess tumor progression. In the treatment period patients were randomized in a 1:1 ratio to receive either lanreotide autogel 120mg or placebo every 28 days. Randomization was stratified by tumor progression (presence or absence) and previous therapies (yes or no) at study entry. For each individual patient, study participation would be 110 weeks (about 2 years), including a screening period of 14 weeks for the longest and a treatment period of 96 weeks duration for the longest. After finishing treatment in this study, the investigator would record overall survival (OS) status annually, on the anniversary of the patient's first study medication administration, until last patient last visit (end of study), irrespective of subsequent treatment.

The primary objective of this study was to compare the treatment effect of lanreotide with that of placebo on progression free survival (PFS). The secondary objectives were to compare the treatment effect of lanreotide with that of placebo on the proportion of patients alive and without progression between both arms at 48 and 96 weeks, time to progression (TTP), and OS.

A total of 204 patients were randomized in a 1:1 allocation with 101 in the lanreotide arm and 103 in the placebo arm. The study was initiated on June 22, 2006 and completed on April 9, 2013.

2.2 Data Sources

Data used for review is from the electronic submission received on June 30, 2014. The network path is

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

Study 2-55-52030-726 (Study 726) was a Phase 3, randomized, double blind, placebo controlled, parallel group, multi-center study to assess the effect of deep subcutaneous injections of lanreotide autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning entero pancreatic endocrine tumor.

The study consisted of two periods: the screening period and the treatment period. The screening period consisted of the screening visit and followed by a period of maximum 14 weeks during which two CT-scans were to be performed in order to assess tumor progression. In the treatment period patients were randomized in a 1:1 ratio to receive either lanreotide autogel 120mg or placebo every 28 days. Randomization was stratified by tumor progression (presence or absence) and previous therapies (yes or no) at study entry. For each individual patient, study participation would be 110 weeks (about 2 years), including a screening period of 14 weeks for the longest and a treatment period of 96 weeks duration for the longest. After finishing treatment in this study, the investigator would record OS status annually, on the anniversary of the patient's first study medication administration, until last patient last visit (end of study), irrespective of subsequent treatment.

The primary objective of this study was to compare the treatment effect of lanreotide with placebo on progression free survival (PFS). The secondary objectives were to compare the treatment effect of lanreotide with placebo on the proportion of patients alive and without progression between both arms at 48 and 96 weeks, TTP, and OS.

A DSMC was set up to undertake interim safety review of the study's progress, approximately every 6 months.

Reviewer's Comments:

1. The original study protocol (dated November 2005) included an efficacy interim analysis at 50% information but was removed at Amendment 1 (dated January 2007). And a plan for sample size re-estimation was added.
2. OS was added as a secondary endpoint at Amendment 6 (dated February 2011).
3. The power for the PFS analysis was increased from 80% to 90% and the number of events required for primary analysis was increased from 120 to 132. Please see more information in Section 3.2.3.
4. Objective response rate (ORR) data was not reported.

3.2.2. Efficacy Measures

The primary endpoint PFS was defined as the time to either disease progression (PD, measured using RECIST criteria and confirmed via centralized review) or death occurring within 96 weeks after first treatment administration.

Secondary endpoint included

- Proportion of patients without PD or death in each treatment arm at Weeks 48 and 96,
- Time to progression for the subset of patients who had a progression,
- Overall survival (OS), defined as the time from randomization to death due to any cause.

3.2.3. Sample Size Consideration

In the final Study 763 protocol, the sample size consideration was based on the following estimates and assumptions:

- 1:1 randomization scheme.
- Two-sided type I error rate of 0.05 and 90% power.
- The expected rate of PFS in placebo arm = 0.80,
- The expected rate of PFS in active treatment arm = 0.60,
- A constant hazard ratio of 0.57 over time.

The planned sample size was 200 patients with 132 PFS events for the final analysis. A total of 204 patients were randomized with 101 in the lanreotide arm and 103 in the placebo arm.

A sample size re-estimation was planned when 100 patients were treated for one year or when 66 events have occurred.

Reviewer's Comments:

1. Assuming the PFS events in both arms follow an exponential distribution, the assumptions of expected rates of PFS being 0.8 in the placebo arm and 0.6 in the lanreotide arm are equivalent to assuming median PFS being 41.3 weeks in the placebo arm and 72.6 weeks in the lanreotide arm.

2. Though the protocol stated that approximately 132 events were required to conduct the final PFS analysis, the study was stopped at 96 PFS events and the final PFS analysis was conducted. The applicant argues that "Study 726 was designed as a fixed-time duration study. Patients were to be treated after randomisation to Somatuline Depot 120 mg or placebo for a defined period of 2 years. Based on the design, the study enrolled 204 patients and the study was considered to be completed after the last patient received 2 years of study treatment (Module 5.3.5.1, Study 726 protocol, Section 4.1.3). As a result, by design, the study was not stopped early but completed as designed."

3. According to the applicant's CSR, a sample size re-estimation was performed on in June 2010. All patients randomized before June 16, 2010 were included in the calculation. There was no evidence to change the planned sample size of the study.

4. Since the OS endpoint was not added to the protocol until late in the course of the study, OS was not adequately powered.

3.2.4. Statistical Methodologies

The Intent-to-Treat (ITT) population was used for the efficacy analysis. The ITT population comprises all randomized patients regardless of whether or not treatment was administered. All patients in the study received at least one dose of study treatment.

The time-to-event endpoints were summarized using the Kaplan-Meier estimates and the difference between the two treatment arms was tested using a stratified log-rank test, stratifying for tumor progression (presence or absence) and previous therapies (yes or no) at study entry.

The proportion of patients alive and without progressive disease (PD) at Weeks 48 and 96 was compared between treatment arms within a multiple logistic regression analysis using baseline stratification factors (presence/absence of progression at baseline and presence/ absence of previous therapy at entry) as covariates.

For the secondary endpoints, a statistical procedure to adjust multiple endpoints was not proposed.

Reviewer's Comments:

Since SAP did not propose a multiplicity adjustment, the secondary endpoints were considered as exploratory.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

A total of 204 patients were randomized to one of two treatment arms using a 1:1 randomization ratio with 101 patients in the lanreotide arm and 103 patients in the placebo arm. A total of 48 study centers enrolled patients in Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, United Kingdom and the United States of America.

The study was initiated (first patient first visit) on June 22, 2006 and completed (last patient last visit) on April 9, 2013. The study had a fixed duration of two years.

A total of 70 sites were opened for this study and 48 sites enrolled patients. A total of 264 patients were screened and 204 patients were randomized into the study. A total of 30 patients were enrolled in the USA, with 16 in the lanreotide arm and 14 in the placebo arm. The patient disposition is summarized in Table 1.

Table 1. Patient Disposition

	Lanreotide N = 101	**Placebo** N = 103
Randomized	101 (100)	103 (100)
Received Investigational Product	101 (100)	103 (100)
Completed study	56 (55.4)	34 (33.0)
Withdrawal	45 (44.6)	69 (67.0)
Adverse Event	3 (3.0)	3 (2.9)
Protocol Violation	2 (2.0)	2 (1.9)
Consent Withdrawn	3 (3.0)	5 (4.9)
Disease Progression*	27 (26.7)	49 (47.6)
Locally Assessed Progression**	6 (5.9)	9 (8.7)
Other	3 (4.0)	1 (1.0)

* Centrally assessed disease progression (using RECIST criteria).
** Withdrawn due to disease progression based on the investigator's judgment despite there being a central assessment of stable disease.

Demographic characteristics at baseline are summarized in Table 2.

Table 2. Demographics

	Lanreotide N = 101	**Placebo** N = 103
Randomized	101 (100)	103 (100)
Gender		
Male	53 (52.5)	54 (52.4)
Female	48 (47.5)	49 (47.6)
Race		
Caucasian	97 (96.0)	96 (93.2)
Non-Caucasian	4 (4.0)	7 (6.8)
Age		
< 65	55 (54.5)	60 (58.3)
≥ 65	46 (45.5)	43 (41.7)
Region		
USA	16 (15.9)	14 (13.6)
Western EU	53 (52.5)	67 (65.0)
Eastern EU + India	32 (31.7)	22 (21.4)

Disease characteristics at baseline are summarized in Table 3.

Table 3. Baseline Characteristics

	Lanreotide N = 101	**Placebo** N = 103
Randomized	101 (100)	103 (100)
ECOG Status		
0	84 (83.2)	84 (81.6)
1	17 (16.8)	17 (16.5)
2	0	2 (1.9)
Krenning Scale		
2	15 (14.9)	15 (14.6)
3	53 (52.5)	51 (49.5)
4	33 (32.7)	37 (35.9)
Progression at Baseline		
Yes	4 (4.0)	5 (4.9)
No	97 (96.0)	98 (95.1)
Previous Therapy at Entry		
Yes	16 (15.8)	16 (15.5)
No	85 (84.2)	87 (84.5)
Primary Tumor Type		
Pancreatic	42 (41.6)	49 (47.6)
Non-pancreatic	59 (58.4)	54 (52.43)
Tumor Grade		
G1	69 (68.3)	72 (69.9)
G2	32 (31.7)	29 (28.2)
Missing	0	2 (1.9)
Hepatic Tumor Load		
0%	16 (15.8)	18 (17.5)
>0% and ≤ 10%	33 (32.7)	40 (38.8)
>10% to ≤25%	13 (12.9)	17 (16.5)
>25% to ≤50%	23 (22.8)	12 (11.7)
>50%	16 (15.8)	16 (15.5)
Proliferation Index Ki67 (%)		
≤2%	52 (51.5)	51 (49.5)
>2% to ≤5%	24 (23.8)	43 (21.1)
>5% to <10%	7 (6.9)	10 (9.7)
Unknown	18 (17.8)	23 (22.3)

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

3.2.6. Results and Conclusions

Primary Endpoint Analysis: PFS

There were 204 patients in the ITT population, with 101 in the lanreotide arm and 103 in the placebo arm. A total of 92 patients progressed or died at time of the primary analysis, of which 32 were in the lanreotide arm and 60 in the placebo arm.

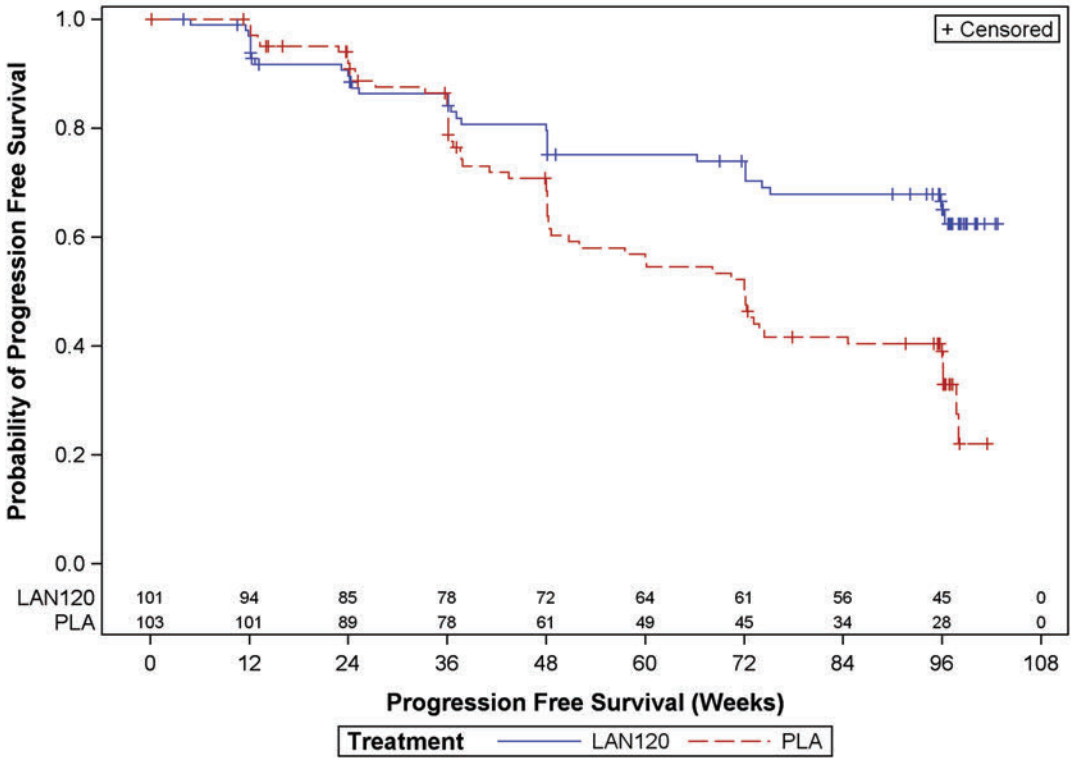
Table 4 summarizes the main efficacy analysis results of the primary endpoint. Lanreotide was shown prolonging PFS to placebo with p-value = 0.0002 based on a stratified log-rank test stratified by progression at baseline and previous therapy at entry. The median PFS was not reached in the lanreotide arm and 72 weeks in the placebo arm. The estimated HR was 0.41 with 95% CI (0.26, 0.64) based on a Cox model stratified by progression at baseline and previous therapy at entry.

