AN INTERNATIONAL, MULTICENTRIC, PROSPECTIVE, OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG ASSOCIATED TO STANDARD OF CARE IN THE TREATMENT OF CLINICAL SYMPTOMS ASSOCIATED WITH INOPERABLE MALIGNANT INTESTINAL OBSTRUCTION (IMIO)

STUDY PROTOCOL

[STUDY number: A-48-52030-269**]**

[EudraCT number: 2013-002174-43**]**

Final Version: 18 October 2013

Sponsor's Medically Responsible Person:
Vincent De Ruyter
Ipsen Group
Guldensporenpark 87
B-9820 Merelbeke
Tel: +[32] (0)9 243 96 00
Fax: PPD

Study Sponsor:
Vincent De Ruyter
Ipsen Group
Guldensporenpark 87
B-9820 Merelbeke
Tel: PPD
Fax: PPD

Monitoring Office:
PPD
Ipsen Group
Guldensporenpark 87
B-9820 Merelbeke

Tel: PPD
Fax: PPD

Co-ordinating Investigator:
Prof. Dr. K. Geboes
Department of Gastro-Enterology
University Hospital of Gent
De Pintelaan 185
Belgium
Tel: PPD
Fax: PPD

Pharmacovigilance/Emergency Contact
PPD
Central Department of Pharmacovigilance
Ipsen Group
190 Bath Road
Slough
Berkshire SL1 3XE
England
Tel: PPD
PPD – mobile telephone for emergencies
Fax: PPD –

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol : **AN INTERNATIONAL, MULTICENTRIC, PROSPECTIVE, OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG ASSOCIATED TO STANDARD OF CARE IN THE TREATMENT OF CLINICAL SYMPTOMS ASSOCIATED WITH INOPERABLE MALIGNANT INTESTINAL OBSTRUCTION**

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[1], local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

INVESTIGATOR NAME: _____

TITLE: _____

SIGNATURE : _____

DATE : _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the Sponsor:

NAME: DE RUYTER VINCENT
TITLE: MEDICAL ADVISOR

SIGNATURE : _____

DATE : _____

[1] ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

SYNOPSIS

Study Title:	**AN INTERNATIONAL, MULTICENTRIC, PROSPECTIVE, OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG ASSOCIATED TO STANDARD OF CARE IN THE TREATMENT OF CLINICAL SYMPTOMS ASSOCIATED WITH INOPERABLE MALIGNANT INTESTINAL OBSTRUCTION**
Study Objectives:	**Primary Objective :** To assess the efficacy of lanreotide Autogel lanreotide Autogel 120 mg for the relief of vomiting due to inoperable malignant intestinal obstruction in patients without nasogastric tube **AND** to assess the efficacy of lanreotide Autogel 120 mg to remove a nasogastric tube without the recurrence of vomiting in patients with an inoperable malignant intestinal obstruction with a nasogastric tube **Secondary Objectives :** 1) To evaluate the impact on Quality of Life (Edmonton Symptom Assessment System) of lanreotide Autogel 120 mg assessed by both the patient and the caregiver 2) To assess the efficacy of lanreotide Autogel 120 mg for the relief of other clinical symptoms due to inoperable malignant intestinal obstruction : - General activity (Karnofsky score) - Nausea (number of daily episodes) - Pain (Visual analogue scale) - Complete/incomplete obstruction: passage of stools 3) To assess the symptom (nausea and vomiting) improvement delay 4) To assess the pharmacokinetic profile of lanreotide in patients with inoperable malignant intestinal obstruction **Safety Objectives :** To assess the clinical and biological safety of the study treatment
Phase of Trial:	Phase II
Study Design:	This is an International, Multicentric, Prospective, Open-label study Phase 1 Initial Injection Lanreotide Autogel 120 mg : Patients meeting the selection criteria for participation will need to provide a written informed consent. Patient and caregiver will be

	asked to complete the Edmonton Symptom Assessment System (ESAS) before any study procedure. Patients will then receive the following treatment : Standard of care + 1 injection of lanreotide Autogel 120 mg Response to the treatment will be assessed based on the % of responders in the treatment group at Day 7, Day 14 and Day 28. Safety of the patients will be followed continuously during the entire study period. A blood sample to assess the serum levels of lanreotide will be taken at Day 1 , Day 7 and Day 14 and Day 28 For patients who are : Non-responders at Day 28 OR Responders at day 28 but who are unwilling to receive a second injection with lanreotide, the participation to the study will stop here. Patients will then receive standard of care by the treating physician. <u>Phase 2 Second injection Lanreotide Autogel 120 mg :</u> Patients completing the 28 days of the first phase and who are responders as defined by this protocol will have the possibility to receive a second injection with lanreotide Autogel 120 mg. Standard of care will be continued for all as described by the protocol. Response to the treatment will continued to be assessed based on the % of responders at Day 35, Day 42 and Day 56 Safety of the patients will be followed continuously during the entire study period. A blood sample to assess the serum levels of lanreotide will be taken just before the second injection at Day 28 and at Day 35, day 42 and at day 56.
Study Population:	Patients with inoperable intestinal obstruction of malignant origin in centres in Belgium and Luxemburg **<u>Inclusion Criteria :</u>** All subjects must fulfil the following: 1) Written informed consent before any study related procedure 2) Male and female patients age 18 years or older at the time of enrolment 3) Diagnosis of an intestinal obstruction of malignant origin 4) In case of peritoneal carcinomatosis, confirmation by CT or MRI scan within the 3 months preceding the inclusion in the study 5) Confirmed as inoperable after surgical advice 6) Patient with a nasogastric tube OR presenting with 3 or more episodes of vomiting / 24h in the last 48 hours 7) Estimated life expectancy 1 month or more