Table 4. Primary analysis of PFS

	Lanreotide N = 101	**Placebo** N = 103
Number of Events (%)	32 (31.7%)	60 (58.3%)
Median PFS (95% CI)	NE (NE, NE)	72.0 (48.6, 96.0)
HR (95% CI)	0.41 (0.26, 0.64)	
p-value	0.0002	

Figure 1 shows the estimated Kaplan-Meier curves for the distribution of PFS.

Figure 1. K-M curves of PFS analysis



Reviewer's comments:

1 The randomization was based on two stratification factors: progression at baseline (yes/no) and previous therapy at entry (yes/no). However, there were very few patients had progression disease at baseline, with 4 in the lanreotide arm and 5 in the placebo arm. Therefore both stratified and unstratified log-rank tests were performed and both generated a p-value of 0.0002.

2 As discussed in Section 3.2.3. The study was stopped early, including 96 events in the primary analysis instead of 132 events as specified in the protocol. Therefore the result of the PFS analysis is considered as an interim analysis of PFS. Based on the O'Brien-Fleming boundary and fraction of information, the result is considered to be statistically significant if the p-value is less than 0.015. The observed p-value is 0.0002 and therefore the study result is still considered as statistically significant.

3 The reviewer conducted sensitivity analysis to check the robustness of the primary analysis results and the sensitivity analysis results were consistent with those of the primary analysis.

Secondary Endpoints Analyses:

The Proportions of patients alive and without PD at Weeks 48 and 96 are summarized in the following table.

Table 5. Proportions of Patients Alive and Progression Free at Week 48 and 96

Subjects Alive and Progression-Free	Lanreotide N = 101	Placebo N = 103
Week 48		
Yes	67 (66.3)	50 (48.5)
No	34 (33.7)	53 (51.5)
Week 96		
Yes	53 (52.5)	26 (25.2)
No	48 (47.5)	77 (74.8)

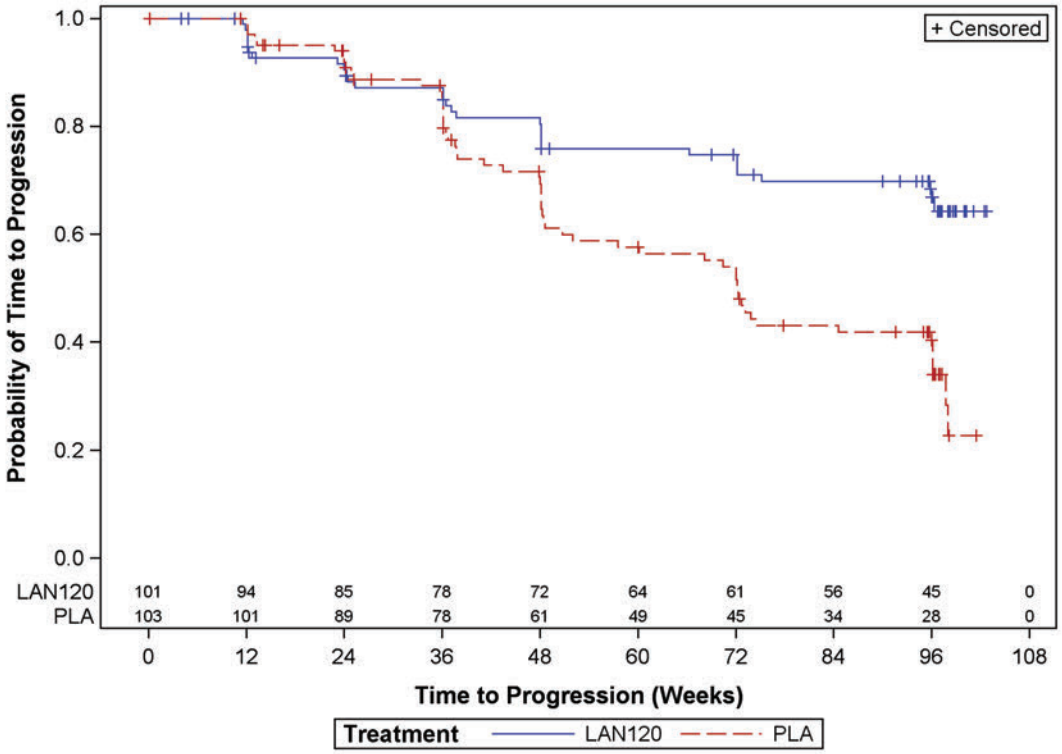
Time to disease progression was another protocol specified secondary endpoint. However there were only 4 deaths during the study with 2 deaths in each arm. Therefore the analysis result of TTP is very similar to PFS. The following table summarizes the analysis result of TTP.

Table 6. Analysis of TTP

	Lanreotide N = 101	Placebo N = 103
Number of Events (%)	30 (29.7%)	58 (56.3%)
Median TTP (95% CI)	NE (NE, NE)	72.1 (50.7, 96.1)
HR (95% CI)	0.40 (0.25, 0.63)	

Figure 2 shows the estimated Kaplan-Meier curves for the distribution of TTP.

Figure 2. K-M Curves of TTP Analysis



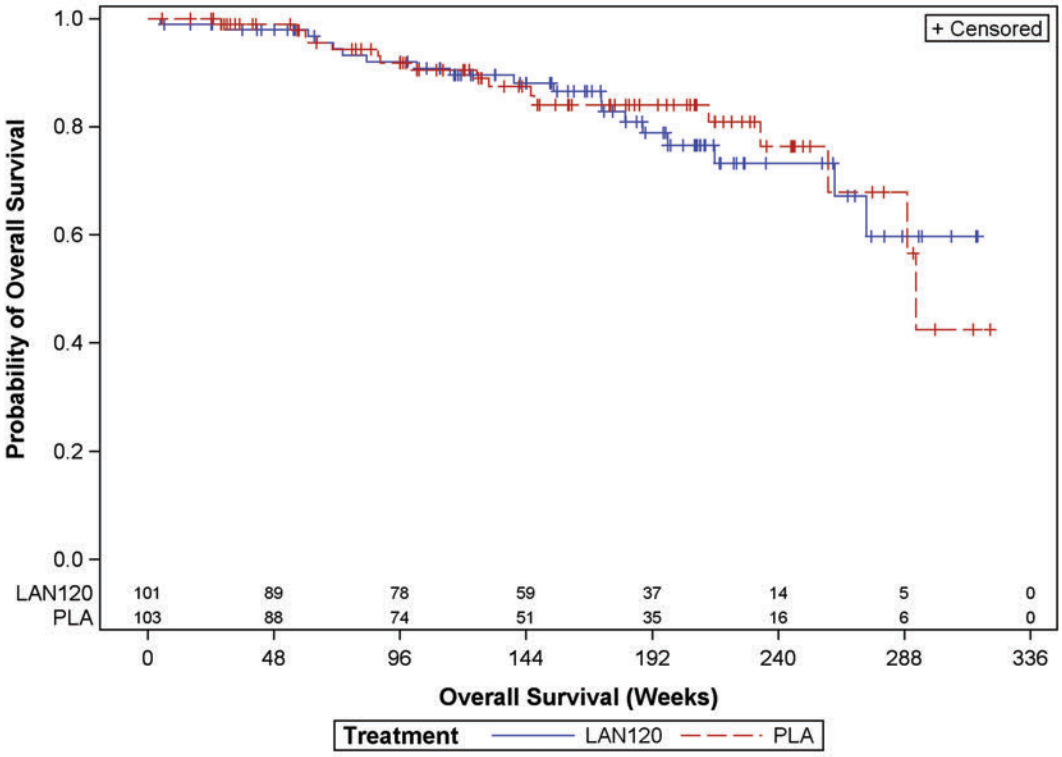
Overall survival (OS) was a secondary endpoint but it was not adequately powered. It was added as a secondary efficacy endpoint in February 2011, more than five years after study initiation. Some patients had already left the study and some patients did not sign the informed consent form to participate in the post-study follow up for OS. Based on the collected data, 19 deaths were observed in the lanreotide arm and 17 deaths in the placebo arm. There were 4 deaths (two in each treatment arm) occurred during the study. The following table summarizes the main analysis results for OS.

Table 7. Analysis of OS

	Lanreotide N = 101	**Placebo** N = 103
Number of Deaths (%)	19 (18.8%)	17 (16.5%)
Median OS (95% CI)	NE (261.4, NE)	292.4 (258.9, NE)
HR (95% CI)	0.97 (0.50, 1.90)	

Figure 3 shows the estimated Kaplan-Meier curves for the distribution of OS.

Figure 3. K-M Curves of OS Analysis



Reviewer's comments:

Since there was no adjustment for multiplicity, the results of the secondary endpoints are considered exploratory.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 12 summarizes the subgroup analysis of PFS based the ITT population. Race was not included because the majority of the patients are Caucasians.

Table 8. Subgroups Analyses of PFS: Gender, Age and Region

Subgroups	Events/N		Median PFS		HR (95% CI)
	Lan	Pla	Lan	Pla	
Male	18/53	34/54	NE	72.3	0.38 (0.21, 0.71)
Female	14/48	26/49	NE	60.1	0.31 (0.15, 0.63)
Age <= 65	19/55	34/60	NE	72.3	0.44 (0.25, 0.80)
Age > 65	13/46	26/43	NE	48.3	0.39 (0.20, 0.76)
USA	4/16	9/14	NE	37.6	0.10 (0.01, 0.82)
Western EU	17/53	40/67	NE	72.0	0.45 (0.26, 0.80)
Eastern EU + India	11/32	11/22	NE	72.1	0.66 (0.28, 1.58)

Reviewer's comments:

The analyses showed that the PFS results for subgroups were consistent with the primary result.

4.2 Other Special/Subgroup Populations

The following table summarizes other important subgroup analysis of PFS based on the ITT population.

Table 9. Subgoup Analysis of PFS: Baseline Characteristics

Subgroups	Events/N		Median PFS		HR (95% CI)
	Lan	Pla	Lan	Pla	
ECOG = 0	28/84	51/84	NE	72.0	0.40 (0.25, 0.65)
ECOG >= 1	4/17	9/19	NE	72.3	0.50 (0.15, 1.66)
Krenning Scale = Grade 2	8/15	5/15	72.1	NE	1.79 (0.58, 5.49)
Krenning Scale = Grade 3	14/53	32/51	NE	72.1	0.32 (0.17, 0.62)
Krenning Scale = Grade 4	10/33	23/37	NE	48.6	0.25 (0.11, 0.58)
Pancreatic	18/42	31/49	NE	48.6	0.53 (0.28, 0.97)
non-Pancreatic	14/59	29/54	NE	73.9	0.35 (0.18, 0.66)
Tumor Grade = G1	19/69	40/72	NE	73.1	0.43 (0.25, 0.75)
Tumor Grade = G2	13/32	19/29	NE	48.6	0.40 (0.19, 0.85)
Hepatic Tumor Load 0%	5/16	11/18	NE	96.1	0.52 (0.18, 1.51)
Hepatic Tumor Load (0%, 10%]	5/33	19/40	NE	74.4	0.17 (0.06, 0.51)
Hepatic Tumor Load (10%, 25%]	4/13	11/17	NE	70.4	0.51 (0.16, 1.62)
Hepatic Tumor Load (25%, 50%]	10/23	10/12	NE	37.6	0.37 (0.14, 0.96)
Hepatic Tumor Load > 50%	8/16	9/16	74.1	36.1	0.28 (0.09, 0.87)
Ki67 <= 2%	13/52	27/51	NE	84.6	0.42 (0.21, 0.82)
Ki67 >2% and <= 5%	12/24	13/19	96.0	60.0	0.56 (0.25, 1.26)
Ki67 >5% and < 10%	1/7	6/10	NE	48.1	NE
Ki67 unknown	6/18	14/23	NE	72.0	0.51 (0.19, 1.35)

Reviewer's comments:

Most of the subgroup analyses showed that the PFS results for subgroups were consistent with the primary result except patients with Krenning scale Grade 2 reported a HR point estimate greater than 1.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A total of 204 patients were randomized in a 1:1 allocation with 101 in the lanreotide arm and 103 in the placebo arm. Lanreotide was shown to prolong PFS compared with placebo with p-value = 0.0002 based on a stratified log-rank test stratified by progression at baseline and previous therapy at entry The median PFS was not reached in the lanreotide arm and 72 weeks in the placebo arm. The estimated HR was 0.41 with 95% CI (0.26, 0.64) based on a Cox model stratified by presence/absence of tumor progression and previous therapies at entry.

Though the protocol stated that approximately 132 events were required to conduct the final PFS analysis, the study was stopped at 96 PFS events and the final PFS analysis was conducted. Therefore the result of the PFS analysis is considered as an interim analysis of PFS. Based on the O'Brien-Fleming boundary and fraction of information, the result is considered to be statistically significant if the p-value is less than 0.015. The observed p-value is 0.0002 and therefore the study result is still considered as statistically significant.

The randomization was based on two stratification factors: progression at baseline (yes/no) and previous therapy at entry (yes/no). However, there were very few patients having progressive disease at baseline; 4 in the lanreotide arm and 5 in the placebo arm. Therefore both stratified and unstratified log-rank tests were performed and both generated a p-value of 0.0002.

OS was added as a secondary endpoint at the later stage of the study. Limited amount of OS was collected. Lanreotide also did not show any difference in OS compared with placebo. The median OS not reached in the lanreotide arm and 292.4 weeks (about 67 months) in the placebo arm. The estimated HR was 0.97 with 95% CI (0.5, 1.9) by the Cox model.

5.2 Conclusions and Recommendations

Based on the data and analyses lanreotide showed a statistically significant improvement in PFS compared with placebo. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will defer to the clinical review team.

5.3 Labeling Recommendations

1. The primary analysis set for the efficacy results are based on the ITT population.
2. The PFS results should be the only efficacy results included in the label.
3. The results of all secondary endpoints are considered exploratory and should not be included in the label.

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/s/

WEISHI YUAN
11/25/2014

KUN HE
11/25/2014

THOMAS E GWISE
11/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
sNDA	22,074/SE11 (SDN273)
Submission Type	Efficacy Supplement
Submission Date	6/23/2014
Review Classification	Priority
PDUFA Due Date	12/30/2014
Action Goal Date	12/19/14
Brand Name	SOMATULINE® DEPOT
Generic Name	Lanreotide
Indications	Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) with unresectable, locally advanced or metastatic disease
Formulation	Single-use, prefilled syringe 120 mg
Dosing Regimen	120 mg daily (QD)
Related IND	109,644
Sponsor	IPSEN
OCP Reviewer	Jun Yang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 2 (DOP2)

EXECUTIVE SUMMARY

SOMATULINE® DEPOT (Lanreotide), an octapeptide analog of natural somatostatin, was approved in 2007 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 approved injection dose is 60 mg, 90 mg, or 120 mg given every 4 weeks (Q4W). An orphan designation for the treatment of neuroendocrine tumors was granted for lanreotide acetate in 2011 (Designation 11-3478).

The current efficacy supplement includes a clinical study (Study 726) supporting Somatuline Depot (lanreotide) Injection 120 mg Q4W for the treatment of (b) (4) (b) (4) The efficacy and safety of lanreotide in the treatment of patients with GEP NETs was demonstrated in Study 726, 1:1 randomized study conducted in 204 patients, in which the treatment with lanreotide 120 mg Q4W resulted in a significant increase in progression-free survival (PFS), with a median PFS of beyond 96 weeks (median PFS not reached) in lanreotide arm versus 72 weeks (95% CI: 48.6, 96.0) in placebo arm. The hazard ratio (HR) comparing lanreotide with placebo was 0.41 (95% CI: 0.26, 0.64) with a p-value of 0.0002.

The incidence of anti-drug antibodies (ADAs) to lanreotide ranged from 0.9% after 48 weeks of treatment in Study 730 to 8 to 11% after 92 and 96 weeks of treatment in Studies 166 and 726, respectively. In Study 726, the incidence of positive ADAs was 3.7% (3 of 82) after 24 weeks, 10.4% (7 of 67) after 48 weeks, 10.5% (6 of 57) after 72 weeks, and 9.5% (8 of 84) after 96 weeks of treatment. Assessment for neutralizing antibodies was not conducted. The impact of immunogenicity on duration of treatment cannot be determined due to the relatively low percentage of patients who developed ADAs in Study 726.

No exposure-response (ER) relationship for PFS and no evident E-R relationship for common adverse events (Diarrhea, Abdominal pain, Vomiting, Hypertension) were identified within the exposures achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered Q4W.

1.1 RECOMMENDATIONS

This efficacy supplement is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this sNDA.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested PMRs or PMCs.

Signatures:

Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Clinical Pharmacology Team Leader Division of Clinical Pharmacology 5
Anshu Marathe, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Liang Zhao, Ph. D. Pharmacometrics Team Leader Division of Pharmacometrics

Cc: DOP2: CSO – **M Biable**; MTL – **S Demko**; MO – **J Sul**
DCP5: Reviewers – **J Yang**; PM reviewers: **A Marathe**; TL – **H Zhao**; PMTL – **L Zhao**
Division Deputy Director – **B Booth**; Division Director - **A Rahman**

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

***Registrational Trial Design*:** Study 726 was a randomized, open-label, Phase 3 trial to assess the effect of Somatuline Depot (n=101) 120 mg administered once every 4 weeks (Q4W) for 96 weeks, compared with placebo (n=103), on progression free survival (PFS) in patients with well or moderately differentiated nonfunctioning gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

***Efficacy Results*:** Study 726 met its primary objective of demonstrating that Somatuline Depot was superior to placebo treatment in prolonging PFS with median PFS of beyond 96 weeks (median PFS not reached at 24 months) for lanreotide arm and 72 weeks (95% CI: 48.6, 96.0) for the placebo arm. The hazard ratio (HR) comparing lanreotide with placebo was 0.41 (95% CI: 0.26, 0.64) with a p-value of 0.0002.

Safety profile: The incidences of treatment emergent adverse events (TEAEs) were consistent with the well-known safety profile of somatostatin analogues (SSTas). Treatment with lanreotide in this study was well tolerated with low incidences of related severe adverse events (SAEs) and only one patient withdrew as a result of a related TEAE. Administration of Somatuline Depot 120 mg for up to two years had no discernible adverse impact on assessed parameters relating to vital signs, laboratory parameters and ECG functions in the study population.

***Pharmacokinetics*:** In patients with GEP-NETs treated with Somatuline Depot 120 mg Q4W, steady state concentrations of lanreotide 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.

Immunogenicity: The incidence of anti-drug antibodies (ADAs) to lanreotide in studies 726, 730, 718 and 166 are variable. The rates of ADAs ranged from 0.9% after 48 weeks of treatment in Study 730 to 8 to 11% after 92 and 96 weeks of treatment in Studies 166 and 726, respectively. In Study 726, the incidence of positive ADAs was 3.7% (3 of 82) after 24 weeks, 10.4% (7 of 67) after 48 weeks, 10.5% (6 of 57) after 72 weeks, and 9.5% (8 of 84) after 96 weeks of treatment. Assessment for neutralizing antibodies was not conducted. The impact of immunogenicity on duration of treatment cannot be determined due to the relatively small number of patients who developed ADAs in Study 726.

Exposure-Response: No exposure-response (ER) relationship for PFS and no evident E-R relationship for common AEs (Diarrhea, Abdominal pain, Vomiting, Hypertension) were identified within the exposures achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered Q4W.

QUESTION BASED REVIEW

For brevity only QBR questions related to the current sNDA submission are addressed below. For additional information please refer to the clinical pharmacology reviews in DAARTS: NDA 22,074 (S-000) (SDN 1, submission date: 25-August-2006); NDA 22,074 [S-3, submission dates: 30-April-2010].

2.1 GENERAL ATTRIBUTITES

What pertinent regulatory background or history regarding the study drug?

Somatuline Depot (Lanreotide), an octapeptide analog of natural somatostatin, was approved in 2007 for the long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. Somatuline Depot is an extended release formulation of lanreotide. An orphan designation for the treatment of neuroendocrine tumors was granted for lanreotide acetate in 2011 (Designation 11-3478).

2.1.1 What are the proposed dosage and route of administration?

Somatuline Depot (lanreotide) Injection was approved for acromegaly as single use, prefilled syringe at 60, 90, and 120 mg. The recommended starting dose is 90 mg every 4 weeks (Q4W) for 3 months and adjusts thereafter based on GH and/or IGF-1 levels. For patients with moderate and severe renal and hepatic impairment, the initial dose of 60 mg Q4W for 3 months is recommended.

For the proposed gastroenteropancreatic neuroendocrine tumors (GEP-NETs) indication, the recommended dose is 120 mg Q4W.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical trial used to support dosing or claims?

The registration trial, Study 726 was conducted to demonstrate the efficacy and safety of Somatuline Depot 120 mg Q4W in the treatment of patients with asymptomatic GEP NETs. In this study, a total of 101 patients were treated with Somatuline Depot 120 mg Q4W and 103 patients received placebo Q4W. Additional evidence for the long term safety of Somatuline Depot is provided by its extension phase, Study 729 (N=88). Additional supportive safety data were obtained from one double blind phase 3 trial (Study 730) and three open label studies (Studies 166, 216, and 718) of Somatuline Depot administered using the intended dosing regimen (Q4W) in patients with asymptomatic and symptomatic GEP NETs.

Key features of Study 726 and other supportive studies are summarized in Table 1.

Table 1. Trials to support safety of Somatuline Depot in patients with GEP NETs.

Abbreviated number	Study design	Lanreotide Autogel dose (duration of treatment)	Number of subjects treated with lanreotide Autogel	
			Asymptomatic	Symptomatic
726	Phase III, randomised, double blind, comparative, placebo controlled, parallel group, multicentre study.	120 mg / 4 weeks (96 weeks)	101	0
729	Phase III, open label extension of Study 726	120 mg / 4 weeks (maximum 8 years)	N=41 LA:LA N=47 PB:LA[a]	0
730	Phase III, double blind, randomised placebo controlled study followed by an initial open label phase and a long term open label extension phase [b]	120 mg / 4 weeks (48 weeks)	0	103[c]
166	Phase II, open, single group multicentre study	120 mg / 4 weeks (92 weeks)	11	19
216	Phase IV, international, open label, randomised, cross over study	90 or 120 mg / 4 weeks (7 or 8 months)	0	26
718	Open phase II/III, multicentre, dose titration study	60, 90 or 120 mg / 4 weeks (6 months)	0	71

2.2.2 What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?

Primary Efficacy Endpoint: The primary efficacy endpoint in the registration trial 726 was disease progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, within 96 weeks after first treatment administration. Somatuline Depot demonstrated superiority over placebo for PFS in the targeted patient population (see Table 2).

Table 2. Summary of the primary efficacy result of Study 726

	Somatuline Depot (N = 101)	Placebo (N = 103)
PFS (weeks) (95% CI)	Median not reached at 96 weeks	72.0 (48.6, 96.0)
HR (95% CI)	0.41 (0.26 – 0.64)	
P-value	0.0002	

Secondary Efficacy Endpoints: In Study 726, key secondary efficacy endpoints include proportion of subjects alive and without disease progression (PD) at Weeks 48 and 96,

overall survival (OS), quality of life (QoL), changes in CgA, changes in tumor marker levels, changes in tumor marker levels for patients with elevated values at baseline. The results are summarized below:

- The proportion of patients who were alive and progression-free was higher in the Somatuline Depot group compared to the placebo group (66.3% vs. 48.5% at Week 48; 52.5% vs. 25.2% at Week 96).
- OS in the two treatment groups was similar (HR=1.05, 95% CI: 0.55, 2.03).
- There was no deleterious impact on QoL for patients treated with Somatuline Depot compared to placebo.
- At the last post baseline value, odds of having a 50% or more decrease in CgA levels, a serum marker of NETs from baseline were 15 times greater with Somatuline Depot than placebo (OR=15.2, 95% CI: 4.29, 53.9; p-value from logistic regression model: <0.0001).
- In patients 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 patients with normal levels.

Safety: According to the Applicant, the overall incidence of at least one treatment emergent adverse event (TEAE) in the Somatuline Depot (88.1%) and placebo (90.3%) groups was similar. There were more TEAEs reported in the Somatuline Depot group compared to placebo (49.5% vs. 28.2%). The most commonly reported types of events in patients in the Somatuline Depot and placebo groups were gastrointestinal disorders (67.3% vs 63.1%) diarrhea (34.7% vs. 35.0%,). The majorities of reported events were mild to moderate in severity and were not serious. There were fewer patients with severe TEAEs in the Somatuline Depot 120 mg group compared to the placebo group (25.7% vs. 31.1%). Similarly, there were fewer SAEs in the Somatuline Depot 120 mg group compared to the placebo group (24.8% vs. 31.1%). The overall proportion of patients who experienced at least one TEAE leading to withdrawal from the study in the Somatuline Depot and placebo groups was similar (3.0% vs. 2.9%).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Lanreotide is the main circulating moiety in human blood and it was analyzed using a validated quantitative radioimmunoassay (RIA) technique. The performance of the bioanalytical methods are reviewed in Section 2.4.