	Exclusion Criteria Subjects will not be included in the study if the subject : 1) Operable obstruction or any subobstruction 2) Bowel obstruction due to a non-malignant cause (for example : hypokaliaemia, drug side-effects, renal insufficiency, …) 3) Signs of bowel perforation 4) Prior treatment with somatostatin or any analogue within the previous 60 days 5) A known hypersensitivity to any of the study treatments or related compounds 6) Previous participation in this study 7) Is likely to require treatment during the study with drugs that are not permitted by the study protocol (see Section 9.5). 8) Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety.
Study Treatment:	**Phase 1 Initial Injection Lanreotide Autogel 120 mg** Standard of care + lanreotide Autogel 120 mg **Phase 2 Second injection Lanreotide Autogel 120 mg :** Standard of care + lanreotide Autogel 120 mg **Standard of care** : **Compulsory for all patients :** - No oral food or oral liquid intake during the first 5 days unless there are signs of resolution of the obstruction (passing stools or gas): patients can consume oral or liquids at the discretion of the treating physician - Intravenous corticoids : Solumedrol 40 mg/day or dexamethasone or methylprednisolone or equivalent at a dose of 1 mg/kg/day or more - Intravenous H2 antihistaminics : ranitidine 50 mg 3/d or PPI : omeprazole or pantoprazole or equivalent. **Step up medication if not enough efficacy at Day 7:** - butylhyoscine bromide (Buscopan): 40-120 mg SC or IV **AND**

	- Haloperidol : 5 mg / 2 x day IV **Authorised for all patients :** - Analgesics on request - Metoclopramide 10 mg/4h or Domperidone 10 mg qid or Odansetron 8mg/4ml at the discretion of the investigator - Chemotherapy (if already present at study entry) - Venting Gastrostomy after Day 7 **Non Authorised treatments :** - Somatostatin or any of its analogues other than the study drug
Study Evaluations:	**Primary Efficacy Endpoint(s) and Evaluation(s):** Phase 1 : Initial Injection Lanreotide Autogel 120 mg: Percentage of responding patients before or at D7. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D7 (for patients without NGT at baseline) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D7 without vomiting recurrence. - Number of daily vomiting episodes recorded on diary cards. - Number of days without vomiting **Secondary Efficacy Endpoints And Evaluations:** Phase 1 : Initial Injection Lanreotide Autogel 120 mg: 1) Percentage of responding patients before or at D14 (same for D28). A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D14 (D28) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D14 (D28) without vomiting recurrence. - Number of daily vomiting episodes recorded on diary cards. - Number of days without vomiting 2) Time between first injection and clinical response 3) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 7, Day 14 and Day 28 assessed by both the patient and the caregiver. 4) Changes in daily intensity and frequency at Day 7, Day 14 and Day 28 compared to baseline in - General activity (Karnofsky score)

	- Nausea (number of daily episodes) - Pain (Visual analogue scale) - Complete/incomplete obstruction: passage of stools Phase 2 : Second injection Lanreotide Autogel 120 mg : 1) Overall Percentage of patients continuing from Phase I and confirmed as a responder at the end of phase I , showing a continued response at D35, D42 and D56. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 without vomiting recurrence. - Number of daily vomiting episodes recorded on diary cards. - Number of days without vomiting 2) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 35, Day 42 and Day 56 assessed by both the patient and the caregiver. **Pharmacokinetic Endpoints and Evaluations:** The PK profile of lanreotide Autogel in patients with IMIO using lanreotide concentration data. **Safety Endpoints and Evaluations:** Clinical and biological adverse events and serious adverse events throughout the study
Statistical Methods:	The primary endpoint is the percentage responders at D7. Sample size is calculated by testing 1-sided at 2.5% significance level alpha and a power of 80% using the z-test for binomial proportion assuming a proportion of responders at D7 equal to 50%. Sample size is 44 subjects; however taken into account 15 to 20 % drop outs, 50 patients will be recruited for this study. It is planned to recruit these patients in a 2 year period.