2.2.4 Exposure-response (ER)

2.2.4.1 Is there evidence of exposure-response relationship for efficacy?

No exposure-response (E-R) relationship for PFS was identified within the exposures achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered Q4W. According to the Kaplan-Meir plot based on the population PK predicted steady state AUC_{tau}, there is no trend for increase in PFS with increasing exposure (Figure 1). The analysis included data from 101 patients in the treatment arm of the phase 3 trial.

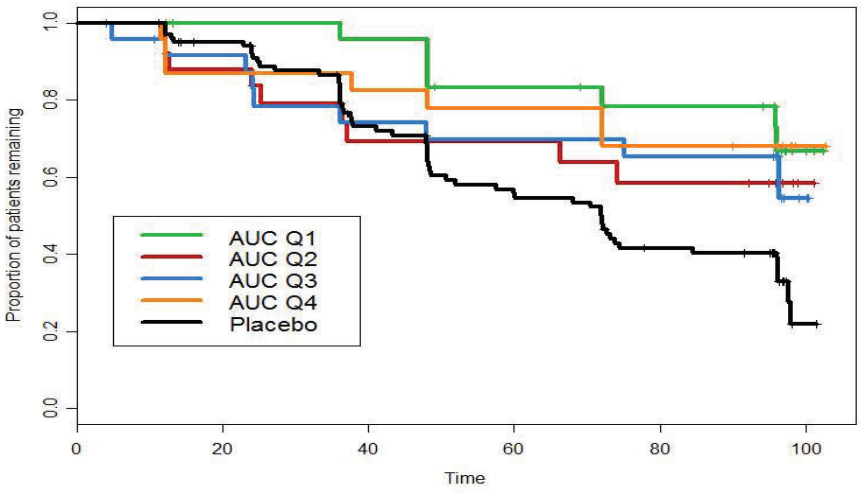


Figure 1: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4 with Q1 to Q4 indicating increasing drug exposure) based on steady state AUC_{tau}

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.2 Is there evidence of exposure-response relationship for safety?

There was no evident E-R relationship identified for common AEs (Diarrhea, Abdominal pain, Vomiting, Hypertension) within the exposures achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered Q4W. Table 3 shows the AEs by exposure quartile based on population PK predicted steady state AUC_{tau}.

Table 3. Incidence rates for AEs (Safety events of all grades for Fatigue, Hot Flush, Headache, Hypertension) for Placebo and Lanreotide Exposure Quartiles

	Placebo (N=103)	Q1 (N=26)	Q2 (N=25)	Q3 (N=25)	Q4 (N=25)
Diarrhea	36 (35 %)	11 (42.3%)	6 (24%)	12 (48%)	5 (20%)
Abdominal pain	17 (16.5%)	4 (15.4%)	5 (20%)	8 (32%)	4 (16%)
Vomiting	9 (8.7%)	8 (30.8%)	2 (8%)	5 (20%)	3 (12%)
Hypertension	5 (4.9%)	2 (7.7%)	3 (12%)	6 (24%)	2 (8%)

(Exposure quartiles were based on steady state AUC_{tau} in treatment arm)

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.5 Pharmacokinetic (PK) characteristics of the drug and its major metabolite

2.2.5.1 What are the PK characteristics of lanreotide in patients with GEP NETs?

The PK of lanreotide in healthy subjects and in patients with Acromegaly were described and included in the previous submission (refer to the clinical pharmacology reviews in DAARTS: NDA 22,074 (S-000) (SDN 1, submission date: 25-August-2006); NDA 22,074 [S-3, submission dates: 30-April-2010]).

In patients with GEP-NETs treated with Somatuline Depot 120 mg Q4W, the mean steady state trough serum lanreotide concentrations ranged from 5.3 to 8.6 ng/mL in Studies 726, 730 and 166. The mean trough concentration for a dose of 120 mg Q4W was somewhat lower in Study 718 (4.1 ng/mL), which was probably due to the titration design of this study with a limited number of patients who received sufficient consecutive doses of Somatuline Depot 120 mg to reach steady state. The value of 4.1 ng/mL was computed using data from subjects who received at least three consecutive doses of Somatuline Depot 120 mg, knowing that steady state is only reached after 4 or 5 injections.

2.2.5.2 How does the PK of lanreotide in patients with GEP NETs compare to that in patients with Acromegaly?

In order to build a population PK model, sparse PK data were obtained in four phase 2/3 studies in patients with GEP NETs including Study 726 (registration trial), Study 730, Study 718, and Study 166. No additional clinical pharmacology studies were performed in support of this GEP NETs application. Table 4 provides a comparison of the PK parameters obtained from:

- Patients with acromegaly from study 076,
- Patients with acromegaly from a population PK model,
- Patients with GEP-NET from a population PK model.

Overall, in patients with GEP NETs, steady state was reached before the 5th or 6^{th} injection of Somatuline Depot 120 mg Q4W, which is consistent with the previous observations in healthy subjects and patients with acromegaly. The steady state AUC and trough concentrations of lanreotide were higher in patients with GEP NET than those of patients with acromegaly (Table 4).

Please refer to Pharmacometrics review by Dr. Anshu Marathe for more information.

Table 4. Descriptive statistics of the PK parameters at steady-state in both acromegalic and GEP-NET populations

	Study 076 N=6 acromegalic patients[a]	Population PK model in acromegalic patients [b]	Population PK model in GEP-NET patients N=290 patients[c]
$C_{max,ss}$ (ng/mL)[d]	7.7 (2.5)	10.0 (5.6) [3.6-19.7]	13.9 (7.4) [7.69-25.5]
$C_{min,ss}$ (ng/mL)	3.8 (0.5)	3.3 (1.9) [1.2-6.7]	6. 6 (2.0) [3.5-10.0]
$AUC_{tau,ss}$ (ng.day/mL)	127 (27.7)	139 (60.2) [68.5-246]	239 (64.8) [158-358]
$C_{avg,ss}$ (ng/mL)	4.5 (1)	5.0 (60.2) [2.45-8. 8]	8.6 (2.4) [5.5-12.9]

a Observed PK parameters from non-compartmental analysis

b Derived PK parameters from 300 simulated PK profiles with the population PK model in acromegaly

c Post-hoc Bayesian PK parameters from the population PK model in GEP-NET

d All PK parameters are provided as Mean (SD) [5^{th} – 95^{th} percentiles]

2.2.5.3 What is the incidence of immunogenicity of lanreotide Depot in patients with GEP NETs?

The immunogenicity profile of Somatuline Depot was evaluated across studies 726, 730, 166, and 718. A radioimmunoprecipitation assay (RIPA) was used to detect the anti-drug antibodies (ADAs) with a multitiered approach. A screening assay was applied to all samples followed by a confirmatory assay. The positive samples after the screening and confirmatory assays were subjected to a titration assay to assess the antibody level. This strategy was employed in Studies 726, 730 and 166. For Study 718, samples were screened and then confirmed using a displacement curve assay. A summary of the study design and immunogenicity results for each study are shown in Table 5.

Table 5. Studies 726, 730, 166 and 718

	Study 726 (Pivotal)	Study 730 (Phase 2/4)	Study 166 (Phase 2/3)	Study 718 (Phase 2)
Dose	120 mg Q4W	120 mg Q4W	60, 90, and 120 mg Q4W	120 mg Q4W
Patient Population	Non functioning entero pancreatic endocrine tumors	Symptoms associated with carcinoid syndrome	Progressive NETs who are ineligible to be treated with either surgery or chemotherapy	Relief of clinical symptoms associated with carcinoid NETs

Sampling times	Baseline, wks 24, 48, 72, 96 (or withdrawal visit)	wks 16, 20, 48	Baseline, wks 8, 20, 32, 44, 56, 68, 80, 92	Baseline, Months 1, 2, 3, 4, 5, 6
N	101	59 (Double Blind), 107 (Open Label)	30	71
Incidence	11/101 (11%)	1/107 (0.93%)	2/30 (6.7%)	4/71 (5.6%)

The incidence of positive ADAs overtime in Studies 726 and 730 is summarized in Table 6. The rates of ADAs ranged from 0.9% after 48 weeks of treatment in Study 730 to 8 to 11% after 92 and 96 weeks of treatment in Studies 166 and 726, respectively. In Study 726, the incidence of positive ADAs was 3.7% (3 of 82) after 24 weeks, 10.4% (7 of 67) after 48 weeks, 10.5% (6 of 57) after 72 weeks, and 9.5% (8 of 84) after 96 weeks of treatment. Assessment for neutralizing antibodies was not conducted.

Table 6. Number and Percentage of ADA Positive patients in Studies 726 and 730

Study 726

Timepoint	**Subjects included N**	**ADA negative subjects**		**ADA positive samples after Screening and confirmatory assay**	
		n	%	Number	% vs T
Week 1	98	98	100.0	0	0
Week 24	82	79	96.3	3	3.7
Week 48	67	60	89.6	7	10.4
Week 72	57	51	89.5	6	10.5
Week 96	84	76	90.5	8	9.5

Study 730

Timepoint	**Subjects included N**	**ADA negative subjects**		**ADA positive samples after Screening and confirmatory assay**	
		Number	%	Number	%
Week 16 (0:0)	95	93[a]	97.89	1	1.05
Week 16 (4:0)	95	94[a] [b]	98.95	1	1.05
Week 20	86	83	96.51	1	1.16
Week 48	30	29	96.67	1	3.33

a. Result for one sample was not valid and not reportable: b One sample was not analyzed due to insufficient volume

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on population PK analysis, body weight was identified as a covariate on drug clearance and gender was identified as a covariate on bioavailability (F1). The overall change in lanreotide serum clearance of a 51 kg individual (5th percentile of weight) and a

105 kg individual (95th percentile of weight) was 23% and 30%, respectively, compared to a 74 kg individual (median weight of the population). No dose adjustment based on body weight is needed because no exposure-response relationship was identified for efficacy or safety in the registration trial (see section 2.2.4). Thus the differences in exposure are unlikely to translate into clinically meaningful differences in efficacy or safety. Although gender was identified as a covariate on F1, this did not translate into significant difference in exposure between men and women as the steady state AUC in women increases by only 13% compared to men. Age and race did not have an effect on drug exposure and were not identified as covariates.

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.3.2 Renal and Hepatic Impairment

In the pooled PK analysis, the dataset consisted of 106 patients with mild [creatinine clearance (CLcr): 60-89 mL/min], 59 patients with moderate (CLcr: 30-59 mL/min) and 1 patient with severe (CLcr: < 30 mL/min) renal impairment. No effect of renal impairment was observed on lanreotide pharmacokinetics in GEP-NET patients and creatinine clearance was not identified as a covariate in the model. The predicted steady state AUC increased by 1.3 fold in patients with moderate renal impairment compared to patients with normal renal function (Table 7). Effects of severe renal impairment on clearance of lanreotide could not be assessed since relevant data only available from one patient with severe renal impairment.

Child Pugh scores were not assessed in Studies 726, 166, 718 and 730. In the pooled population PK analysis, the covariates including total bilirubin, albumin, AST and ALT at baseline were tested and did not show any influence on the PK parameters.

Table 7. Predicted steady state AUC by renal impairment category

Parameter[a]		**Normal renal function [>90 mL/min] N=130**	**Mild renal impaired subjects [60-89 mL/min] N=106**	**Moderate renal impaired subjects [30-59 mL/min] N=59**
$AUC_{0\text{-}28}$ days (ng*day/mL)	Mean (SD)	216 (56.8)	245 (51.8)	277 (75.3)
	Median	208	240	249
	5th and 95th percentiles	143-309	171-345	180-401

Source: Table 11 of Clinical Pharmacology Summary

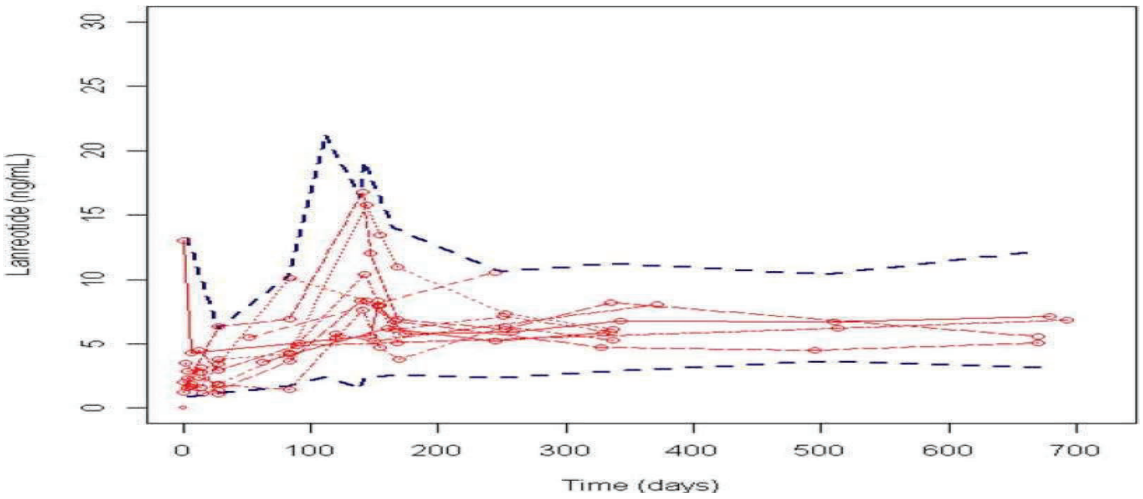
Please refer to Pharmacometrics review by Dr. Anshu Marathe for more information.

2.3.3 What is the impact of immunogenicity of the drug on PK, and/or its pharmacodynamics responses, efficacy and safety?

In Figure 2, PK profiles in patients with positive ADAs (N=11 in Study 726 and N=18 in the pooled population) overlapped those from ADA negative patients (5^{th} and 95^{th} percentiles). In Study 726, there was no correlation between the observation of positive

ADAs to lanreotide and loss of efficacy. Of the 11 patients who developed ADAs, 9 did not progress or die. Only one patient had centrally assessed disease progression (Subjec [redacted] and one patien [redacted] died. Of the 18 patients with a positive ADA result four studies included in the pooled analysis, two did not experience any AEs while enrolled in their respective studies. Two patients experienced AEs prior to the positive ADA results with no further AEs occurring after this period.

Figure 2. Overlay of ADA Positive Individual Observed PK Profiles with 5th and 95th Percentiles of ADA Negative Observed PK Profiles



In conclusion, the impact of immunogenicity on efficacy and safety cannot be determined due to the relatively small number of patients who developed ADAs in Study 726.

2.4 ANALYTICAL SECTION

2.4.1 Was the active moiety identified and measured in the clinical trial?

Yes. Lanreotide is the primary active moiety and was assessed in plasma of patients in the clinical trials.

2.4.2 What bioanalytical procedures are method were used to determine drug concentrations? Are they acceptable for this sNDA?

Radioimmunoassays (RIAs) were used for both the quantification of serum lanreotide and for the detection of serum ADAs. The RIA used for the quantification of lanreotide in serum was developed in 1993 using polyclonal rabbit antilanreotide antiserum 582 (AS582). This antiserum has been demonstrated to be specific for lanreotide, and its use has been validated for the quantification of lanreotide and as a positive control for the detection of anti-lanreotide antibodies in human serum.

The RIA method is based on the competitive binding of ^{125}I-labeled lanreotide (tracer) and unlabeled lanreotide (present in the sample) to the specific anti-peptide antibody, AS582. Therefore, the amount of radioactivity detected is inversely proportional to the amount of

unlabeled lanreotide present in the sample. The applicant reported that this RIA method was first validated at Ipsen Pharma SA (Barcelona, Spain) with a lower limit of quantification (LLOQ) of 0.078 ng/mL, prior to the quantification of lanreotide concentrations for Studies 718 and 166. To support the quantification of lanreotide in Studies 726 and 730, the bioanalytical method was transferred and validated in a contract research organization (CRO (b) (4) The assay validation was completed by measur which the coefficient of variation (CV) was 10.3% (Table 8). The methods used at Ipsen an (b) (4) were also cross validated by the analysis a (b) (4) of external quality control (QC) samples (0.01, 0.25, 0.4, 0.8 and 50 ng/mL) with CV of 1.9 to 11.1% and inaccuracy from -5.1 to 18.2%. Finally, a panel of 30 clinical samples with high and low concentrations of lanreotide was analyzed at both th (b) (4) and Ipsen Pharma SA facilities. Results demonstrated a recovery of 92.6% with CV of 8.7%.

Table 8. Summary of RIA Validation Studies for Pharmacokinetic Measurement

Method validation report	Sensitivity	Recovery	Precision (%CV)	Testing facility	Study samples assayed
95/PKS/015: Validation of a RIA method in human serum	LLOQ: 0.078 ng/mL	102.4 to 106.9% (0.1 to 0.8 ng/mL)	Repeatability (intra-assay precision): 5.5 to 13.6% Inter assay: 2.3 to 4.99% Reproducibility: 6.2 to 13.2%	Ipsen Pharma SA, Barcelona, Spain	Study 718 Study 166
P98815: Validation of a RIA for the determination of lanreotide in human serum	LLOQ: 0.078 ng/mL	94.9 to 118.2%	Intra batch: 2.7 to 5.8% Inter batch: 3.5 to 6.5%	(b) (4)	Study 726 Study 730
07/E00/147: Complementary validation of a RIA method for the determination of lanreotide in human serum	NA	Validation of a QC at 120 µg/mL diluted at 1/400: Recovery=89%	Validation of a QC at 120 µg/mL diluted at 1/400: CV=10.3%	(b) (4)	NA

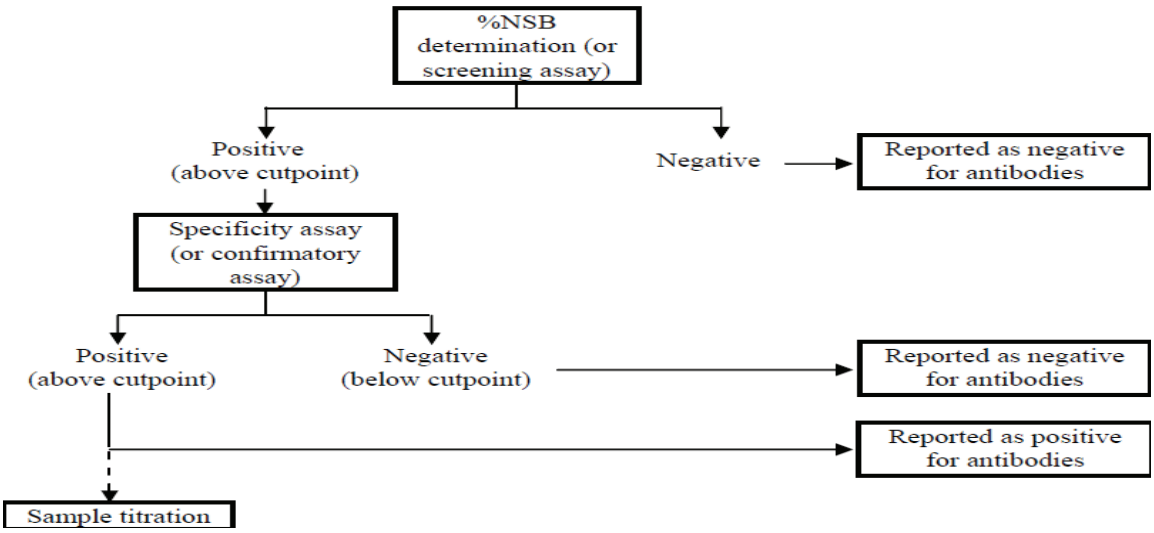
CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; QC=quality control; RIA=radioimmunoassay; (b) (4)=a contract research organisation.
Data Source: Module 5.3.1.4, Reports 95/PKS/015, P98815 and 07/E00/147.

Stability of Lanreotide in Serum Samples

According to the applicant, the short term and long term stabilities of lanreotide in serum samples were examined. Lanreotide in human serum was stable allowing the storage at 4°C and manipulation of samples for up to 24 hours at 20°C. After three freeze thaw cycles, the estimated concentrations of lanreotide were within the variability ranges of the method. In a long term study, lanreotide was stable in human serum when stored at -24°C ±6°C for up to 28 months.

Radioimmunoprecipitation (RIPA) Assay for the Detection of ADAs
All steps of the RIPA involved measuring immune complexes formed by the binding of ADAs to ^{125}I-lanreotide after precipitation following the addition of propanol and centrifugation. The pellets were washed and radioactivity counted using a gamma counter. The nonspecific binding (NSB) samples are clinical samples incubated in the absence of AS582. The general strategy for detecting ADAs is shown in Figure 3.

Figure 3. General Strategy Employed for the Detection of ADAs



The RIPA method was first validated at Ipsen Pharma SA (Barcelona, Spain) for the detection of ADAs in serum samples collected in Study 166. Assay validation performances were also reported previously. During Study 166 and the first part of Study 726, samples were analyzed at Ipsen Pharma SA (Barcelona, Spain). Due to the closure of activities at Ipsen Pharma SA, the method was transferred and validated at a CRO (b) (4) (b) (4) using the same equipment and staff that were used at Ipsen Pharma SA. The method was revalidated in accordance with the requirements specified in the European Medicines Agency guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins and was used to analyze the remaining samples from Study 726. In addition, the method was also transferred and validated a (b) (4) (b) (4). Assay performances between Ipsen Pharma SA and (b) (4) were compared using 40 validation samples at four concentration levels of AS582. According to the applicant, no significant difference was observed between results obtained by Ipsen Pharma SA and (b) (4) The validated method a (b) (4) was used to assay samples from Study 730. Table 9 summarizes assay performance obtained during the validation of the RIPA methodology.

Table 9. Summary of RIPA Validation Studies for ADAs

Validation report	Sensitivity	Precision (%CV)	Facility	Study samples assayed
05/INM/157: Validation of the RIA methods for determination of antibodies to lanreotide in human serum samples	AS582: 1/3,200,000	**Screening assay** *Using rabbit positive control (AS582):* Repeatability: QC(+): 2.75; QC(-): 5.68 Inter batch: QC(-): 0; QC(+): 1.04 Intermediate precision: QC(+): 2.94; QC(-): 5.34	Ipsen Pharma SA, Barcelona, Spain	Study 166 Study 726
TR-001148: Validation of a RIA method for determination of antibodies to lanreotide in human serum samples	AS582: 1/1,779,298	**Screening assay** *Using rabbit positive control (AS582):* Intra-assay: from 0.66 to 3.10% Inter assay: from 1.57 to 6.80% **Confirmatory assay** *Using rabbit positive control (AS582):* Intra-assay: from 0.28 to 22.73% Inter assay: from 0.63 to 28.43%	(b) (4)	Study 726
10/E00/026: Validation of a RIA method for the determination of antilanreotide antibodies in human serum from Caucasian population	AS582: 1/256,000	**Screening assay** *Using rabbit positive control (AS582):* Intra-assay: from 0.69 to 6.45% Inter assay: from 3.35 to 8.25%	(b) (4)	Study 730
09/INM/143: Comparison of the RIA method for the determination of antilanreotide antibodies in human serum performed at two different sites	NA	No precision was determined: Of the 40 samples tested at both sites, only two samples had discrepant results. The methods were considered cross validated. Correlation factor: R^2=0.9787	(b) (4)	–

CV=coefficient of variation; NA=not applicable; QC=quality control; RIA=radioimmunoassay.
Data Source: Module 5.3.1.4, Reports 05/INM/157, TR-001148, 10/E00/026, and 09/INM/143.
Note: (b) (4) and (b) (4) are contract research organisations.

DETAILED LABELING RECOMMENDATIONS

FDA recommended clinical pharmacology labeling modifications are presented below. The modifications made by the Agency are in BLUE.

FULL PRESCRIBING INFORMATION

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

6.2 Immunogenicity

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 (<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.

Development of anti-lanreotide antibodies was assessed using a radioimmunoprecipitation assay (b) (4) (b) (4) The incidence of positive ADAs was 3.7% (3 of 82) after 24 weeks, 10.4% (7 of 67) after 48 weeks, 10.5% (6 of 57) after 72 weeks, and 9.5% (8 of 84) after 96 week (b) (4) Assessment for neutralizing antibodies was not conducted.

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 SOMATULINE DEPOT with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

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)*].

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)*].

Gastroenteropancreatic Neuroendocrine Tumors

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

12 CLINICAL PHARMACOLOGY

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)*]. 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.

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)*].

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 20-30% 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)*].

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.

(b) (4)

[redacted]

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, 90, 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.

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.

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.