STUDY FLOW

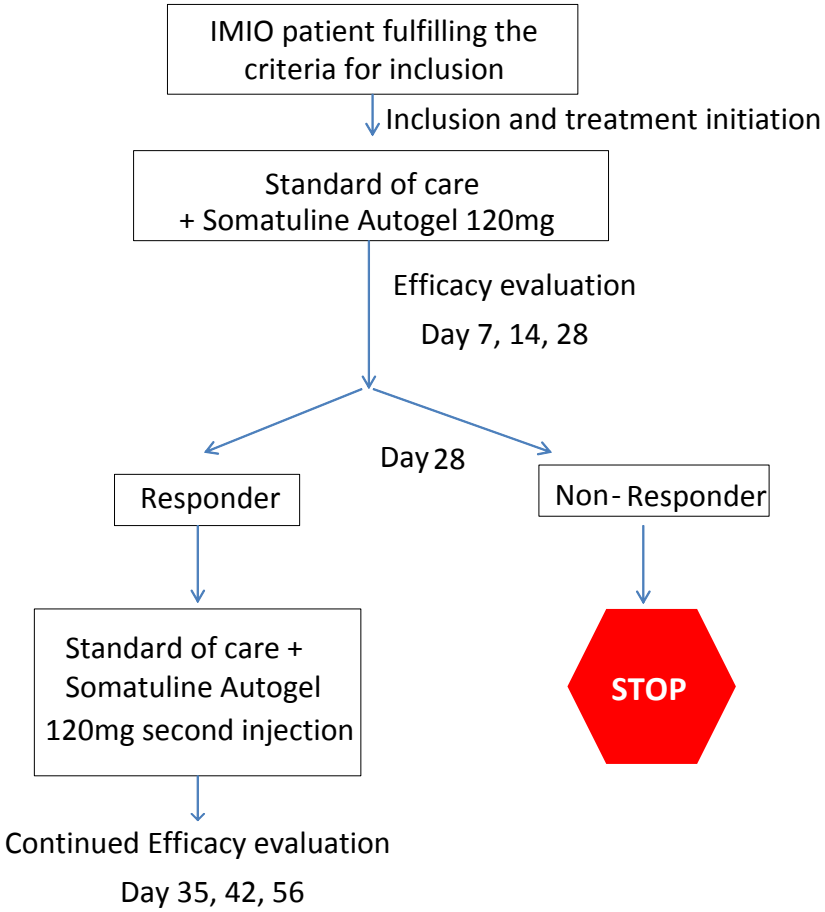

IMIO patient fulfilling the criteria for inclusion
Inclusion and treatment initiation
Standard of care + Somatuline Autogel 120mg
Efficacy evaluation
Day 7, 14, 28
Day 28
Responder
Non- Responder
Standard of care + Somatuline Autogel 120mg second injection
STOP
Continued Efficacy evaluation
Day 35, 42, 56

Table 1. Phase I

Visit	V1	V2	V3	V4 Last visit
Day	D1	D7	D14	D 28
Informed consent	●			
Eligibility review	●			
Demography	●			
Medical history	●			
Malignancy history##	●			
Clinical examination###	●	●	●	●
Nutrition procedure	●	●	●	●
Symptoms and QOL assessment *	●	●	●	●
Vomiting and nausea episodes assessment (diary cards)**	●	●	●	●
Concomitant medications	●	●	●	●
Safety biological ####assessment (if applicable)	●	●	●	●
Injection Study Treatment Lanreotide Autogel 120 mg	●			
Lanreotide concentrations (PK)	●#	●	●	●
Adverse Events***	●	●	●	●

*: VAS for abdominal pain, Karnofsky for daily activities, QOL by means of Edmonton Symptom Assessment System (caregiver and patient), and presence of partial/complete intestinal obstruction. Nausea and vomiting will be separately recorded
**: Diary cards will be completed every day for a total of 28 days.
***: At Day 1 (baseline) after signature of the informed consent and after clinical examination and medical history
: Between 2 and 12h after the injection of lanreotide Autogel 120 mg
##: Malignancy history causing Obstruction
###: including vital signs as height, Weight, BP and HR
####: including hematology and biochemistry (only at discretion of investigator)

Table 2. Phase II

Visit	V5	V6	V7	V8 Last visit
Day	D28	D35	D42	D56
Eligibility review	X			
Clinical examination##	X	●	●	●
Nutrition procedure	X	●	●	●
Symptoms and QOL assessment *	X	●	●	●
Vomiting and nausea episodes assessment (diary cards)**	X	●	●	●
Concomitant medications	X	●	●	●
Safety biological ### assessment (if applicable)	X	●	●	●
Second lanreotide Autogel 120 mg injection	●			
Adverse Events	●	●	●	●
Lanreotide concentrations	●#	●	●	●

*: VAS for abdominal pain, Karnofsky for daily activities, QOL by means of Edmonton Symptom Assessment System (caregiver and patient), and presence of partial/complete intestinal obstruction. Nausea and vomiting will be separately recorded

**: Diary cards will be completed every day for a total of 28 days.

X : These data will be copied from V4 of Phase I.

: Before the second lanreotide Autogel 120 mg injection
##: including vital signs as height, Weight, BP and HR
###: including hematology and biochemistry (only at discretion of investigator)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event/Experience
CA	Competent Authorities
CDDS	Clinical Development Data Sciences (relates to Sponsor)
CRF	Case Report Form
CRO	Contract Research Organisation
CTSU	Clinical Trial Supplies Unit (relates to Sponsor)
DMC	Data Monitoring Committee
E	Electronic
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product synonymous with “study drug”
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NOS	Not Otherwise Specified
PI	Package Insert
PP	Per Protocol
PD	Pharmacodynamics
PK	Pharmacokinetics
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event/Experience
SAS®	Statistical Analysis Software®
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File

2.INTRODUCTION

2.1Disease Review

Intestinal obstruction is an important complication in patients with advanced abdominal or pelvic cancer. It occurs in 5-42 % of patients with ovarian cancer and in 4-24% of patients with advanced colorectal cancer. In bowel obstruction, the propulsion of intestinal contents is delayed or blocked completely, leading to symptoms of nausea, vomiting and spasmodic pain. Bowel distension proximal to the site of obstruction will lead to an increase in intestinal secretion which, acting as a feed-back, worsens the patient's symptoms (6,7,8).