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 a population PK analysis in patients with GEP-NET which included 122 patients aged 65 to 85 years with neuroendocrine tumors (b) (4)

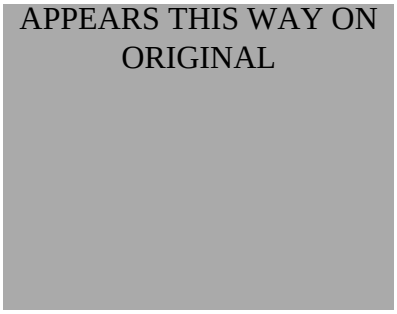
Hepatic Impairment

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-NE [redacted] (b) (4)

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. APPENDIX: Pharmacometrics Review



OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	sNDA 22074/SE11 (SDN 273)
Submission Date	June 23, 2014
Compound	Lanreotide
Dosing regimen (route of administration)	120 mg every 4 weeks (deep subcutaneous administration)
Indication	Gastroenteropancreatic neuroendocrine tumors (GEP-NETs (b) (4) (b) (4)
Clinical Division	Division of Oncology Products 2 (DOP2)
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Liang Zhao, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1.1 Is there exposure-response relationship for effectiveness?

No exposure-response (ER) relationship for progression free survival (PFS) was identified within the exposures achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered every 4 weeks. According to the Kaplan-Meir plot based on the population PK predicted steady state AUC_{tau}, there is no trend for increase in PFS with increasing exposure (Figure 1). The analysis included data from 101 patients in the treatment arm of the phase 3 trial.

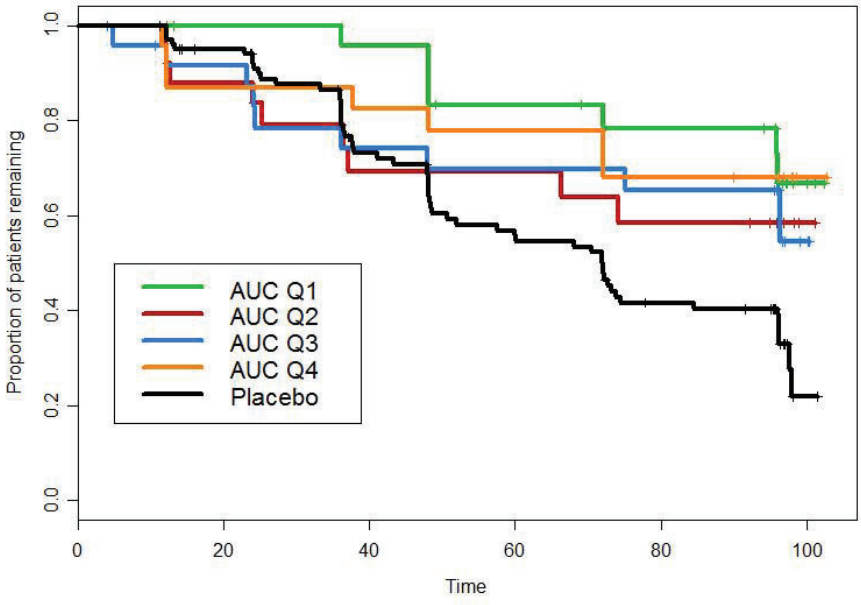


Figure 1: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4 with Q1 to Q4 indicating increasing drug exposure) based on steady state AUC_{tau}. Source: Reviewer's analysis

1.1.1.2 Is there exposure-response relationship for safety?

There was no clinically meaningful exposure-response relationship identified for common adverse events (Diarrhea, Abdominal pain, Vomiting, Hypertension) within the exposure range achieved in the Phase 3 trial (Study 726) following a dose of 120 mg administered every 4 weeks.

Table shows the AEs by exposure quartile based on population PK predicted steady state AUC_{tau}.

Table 1: Incidence of AEs (Safety events of all grades for Fatigue, Hot Flush, Headache, Hypertension) for Placebo and Lanreotide Exposure Quartile Based Groups

	Placebo (N=103)	Q1 (N=26)	Q2 (N=25)	Q3 (N=25)	Q4 (N=25)
Diarrhea	36 (35 %)	11 (42.3%)	6 (24%)	12 (48%)	5 (20%)
Abdominal pain	17 (16.5%)	4 (15.4%)	5 (20%)	8 (32%)	4 (16%)
Vomiting	9 (8.7%)	8 (30.8%)	2 (8%)	5 (20%)	3 (12%)
Hypertension	5 (4.9%)	2 (7.7%)	3 (12%)	6 (24%)	2 (8%)

(Exposure quartiles were based on steady state AUC_{tau} in treatment arm)
Source: Reviewer's analysis

1.2 Recommendations

Division of Pharmacometrics has reviewed sNDA 22074/SE11 and finds the sNDA acceptable provided an agreement regarding the label language can be reached between the sponsor and the Agency.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for sNDA 22074. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

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 studi (b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations
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.

(b) (4)

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 that included 106 patients with mild and 59 patients with moderate renal impairment.

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 subject (b) (4) (b) (4)population PK analysi (b) (4) 122 patients aged 65 to 85 year (b) (4) (b) (4)

Reviewer comments: The reviewer agrees with sponsor's labeling language and minor changes are only suggested. See reviewer comments in section 2

2 Results of Sponsor's Analysis

2.1 Population PK Analysis

The objectives of sponsor's population PK analysis were:

1. To describe the PK characteristics of deep subcutaneous injections of lanreotide Autogel® administered as 60, 90, or 120 (mainly) mg every four weeks in patients with symptomatic and asymptomatic GEP-NETs.
2. To quantify the degree of inter-patient variability (IPV) on the pharmacokinetic parameters of LA, and the residual unexplained variability in the data.
3. To identify the individual patient characteristics (covariates) than can have an impact on the PK parameters explaining part of their inter-patient variability.

2.1.1 Methods

Data

The population PK analysis was based on studies 2-55-52030-730, 2-55-52030-726, A92-52030-166, E47-52030-718 in GEP-NETs (

Table 22). For study trial 2-55-52030-730, concentrations until date of 6th of May 2013 were available for the analysis. A total of 1541 serum concentration values of lanreotide were included in the dataset. The population PK analysis was performed with data from 290 patients. A summary of demographics of patients included in the analysis are shown in Table 3.

Table 2: Summary of Studies/Data included in Population PK Analysis

		Number of Samples			
Study	**Patients**	**Total**	**Mean**	**Minimum**	**Maximum**
726	96	793	8.26	1	11
730	98	286	2.91	1	4
718	69	351	5.08	1	6
166	27	111	4.11	1	8

Source: Table 1 of sponsor's population PK report, TR-001807

Table 3: Summary of Demographics included in Population PK Analysis

Covariate	726(N=96)	730 (N=98)	718 (N=69)	166(N=27)	Pool (N=290)
Age (years)	63.26 (15.43)	58.50 (19.31)	59.69 (19.99)	62.26 (16.63)	60.71 (18.17)
WGT (Kg)	78.01 (21.37)	75.51 (22.34)	72.42 (23.49)	69.35 (18.64)	75.07 (22.22)
SGPT (IU/L)	28.28 (77.97)	26.39 (75.55)	31.31 (51.73)	26.70 (44.17)	28.22 (68.28)
SGOT (IU/L)	29.419 (62.88)	27.62 (51.71)	28.07 (40.93)	26.29 (33.26)	28.13 (52.49)
BILI (mg/dL)	0.65 (91.12)	0.54 (79.79)	0.55 (58.59)	0.69 (44.37)	0.59 (77.79)
ALB (g/L)	4.39 (7.94)	4.29 (9.95)	4.02 (11.73)	4.13 (7.07)	4.25 (10.07)
CRCL (mL/min)	88.92 (35.24)	95.55 (37.10)	87.09 (38.20)	77.51 (33.28)	89.75 (36.86)

Values are expressed as mean [coefficient of variation (%))]

Covariate		726	730	718	166	Pool
SEX	Male	50	41	35	14	140
	Female	46	57	34	13	150
FCTN	asymptomatic GEP-NET	96	0	0	10	106
	symptomatic GEP-NET	-	98	69	17	184
RACE	Asian	2	8	0	0	10
	African American	1	8	1	0	10
	Caucasian	93	81	68	27	269
	Multiple	0	1	0	0	1
TLOC	Pancreas	39	0	0	7	46
	Fore gut	0	0	4	6	10
	Mid gut	31	0	46	10	87
	Hind gut	11	0	1	1	13
	Other	1	0	12	0	13
	Unknown	14	98	6	3	121

Values are listed as total number per category.

Source: Table 3 and Table 4 of sponsor's population PK report, TR-001807

2.1.2 Results

The pharmacokinetic characteristics of lanreotide were best described with a one compartment disposition model and with an absorption process characterized by two parallel absorption pathways following first and zero order kinetics (Figure). Inter-patient variability was included on the first order rate constant of absorption (KA), the apparent volume of distribution (V/F), apparent total plasma clearance (CL/F), and the fraction of the dose absorbed following the first order rate process (F1). The parameters of the final model are shown in Table . The model diagnostics are shown in Figure .

Covariate Analysis

The results from the covariate selection analysis indicate that CL/F was correlated with the body weight recorded at baseline, and that F1 was affected by the gender. Figure shows the relationship between the individual CL/F and F1 empirical Bayes estimates obtained from the selected population pharmacokinetic model and weight and sex, respectively. The overall change in lanreotide serum clearance of a 51 kg individual (5^{th} percentile of weight) and a 105 kg individual (95th percentile of weight) was 23% and 30%, respectively, compared to a 74 kg individual (median weight of the population). The steady state AUC in women increases by only 13% compared to men Table 5.

No effect of renal impairment, age and race was observed on lanreotide pharmacokinetics and they were not identified as covariates in the model. Table shows the predicted steady state AUC for patients with normal, mild and moderate renal function. The AUC increased only by 1.3 fold in subjects with moderate renal impairment compared to subjects with normal renal function. Data in subjects with severe renal impairment (N=1) was limited for any meaningful assessment.

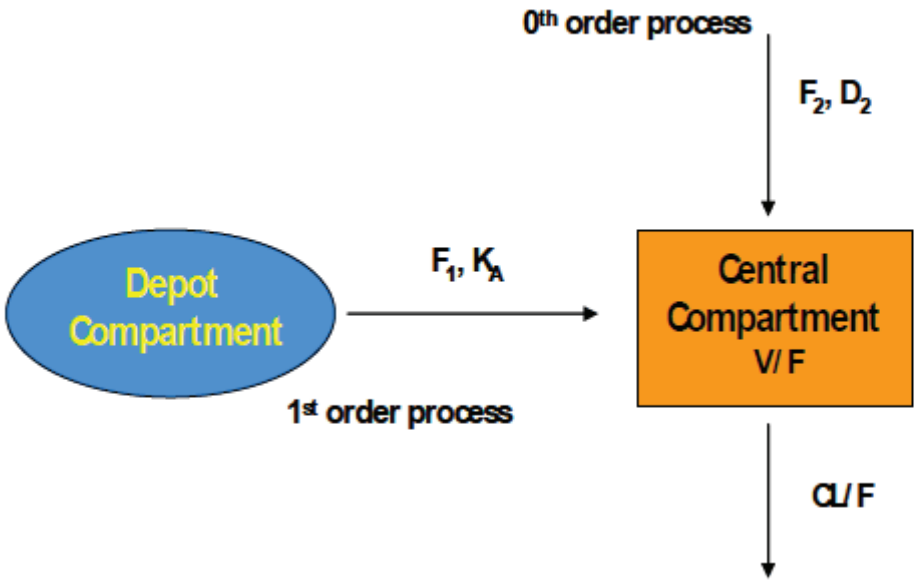


Figure 2: Schematic representation of the pharmacokinetic model for lanreotide. Source: Figure S1 of sponsor's population PK report, TR-001807

Table 4: Parameter estimates of the final population PK model for lanreotide

Parameter/Covariate Model	Estimates	2.5th – 97.5th	Shrinkage (%)
CL/F (L/h)=θ_{CL}x[1+θ_{WGT}x(Weight-74)]	θ_{CL}=513 θ_{WGT}=9.77x10^{-3}	491-537 (6.95-0.12)x10^{-3}	-
V/F (L	18.3	10.2-41.5	-
K_A (day^{-1})	1.59x10^{-2}	(1.44-1.82)x10^{-2}	-
F1=θ_{F1}x(1+θ_{SEX})	θ_{F1}=0.994 θ_{SEX}=-0.024 (Males) θ_{SEX}=0 (Females)	0.977-0.996 -0.0058 – 0.058	-
D (day)	2.96	2.05 - 3.03	-
IIV$_{CL}$ (%)	27	21 - 32	24.2
IIV$_{V}$ (%)	150	107 - 197	63.02
IIV$_{KA}$ (%)	61	49 – 70	21.98
IIV$_{F1}$(%)	1.05	1.07 - 1.3	42.87
Residual error [log(ng/mL)]	0.275	0.25 – 0.3	17.5

F_1, fractions of the absorbed dose following a first and a zero order rate absorption process, respectively; K_A, first order rate constant of absorption; D, duration of the zero order input process; V/F, apparent volume of distribution; CL/F, apparent total serum clearance; F, absolute bioavailability (not known and arbitrarily set to 1). *. Percentiles computed from 500 bootstrap analyses

Source: Table S1 of sponsor's population PK report, TR-001807

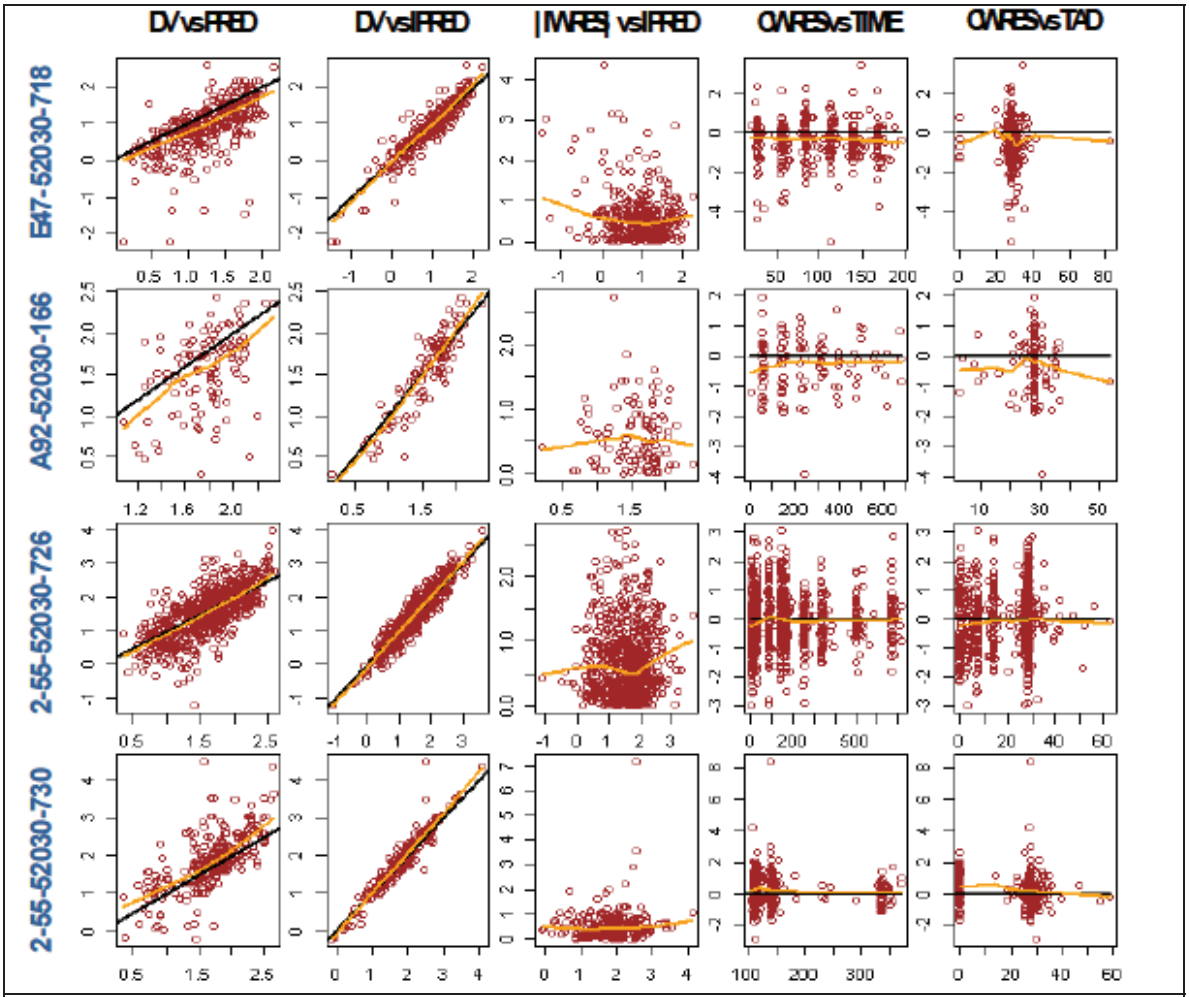


Figure 3: Goodness of fit plots from the final population PK model by study. Source: Figure 6 of sponsor's population PK report, TR-001807

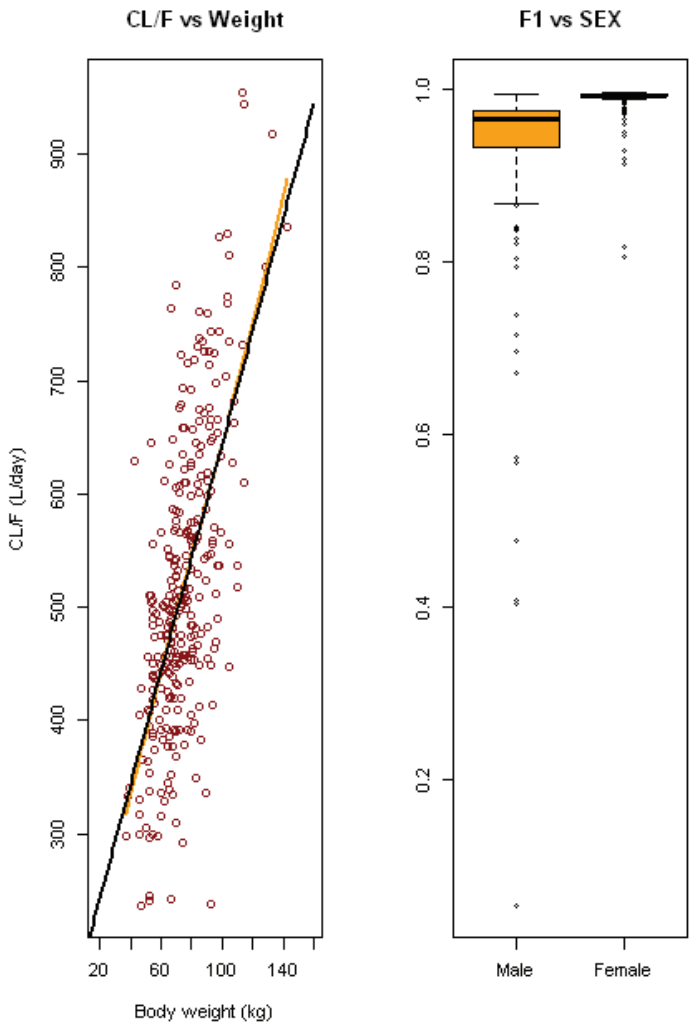


Figure 4: Parameter vs covariate relationships included in the final population model selected. A) CL/F versus Body Weight and B) F1 versus Sex. Source: Figure S2 of sponsor's population PK report, TR-001807

Table 5: Summary of steady state PK Parameters for Males and Females

Male

	GeomM	Mean	SD	5th	50th	95th	Min	Max
Cmin(ng/mL)	5.482	5.83	1.884	3.139	5.92	8.847	0.303	14.536
Cavg(ng/mL)	7.728	8.01	2.31	5.283	7.573	11.944	4.489	17.951
Cmax(ng/mL)	13.707	15.395	9.385	7.823	12.525	33.003	6.054	63.758
AUC(µgxday/L)	216.277	223.947	64.072	150.94	212.1	335.26	123.7	490

Female

	GeomM	Mean	SD	5th	50th	95th	Min	Max
Cmin(ng/mL)	7.025	7.253	1.842	4.759	7.047	10.535	1.986	14.689
Cavg(ng/mL)	8.987	9.242	2.253	6.327	8.982	13.769	3.796	18.016
Cmax(ng/mL)	11.948	12.568	4.559	7.678	11.459	18.634	4.197	40.183
AUC(µgxday/L)	246.983	254.082	62.286	174.52	246.6	378.72	103.1	492

Source: Table A.9.1.4 and A.9.1.5 from sponsor's population PK report, TR-001807

Table 6: Predicted steady state AUC by renal impairment category

Parameter[a]		Normal renal function [>90 mL/min] N=130	Mild renal impaired subjects [60-89 mL/min] N=106	Moderate renal impaired subjects [30-59 mL/min] N=59
AUC_{0-28} days (ng*day/mL)	Mean (SD)	216 (56.8)	245 (51.8)	277 (75.3)
	Median	208	240	249
	5th and 95th percentiles	143-309	171-345	180-401

Source: Table 11 of Clinical Pharmacology Summary

Reviewer's comments:

- *Sponsor utilized a one-compartment disposition model to describe the pharmacokinetics of Lanreotide in GEP-NET patients. Based on the diagnostic plots (Figure), the sponsor's population PK model appears to characterize the pharmacokinetics of lanreotide reasonably well. Of note, in an earlier population PK analysis that was conducted using data from acromegaly patients, the PK was described by a three compartment model by the sponsor (Clinical Pharmacology Review in DARRTs for NDA 22074 dated 07/13/2007). It is unclear from sponsor's current report if a two- or a three-compartment model was tested for describing the PK in GEP-NET patients.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on age, race or renal impairment is warranted because these were not identified as covariates in population PK analysis.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on gender is warranted. Although gender was identified as a covariate on F1, this did not translate into significant difference in exposure between men and women as observed in Table 5.*
- *Body weight was identified as a covariate on drug clearance. No dose adjustment based on weight is needed because no exposure-response relationship was identified for efficacy or safety (see section 1.1.1.1 and 1.1.1.2). Thus the differences in exposure are unlikely to translate into clinically meaningful differences in efficacy or safety.*

- *The effect of disease status was not tested as a covariate in the population PK model because only data from GEP-NET patients were included in the current analysis. However a cross-trial comparison suggests higher exposure in GEP-NET patients compared to patients with acromegaly (Table 7). In order to explore the possible reasons for the observed differences, the sponsor compared the demographic characteristics across the trials (Table). Although differences are observed in the demographics among trials, these are not likely to explain the differences in exposure observed between patient populations. In the population PK analysis, age, gender, race and creatinine clearance had no significant effect on exposure, thus differences observed in these demographics are not likely to translate into exposure differences. Body weight was identified as covariate and acromegalic patients had higher body weight (~14%) compared to GEP-NET patients. According to the sponsor this is unlikely to translate in exposure differences because although healthy volunteers had ~22% lower body weight compared to acromegalic patients, their PK profiles were similar. Thus, there is an apparent difference in PK profile between acromegalic and GEPNET patients which remains unexplained with the parameters assessed in the various trials.*

Table 7: Descriptive Statistics of PK parameters at steady state in acromegalic and GEP-NET patients

	Study 076 N=6 acromegalic patients[a]	Population PK model in acromegalic patients [b]	Population PK model in GEP-NET patients N=290 patients[c]
$C_{max,ss}$ (ng/mL)[d]	7.7 (2.5)	10.0 (5.55) [3.57-19.7]	13.9 (7.44) [7.69-25.5]
$C_{min,ss}$ (ng/mL)	3.8 (0.5)	3.27 (1.88) [1.16-6.72]	6.56 (1.99) [3.53-9.99]
$AUC_{tau,ss}$ (ng.day/mL)	127 (27.7)	139 (60.2) [68.5-246]	239 (64.8) [158-358]
$C_{avg,ss}$ (ng/mL)	4.5 (1)	4.96 (60.2) [2.45-8.78]	8.64 (2.36) [5.49-12.9]

a Observed PK parameters from non-compartmental analysis

b Derived PK parameters from 300 simulated PK profiles with the population PK model in acromegaly

c Post-hoc Bayesian PK parameters from the population PK model in GEP-NET - Module 2.7.2 section 3.2.3

d All PK parameters are provided as Mean (SD) [5^{th} – 95^{th} percentiles]

Source: Table 1 of response to Clinical Pharmacology IR

Table 8: Descriptive Statistics of demographic characteristics in healthy volunteers, acromegalic patients and GEP-NET patients

	Study 149 – Healthy volunteers[a]	Study 076 – Acromegalic patients[b]	Study 717 – Acromegalic patients[c]	Pooled population PK analysis – GEP-NET patients
Number of subjects	54	6	83	290
Age (years)[d]	28 (6.3)	39 (9.3)	54 (14)	61 (11)
Gender (M/F)	27/27	2/4	38/45	140/150
Weight (kg)	67 (13)	88 (21)	82.9 (16.5)	75 (17)
Race	100% Caucasian	100% Caucasian	86% Caucasian 8.4% Asian 3.6% Black 2.4% Hispanic	93% Caucasian 3.5% Asian 3.5% Black
Creatinine clearance (mL/min)	-	146	132	89.8 (33)

a Study used to build the population PK model in healthy volunteers

b Study in acromegalic patients: PK parameters provided in USPI

c Study used to validate the healthy volunteers population PK model with acromegalic patients

d Age, weight and creatinine clearance provided as Mean (SD) or Mean

Source: Table 2 of response to Clinical Pharmacology IR.