Surgery remains the treatment of choice for malignant intestinal obstruction. However, not all patients are eligible for surgery. The most frequent contraindications are the presence of multiple partial obstructions, intra-abdominal carcinomatosis, poor nutritional status or large amounts of ascites.

In inoperable patients, there is a need for a non-invasive and efficacious treatment to alleviate patient discomfort. Several authors have confirmed the efficacy of a pharmacological treatment of symptoms (8,9,10,11). Pharmacological therapy consists of analgesics (opioids or non-opioids), anti-emetics (e.g. Metoclopramide, haloperidol), anti-inflammatory agents (corticosteroids) and anti-secretory drugs (e.g. scopolamine butylbromide, somatostatin analogues) (9,10,11,12)

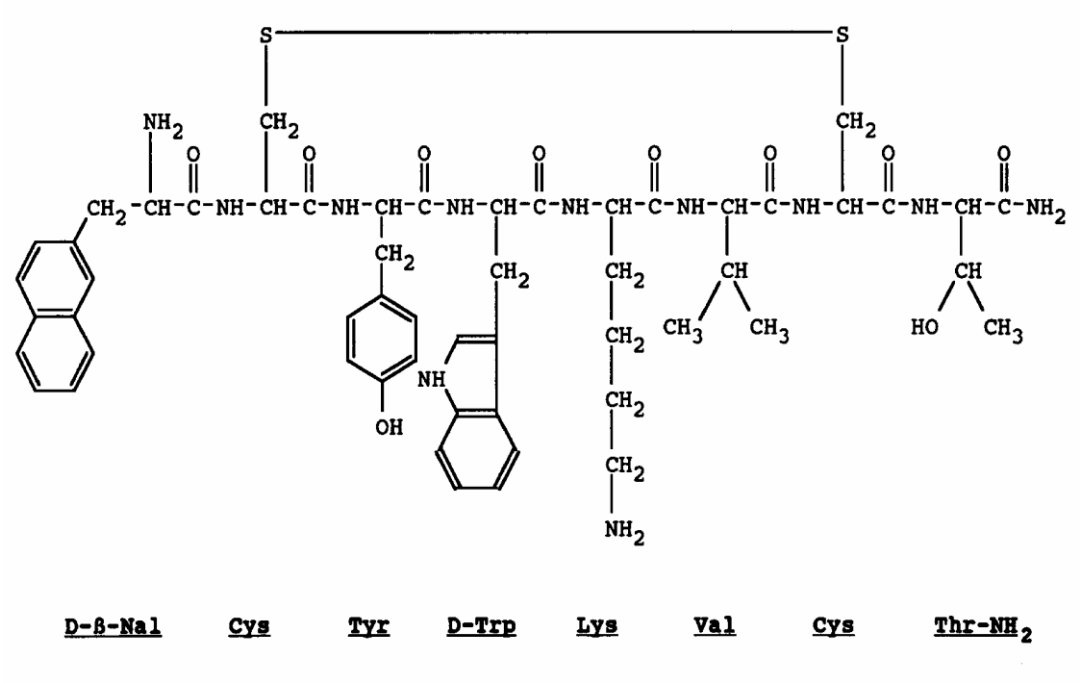
Somatostatin produced by neurones of the gastrointestinal tract acts as an inhibitor of numerous digestive endocrine and exocrine secretions. Somatostatin also promotes intestinal water absorption and influences gut transit time (13, 14).

Somatostatin's inhibitory effect on gastrointestinal secretions reduces the distension of the bowel. Somatostatin decreases the water and sodium secretion of the intestinal epithelium, thereby reducing pain and vomiting.

The therapeutic use of somatostatin is, however, limited by its short half-life of only two to three minutes, thus necessitating continuous intravenous infusion. Therefore, synthetic somatostatin analogues with increased specificity and half-life duration have been developed for medicinal use (15, 16).

2.2Compound Review

Figure 1 Lanreotide structural formula



Lanreotide is an octapeptide analogue of somatostatin. It has marked release-inhibiting activity on growth hormone (GH), and a longer duration of actionthan the native peptide. When administered intravenously (i.v.) or subcutaneously (s.c.), lanreotide has a short half-life (T½) of approximately 1 to 2 hours, and is eliminated from the blood in a short time. Lanreotide was previously developed as a microparticle formulation (MPF). The Autogel® formulation, which was developed after the MPF, is a controlled release preparation of lanreotide acetate and water for injection which together form a supersaturated solution of the peptide. Prolonged release of the peptide occurs by the physical nature of the supersaturated solution. The formulation enables active serum levels to be maintained for 1 to 2 months. The usual clinical dosing regimen is one deep s.c. injection of lanreotide Autogel 60, 90 or 120 mg into the buttocks every 28 days in adults, using a formulation that contains lanreotide base 0.246 mg/mg of solution. In addition, patients whose GH levels are controlled with lanreotide Autogel 90 or 60 mg every 4 weeks may benefit from transferring to treatment at 120 mg every 6 or 8 weeks, respectively. Lanreotide Autogel was first launched in France in 2001, and is registered in approximately 50 countries worldwide including countries in Africa, Asia, Central and Eastern Europe, the Middle East, Australasia, and North, Central and South America. The information provided in this protocol represents a summary of the available data. This protocol focuses primarily on the lanreotide Autogel formulation. Data from studies in other formulations has been presented where

relevant.

Pharmacology, pharmacokinetic (PK), safety pharmacology and toxicology studies (including cardiovascular tolerance) have shown that lanreotide Autogel is safe for chronic use in humans.

Lanreotide is an effective treatment for acromegaly that relieves clinical symptoms in a high proportion of patients. It achieves its effect by inhibiting GH secretion and controlling serum concentrations of GH and insulin-like growth factor (IGF-1). The efficacy of lanreotide Autogel in patients with acromegaly was confirmed in a placebo controlled clinical study where a reduction in serum GH concentration was observed after 1 month of treatment. A dose related reduction in serum GH and IGF-1 concentrations was observed for the 60, 90 and 120 mg doses and serum GH concentrations were reduced to ≤1 ng/mL in 26.5% of patients following up to 52 weeks of treatment. Forty percent of patients achieved a mean serum GH concentration of ≤2.5 ng/mL The studies also confirmed that optimal doses of lanreotide Autogel, administered for up to 52 weeks, reduced most symptoms of acromegaly in the majority of symptomatic patients.

Lanreotide is also approved for the treatment of carcinoid neuroendocrine tumours (NET). The effectiveness of lanreotide Autogel has been demonstrated in terms of treatment response in one open label, dose titration (60, 90 and 120 mg) study, where 71 patients demonstrated the effectiveness of lanreotide Autogel in treating the clinical symptoms (diarrhoea or flushing) associated with carcinoid NET. The primary efficacy endpoint demonstrated that 38% of patients were classified as treatment responders at Month 6. The effectiveness of lanreotide Autogel was supported by the secondary efficacy endpoints that showed improvements in the individual symptoms of carcinoid NET, including the severity of flushing, as well as reductions in the levels of tumour markers, Chromogranin A and 5-hydroxyindole acetic acid (5-HIAA).

Overall, across clinical studies, the efficacy and safety profiles did not vary with age, gender, body mass index (BMI), bodyweight or race, and efficacy was comparable for previously treated and treatment naive patients. The tendency to develop antibodies to lanreotide is low, does not appear to affect efficacy, and does not increase with long term treatment.

Lanreotide Autogel was well tolerated by patients with acromegaly or carcinoid NET and most adverse events (AEs) observed during clinical studies were consistent with the known safety profile of somatostatin analogues (SSAs). The most common treatment emergent adverse events (TEAEs) were: gastrointestinal (GI) disorders (diarrhoea, abdominal pain, nausea, vomiting and constipation); hepatobiliary disorders (cholelithiasis); and nervous system disorders (headache).

Data from renally impaired, hepatically impaired or elderly subjects indicate that lanreotide Autogel is safe in these groups. As the dose of lanreotide Autogel is intended to be tailored to individual response the starting dose in patients with renal or hepatic impairment should be determined based upon local prescribing information or protocol requirements in the case of clinical studies. For patients with acromegaly and NET, similar results are expected with regard to renally impaired subjects.

Varying formulations of lanreotide (including lanreotide Autogel) have been studied in at least 1270 patients in other indications including cardiac disorders, GI bleed,

diabetes, oncology, ophthalmic Graves disease and studies in the paediatric population such as those in obesity and constitutional tall stature.
The number of post marketing spontaneous safety reports was low (approximately one reaction per >40 patient-years of exposure), and the post marketing adverse reaction profile was consistent with that for treatment related AEs in clinical studies. These findings support the safety of lanreotide including the Autogel formulation. Cardiac serious adverse reactions (SARs) were reported at the low rate of <1 per 3,800 patient-years of exposure. Since lanreotide has similar effects on heart rate to those of octreotide there is potential for it to cause bradycardia in some patients in rare cases. Lanreotide is not associated with any increased risk of heart valve regurgitation or cardiovascular disease. Pregnancies that occurred during lanreotide treatment did not raise any safety concerns however the numbers are small so lanreotide Autogel should be administered to pregnant women only if clearly needed. It is not known whether lanreotide is excreted in human milk. Lanreotide should not be used during breast feeding unless clearly necessary.

Further details can be found in the Investigator's brochure (Reference 1).

2.3Clinical Trial Rationale

Lanreotide has obtained a marketing authorisation in the treatment of acromegaly and neuroendocrine tumours.
Previous studies have shown that vomiting and pain due to bowel obstruction can be controlled by somatostatin analogues administered daily by subcutaneous injections in patients unresponsive to conventional therapy (9, 10, 11, 17) and more recently for a slow release microparticles formulation delivering lanreotide for 14 days in patients suffering from symptoms of obstruction due to peritoneal carcinomatosis (18)
A slow release formulation that is capable of maintaining therapeutic somatostatin analogue levels up to 28 days, that can be administered subcutaneously would be more convenient for clinical use. It would enable clinicians to treat patients ambulatory. Therefore, in this study, the efficacy of lanreotide autogel 120 mg in the management of symptoms secondary to inoperable intestinal obstruction in palliative cancer patients will be studied.