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/s/

JUN YANG
12/02/2014

LIANG ZHAO
12/02/2014

HONG ZHAO
12/02/2014
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022074Orig1s011

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 25, 2014
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carole Broadnax, RPh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route:	SOMATULINE DEPOT (lanreotide) Injection
Application Type/Number:	NDA 22074
Supplement Number:	S-011
Applicant:	Ipsen Biopharmaceuticals Inc. on behalf of Ipsen Pharma SAS

1 INTRODUCTION

On June 23, 2014, Ipsen Biopharmaceuticals Inc. on behalf of Ipsen Pharma SAS submitted for the Agency's review a Prior Approval Efficacy Supplement to their approved New Drug application (NDA) 22074/S-011 for SOMATULINE DEPOT (lanreotide) Injection. With this supplement, the applicant proposes the addition of a new indication for the treatment SOMATULINE DEPOT (lanreotide) Injection 120 mg for the treatmen (b) (4) (b) (4)

SOMATULINE DEPOT (lanreotide) Injection was original approved on August 30, 2007 and is currently 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on August 26, 2014 for DMPP and OPDP to provide a review of the Applicant's proposed Patient Package Insert (PPI) for SOMATULINE DEPOT (lanreotide) Injection.

2 MATERIAL REVIEWED

- Draft SOMATULINE DEPOT (lanreotide) Injection PPI received on June 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2014.
- Draft SOMATULINE DEPOT (lanreotide) Injection Prescribing Information (PI) received on June 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2014.

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. In our review of the PPI the target reading level is at or below an 8th grade 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 have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- 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/

MORGAN A WALKER
11/25/2014

CAROLE C BROADNAX
11/25/2014

LASHAWN M GRIFFITHS
11/25/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

To: Mona Patel, Regulatory Project Manager
Missiratch Biable, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: November 24, 2014

Re: **Somatuline Depot (lanreotide) Injection**
NDA 022074/S-11
Comments on proposed product labeling (PI and PPI)

In response to the Division of Oncology Products 2 (DOP 2)'s August 26, 2014, consult request, OPDP has reviewed proposed product labeling (PI and PPI) for Somatuline Depot (lanreotide) Injection. The version of the PI used in this review was sent via electronic mail from DOP-2 on November 18, 2014, and is titled, "2014 11 18-draft-pi-tracked_FDA Edits.doc."

OPDP's comments for the PI are provided directly in the attached PDF document.

OPDP's comments for the proposed PPI were provided in a separate patient labeling review from the Division of Medical Policy Programs dated November 25, 2014.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
11/25/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: November 24, 2014

TO: Mona Patel, Regulatory Project Manager
Joohee Sul, M.D, Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH**:** Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

sNDA: 22074 S-011

APPLICANT: Ipsen Pharma

DRUG: Somatuline Depot (Lanreotide)

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): (b) (4)

CONSULTATION REQUEST DATE: September 4, 2014
INSPECTION SUMMARY GOAL DATE: December 2, 2014
DIVISION ACTION GOAL DATE: December 19, 2014
PDUFA DATE: December 30, 2014

I. BACKGROUND:

Ipsen Pharma, seeks approval to market lanreotide for the treatmen (b) (4)
(b) (4)
(b) (4) Lanreotide is a synthetic analogue of somatostatin (SST), a naturally occurring inhibitory hormone which blocks the release of several other hormones, including growth hormone, thyroid-stimulating hormone (TSH), insulin and glucagon. Like SST, lanreotide is believed to stimulate growth inhibitory pathways, induce apoptosis, and inhibit angiogenesis. Lanreotide binds to the same receptors as somatostatin, although with higher affinity to peripheral receptors, and has similar activity. Lanreotide has a much longer half-life, and produces far more prolonged effects.

On August 30, 2007, the U. S. Food and Drug Administration approved lanreotide (Somatuline Depot®) injection 60 mg, 90 mg, and 120 mg 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 supplement application is supported by safety and efficacy results of the pivotal Phase 3 Study 2-55-52130-726, "Phase III, randomized, double blind, stratified comparative, placebo controlled, parallel group, multicenter study to assess the effect of deep subcutaneous injections of lanreotide Autogel 120 mg administered every 28 days on tumor progression free survival in patients with nonfunctioning entero pancreatic endocrine tumor". Study 2-55-52130-726 was a global study conducted at 48 investigative sites in Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, United Kingdom and the United States of America. Planned enrollment was 200 subjects. The study screened 264 subjects and randomized 204 patients, which constituted the ITT population.

This study was initiated in Europe in 2006. The study was initiated in the US in 2008 under IND 63,239, which is held by the Division of Gastroenterology and Inborn Errors Products. In accordance with the Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs – Frequently Asked Questions – Statement of Investigators (Form FDA 1572) issued by the FDA on May 2010, only U.S. investigators site documentation was submitted to the IND. This study protocol was subsequently transferred under the IND 109,644 in April 2011 held by the Division of Oncology Products 2 (DOP2).

This was a phase III, randomized, double blind, comparative, placebo controlled, parallel group, multicenter study. The study consisted of a screening period and a treatment period.

The screening period consisted of a screening visit (Visit 1) followed by a maximum period of 14 weeks during which two computed tomography (CT) scans or magnetic resonance imaging (MRI) were performed in order to assess tumor progression. An MRI was permitted but was

considered as an alternative method where CT scans were not possible. The screening process was to assess whether subjects had progressive disease (PD) and this was used as a stratification factor along with the presence/absence of previous therapy at entry.

The treatment period started at the baseline visit (Visit 2), and took place as soon as possible after assessment of tumor progression. Subjects were stratified and randomized to either the lanreotide Autogel 120 mg or the placebo group. Injections were then administered on site every 28 days for both treatment groups. Subjects attended treatment period visits to assess tumor progression every 12 weeks during the first study year and every 24 weeks during the second study year. During the second year of treatment, chromogranin A (CgA) levels were assessed at Week 60 and Week 84, and if they had increased by >50% over baseline an additional CT-scan was performed to assess possible disease progression. All scans were reviewed centrally by an Independent CRO and central evaluations were used in the analysis.

After a subject completed (or withdrew from) the treatment phase, the Investigator would record the survival status of the subject annually, on the anniversary of the subject's first study treatment administration. Subjects were followed for overall survival (OS) during a follow up period that ended when the last subject last visit occurred.

Two clinical sites were chosen for inspection: Site 616005 (Dr. Jerzy Walecki, Warzzawa, Poland), and Site 840003 (Dr. Nageshwara Vijaya Arvind Dasari, Houston, TX), based on enrollment of large numbers of study subjects at both sites (14% and 7%, respectively), and a relatively high number of protocol deviations coupled with a high number of screen failures at the site in Poland.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Walecki, Jerzy, M.D. Zaklad Diagnosttyki Radiologicznej, Centralny Szpital Klincny, Ministrerstwa Spraw Wewnetrznych i Administratracji w Warzawie, UL Woloska 137, 02-507 Warzzawa, Poland	Protocol: 2-55-52130-726 Site Number: 616005 Number of Subjects: 29	November 12-18, 2014	Pending Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#2: Dasari, Nageshwara Vijaya Arvind, M.D. MD Anderson Cancer Center, Gastrointestinal Medical Oncology, 1515 Holcombe Blvd Mail stop 0426 Houston, TX 77030-4009	Protocol: 2-55-52130-726 Site Number: 840003 Number of Subjects: 14	October 28, 2014 - November 7, 2014	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: Jerzy Walecki, M.D. (Site 616005)**

a. **What was inspected:** The site screened 41 subjects, and 29 subjects were enrolled. At the time of this inspection 14 subjects had completed the study. The study records of 16 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to sNDA 22074 S-011, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. There was no evidence of underreporting of adverse events. The records were well organized. Review of source documentation for eligibility, randomization, treatment regimens, AE reporting, and study drug administration cycles, and drug accountability found no discrepancies. The primary efficacy endpoints were supported by source documentation at the site. There were a few minor discussion points at the conclusion of this inspection. A Form FDA 483 was not issued.

c. **Assessment of data integrity:** The data for Dr. Walecki's site, associated with Study 2-55-52130-726 submitted to the Agency in support of sNDA 22074 S-011, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Nageshwara Vijaya Arvind Dasari, M.D. (Site 840003)

a. What was inspected: The site screened 16 subjects, and 14 subjects were enrolled. Eight subjects completed the study and 6 subjects withdrew prior to completion. The study records of all 16 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to sNDA 22074 S-011, and focused on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents for all screened subjects, test article accountability, and monitoring reports. Correspondence records, regulatory records, and IRB approval and submission records were also reviewed.

b. General observations/commentary: Generally, the investigator's execution of the protocol was adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. There was no evidence of underreporting of adverse events. There were 4 SAE's reported by this site, for Subject (b) (6) an (b) (6) They were all reported to the sponsor in a timely manner. The primary efficacy endpoint was the time of randomization to the time of either progressive disease or death. The primary efficacy endpoints were supported by source documentation at the site. The subjects were followed up two years after their last dose of investigational product. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. There were multiple protocol deviations for out of window protocol-specified procedures such as labs and EKGs. The site did receive a sponsor waiver for the EKG protocol deviations. These observations were discussed with the site. The site did not always obtain informed consent from each human subject prior to conducting study-related tests. A one item Form FDA 483 was issued.

Observation 1. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests .

Specifically,

1. O (b) (6), Subjec (b) (6) signed an Informed Consent (IC) to not allow additional blood to be drawn for Pharmokinetic Testing (PK). The IRB approval date of the IC wa (b) (6) The blood was drawn on two separate visits, and then shipped to Sponsor's central laborato (b) (4) The visits are as follows:

a) Baseline (Visit 2)/Week 1, o (b) (6)
b) Visit 3/Week 12, on (b) (6)

2. On (b) (6) Subjec (b) (6) signed an Informed Consent (IC) to not allow additional blood to be drawn for Pharmokinetic Testing (PK). The IRB approval date of the IC wa (b) (6) The blood was drawn on two separate visits, and then shipped to the Sponsor's central laboratory (b) (4) The visits are as follows:

   a) Baseline (Visit 2)/Week 1, on (b) (6)
   b) Visit 3/Week 12, o (b) (6)

3. O (b) (6), Subjec (b) (6) signed an Informed Consent (IC) to not allow additional blood to be drawn for Pharmokinetic Testing (PK). The IRB approval date of the IC was 09/01/2010. The blood was drawn and then shipped to the Sponsor's central la (b) (4) during the Baseline Visit (Visit 2)/Week1 o (b) (6)

OSI Reviewer Note: The FDA field investigator confirmed via email that they have collected the signed informed consent forms for the subjects listed above, verifying that they (Subjects (b) (6) an (b) (6) did decline to consent to participating in the PK substudy. eld investigator also found documentation that the site notified the central laboratory (b) (4) in January 2010 and October 2011, of these errors associated with Subject (b) (6) an (b) (6) an (b) (6) respectively, and requested they destroy the "tubes received". Therefore observations should not impact PK data submitted to the application.

c. **Assessment of data integrity**: The data for Dr. Dasari's site, associated with Study 2-55-52130-726 submitted to the Agency in support of sNDA 22074 S-011, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Jerzy Walecki (Site 616005) and Dr. Nageshwara Vijaya Arvind Dasari (Site 840003), the Study 2-55-52130-726 data submitted to the Agency in support of sNDA 22074 S-11 appear reliable based on available information.

The preliminary classification for clinical investigator Dr. Walecki, is No Action Indicated (NAI). The preliminary classification for clinical investigator Dr. Dasari, is Voluntary Action Indicated (VAI).

Dr. Dasari's site did not always obtain informed consent from each human subject prior to conducting study-related tests. Specifically, the study informed consent document included an option to participate in an investigational product (IP) PK substudy. Subject (b) (6) an (b) (6) did not consent to participate in the additional blood draws for IP PK analyses. However, the site took blood samples from Subject (b) (6) and (b) (6) and shipped these samples to the Sponsor's central laboratory for analysis. Based upon information and documentation found at the site, the site staff found the errors and notified the central laboratory on January 2010 and October 2011, of these errors associated with Subject (b) (6) an (b) (6) an (b) (6) respectively, and requested they destroy the "tubes received". The , these observations should not impact PK data submitted to the application.

Notwithstanding the inspection observations noted above for Dr. Dasari's site, associated with Study 2-55-52130-726, the data submitted to the Agency in support of sNDA 22074 S-011, appear reliable.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
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/s/

LAUREN C IACONO-CONNORS
11/24/2014

SUSAN D THOMPSON
11/25/2014

KASSA AYALEW
11/26/2014