3 STUDY OBJECTIVES

3.1 Primary Study Objective

To assess the efficacy of lanreotide Autogel lanreotide Autogel 120 mg for the relief of vomiting due to inoperable malignant intestinal obstruction in patients without nasogastric tube AND to assess the efficacy of lanreotide Autogel 120 mg to remove a nasogastric tube without the recurrence of vomiting in patients with an inoperable malignant intestinal obstruction with a nasogastric tube

3.2 Secondary Study Objectives

1) To evaluate the impact on Quality of Life (Edmonton Symptom Assessment System) of lanreotide Autogel 120 mg assessed by both the patient and the caregiver

2) To assess the efficacy of lanreotide Autogel 120 mg for the relief of other clinical symptoms due to inoperable malignant intestinal obstruction :
- General activity (Karnofsky score)
- Nausea (number of daily episodes)
- Pain (Visual analogue scale)
- Complete/incomplete obstruction: passage of stools

3) To assess the symptom (nausea and vomiting) improvement delay

4) To assess the pharmacokinetic profile of lanreotide in patients with inoperable malignant intestinal obstruction

4 STUDY DESIGN

4.1 Overview

4.1.1 Population Characteristics

It is planned to include 50 patients in this study. Male or female patients of 18 years of age or older, diagnosed with intestinal obstruction due to malignant origin, who are unsuitable candidates for surgery. Patients should have 3 or more episodes of vomiting per 24 hours in the last 48 hours or should have a nasogastric tube

4.1.2 Design

This is a Phase II, single arm, non-randomised, prospective, open label, multicentre study.

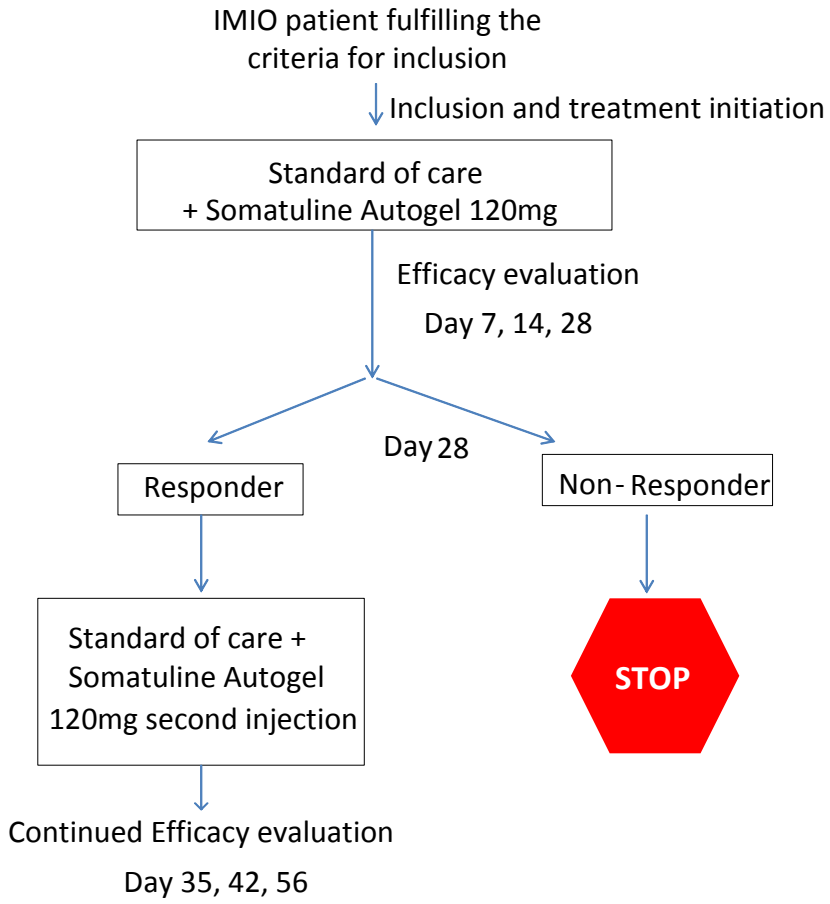


Figure 2 Study flow

The study will consist of 2 phases (see Figure 2)

Phase 1 Initial Injection Lanreotide Autogel 120 mg :
Patients meeting the selection criteria for participation will need to provide a written informed consent. Patient and caregiver will be asked to complete the Edmonton Symptom Assessment System (ESAS) before any study procedure. Patients will then receive the following treatment : Standard of care + 1 injection of lanreotide Autogel 120 mg. Response to the treatment will be assessed based on the % of responders in the treatment group at Day 7, Day 14 and Day 28.
Safety of the patients will be followed continuously during the entire study period. A blood sample to assess the serum levels of lanreotide will be taken on Day 1 and then on Day 7, Day 14 and Day 28.

For patients who are :

Non-responders at Day 28 OR Responders at day 28 but who are unwilling to receive a second injection with lanreotide, the participation to the study will stop here. Patients will then receive standard of care by the treating physician.

Phase 2 Second injection Lanreotide Autogel 120 mg :
Patients completing the 28 days of the first phase and who are responders as defined by this protocol will have the possibility to receive a second injection with lanreotide Autogel 120 mg. Standard of care will be continued for all as described by the protocol.
Response to the treatment will continued to be assessed based on the % of responders at Day 35, Day 42 and Day 56
Safety of the patients will be followed continuously during the entire study period.
A blood sample to assess the serum levels of lanreotide will be taken just before the second injection at Day 28 and at Day 35, Day 42 and at Day 56.

4.1.3 Stopping Rules and Discontinuation Criteria

Patients will be discontinued from the study if there is insufficient efficacy of the study treatment at Day 28.

4.1.4 Early Study Termination

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of adverse events (AE) in this or other studies point to a potential health hazard for trial subjects.
- Insufficient subject enrolment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

4.2 Endpoints

Primary Efficacy Endpoint(s) and Evaluation(s):

Phase 1 : Initial Injection Lanreotide Autogel 120 mg:
Percentage of responding patients before or at D7. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D7 (for patients without NGT at baseline) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D7 without vomiting recurrence.

- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting

Secondary Efficacy Endpoints And Evaluations:

Phase 1 : Initial Injection Lanreotide Autogel 120 mg:
1) Percentage of responding patients before or at D14 (same for D28). A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D14 (D28) **or** as a patient in

whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D14 (D28) without vomiting recurrence.
- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting episodes

2) Time between first injection and clinical response

3) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 7, Day 14 and Day 28 assessed by both the patient and the caregiver.

4) Changes in daily intensity and frequency at Day 7, Day 14 and Day 28 compared to baseline in
- General activity (Karnofsky score)
- Nausea (number of daily episodes)
- Pain (Visual analogue scale)
- Complete/incomplete obstruction: passage of stools

Phase 2 : Second injection Lanreotide Autogel 120 mg :
1) Overall Percentage of patients continuing from Phase I and confirmed as a responder at the end of phase I , showing a continued response at D35, D42 and D56. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 without vomiting recurrence.
- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting

2) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 35, Day 42 and Day 56 assessed by both the patient and the caregiver.

4.2.1 PK Endpoints

The PK profile of lanreotide based on lanreotide concentration-time data.

4.2.2 Safety Endpoints

Clinical and biological Adverse events and serious adverse events throughout the study

4.3 Justification of Design

4.3.1 *Study Population for Analysis*

Patients with inoperable intestinal obstruction of malignant origin who have at least 3 or more episodes of vomiting/24 hours for the last 48 hours or who have a nasogastric tube, are the candidates to be included in this study.

This study aims to recruit a total of 50 patients – male or female of 18 years or older who fulfil the listed criteria.
The primary study population for the analysis will be the ITT population.

4.3.2 Study Duration

The overall duration of the study will be approximately 3 years; this includes 2 years of recruitment: this period may be extended if needed to allow for the recruitment of the required number of patients. The study will be considered to have started when the first patient has provided signed informed consent. The study will be considered to have finished after the last patient has completed the last follow-up period in the study, this will also be considered as the "end of study ".
For each individual subject, study participation will be 2 months. The subjects participation in the study is considered to have ended at the time of the last visit.

5 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS & INFORMED CONSENT

5.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with independent ethics committees (IECs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) (2) Good Clinical Practice (GCP) Guidelines.
In addition, this study will adhere to all local regulatory requirements.
Before initiating a trial, the Investigator/institution should have written and dated approval from the IEC for the trial protocol/amendment(s), written informed consent form, any consent form updates, patient emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC that they comply with GCP requirements. The IEC approval must identify the protocol version as well as the documents reviewed.
After IEC approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC.

5.2 Informed Consent

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The Sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the Sponsor, and the IEC and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical trial.

6 STUDY POPULATION

6.1 Screening Log and Number of Subjects

Each Investigator will maintain a record of all subjects who were considered eligible for entry into the study but who were not enrolled. For each subject, the primary reason for exclusion will be recorded.

Each Investigator will also maintain a record of all subjects enrolled into the study (i.e., who signed the informed consent form). In the event that the subject was not receiving IMP, the primary reason will be recorded.

It is planned to recruit approximately 50 subjects at approximately 20 centres in Belgium and Luxemburg. Each centre should enrol approximately 3 subjects. Section 11.2 provides a discussion of sample size.

6.2 Inclusion Criteria

All subjects must fulfil the following:

1) Written informed consent before any study related procedure
2) Male and female patients age 18 years or older at the time of enrolment
3) Diagnosis of an intestinal obstruction of malignant origin
4) In case of peritoneal carcinomatosis, confirmation by CT or MRI scan within the 3 months preceding the inclusion in the study
5) Confirmed as inoperable after surgical advice
6) Patient with a nasogastric tube OR presenting with 3 or more episodes of vomiting / 24h in the last 48 hours
7) Estimated life expectancy 1 month or more

6.3 Exclusion Criteria

Subjects will not be included in the study if the subject :

1) Operable obstruction or any sub-obstruction
2) Bowel obstruction due to a non-malignant cause (for example : hypokaliemia, drug side-effects, renal insufficiency, …)
3) Signs of bowel perforation
4) Prior treatment with somatostatin or any analogue within the previous 60 days
5) A known hypersensitivity to any of the study treatments or related compounds
6) Previous participation in this study
7) Is likely to require treatment during the study with drugs that are not permitted by the study protocol (see Section 9.5).
8) Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject's safety.

6.4 Subject Withdrawal Criteria

Patients will be discontinued from the study any time during the treatment period in case of any AE if serious Adverse Event (SAE) that may jeopardize the patient safety. Patients may also be withdrawn according to the clinical judgement of the investigator or at their own request. See Section 10.6 for further details. Under no circumstances will subjects be enrolled more than once.

6.5 Discontinuation/Withdrawal Procedures

If the subject is withdrawn from the study (i.e., ceases participation in the study prior to completion of the assessments planned in the protocol), the primary reason should be recorded in the case report form (CRF). Withdrawal due to AEs should be distinguished from withdrawal due to insufficient response.
In case of discontinuation due to insufficient response, the patient will be asked to attend the study withdrawal visit.
In case of withdrawal due to AEs, if possible, the patient should also attend the study withdrawal visit and undergo the assessments of this visit or as deemed necessary by the Investigator.
The withdrawal visit should be performed 4 weeks after the patient has received the last study drug injection.
The Investigator will provide or arrange for appropriate follow-up (if required) for subjects withdrawing from the study, and will document the course of the subject's condition. Where the subject has withdrawn due to an AE the Investigator should follow the procedures documented in Section 10 in order to assess the safety of the IMP.

7 METHODOLOGY

7.1 Study Schedule of assessments

The schedule of observations and assessments during the study are summarised below.

Table 1. Phase I

Visit	V1	V2	V3	V4 End of part 1 or EOS Visit****
Day	D1	D7	D14	D 28
Informed consent	●			
Eligibility review	●			
Demography	●			
Medical history	●			
Malignancy history	●			
clinical examination ##	●	●	●	●
Nutrition procedure	●	●	●	●
Symptoms and QOL assessment *	●	●	●	●
Vomiting and nausea episodes assessment (diary cards)**	●	●	●	●
Prior and Concomitant medications	●	●	●	●
Safety biological ### assessment (if applicable)	●	●	●	●
Injection Study Treatment Lanreotide Autogel 120 mg	●			
Lanreotide Concentration	●#	●	●	●
Adverse Events***	●	●	●	●

*: VAS for abdominal pain, Karnofsky for daily activities, QOL by means of Edmonton Symptom Assessment System (caregiver and patient), and presence of partial/complete intestinal obstruction. Nausea and vomiting will be separately recorded

**: Diary cards will be completed every day for a total of 28 days.

***: At Day 1 (baseline) after signature of the informed consent and after clinical examination and medical history

: Between 2 and 12 h after the injection of lanreotide Autogel 120 mg

##: including Vital signs as Height, Weight, BP and HR

###: including hematology and biochemistry(upon discretion of the investigator)

Hematology could include: RBC,Hb,Ht,MCV,MCHC,WBC,Neutro,Lymph,Monocytes,Eosino, Baso,other differentials, platelets..

Biochemistry could include Urea,creat,biliT,Na,K,Ca,Cl,Bicar,AlkPh,ASAT,ALAT,GGT,Alb,Prot.tot,CholT,Trigl,glucose..

****: if patient is not responder then V4 is EOS – if the patient is responder he will be reinjected and will continue in the study until the EOS at V7

##: clinical examination will consist in vital signs: BP, HR,T°, (weight: optional)

Table 3. Phase II

Visit	V4	V5	V6	V7 EOS or EWD Visit
Day	D28	D35	D42	D56
Eligibility review	X			
clinical examination##	X	●	●	●
Nutrition procedure	X	●	●	●
Symptoms and QOL assessment *	X	●	●	●
Vomiting and nausea episodes assessment (diary cards)**	X	●	●	●
Concomitant medications	X	●	●	●
Safety biological assessment (if applicable)	X	●	●	●
Second lanreotide Autogel 120 mg injection	●			
Lanreotide concentration	●#	●	●	●
Adverse Events	●	●	●	●

*: VAS for abdominal pain, Karnofsky for daily activities, QOL by means of Edmonton Symptom Assessment System (caregiver and patient), and presence of partial/complete intestinal obstruction. Nausea and vomiting will be separately recorded

**: Diary cards will be completed every day for a total of 28 days.

X : These data will be copied from V4 of Phase 1

##: clinical examination will consist in BP, HR,T°

Lanreotide Adminitration at V4 only for responders

: Before the second lanreotide Autogel 120 mg injection

Adverse Events: At Day 1 (baseline) after signature of the informed consent and after clinical examination and medical history
Visit 4 Day 28: For subject who received an administration of Lanreotide Autogel 120 mg at Day 1 and who stops the study at Day 28 the EOS/EWD visit should be completed
Lanreotide Administration at V4 only for responders

7.2. Study Visits

Allowed time deviation for the visits :
Phase I :
Visit 1 (Day1) : Not applicable
Visit 2 (Day 7): No deviations allowed
Visit 3 (Day 14) : ± 2 days
Visit 4 (Day 28) : ± 2 days

Phase II :
Visit 4 (Day 28) : ± 2 days *(this is Visit 4 for Phase I)*
Visit 5 (Day 35) : ± 2 days
Visit 6 (Day 42): ± 2 days
Visit 7 (Day 56): ± 2 days

The exact date and clock-time of lanreotide Autogel 120 mg administration will be entered into the CRF. The exact date and clock-time of the PK blood samples will be entered into the CRF.

7.2.1 Day 1 (Visit 1)

Written informed consent should be obtained prior to enrolment when the following assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Demographics (sex, age, race,)
- Medical history, including ongoing medical history and physical examination
- Prior and concomitant medications/therapies
- Blood sampling for haematology and biochemistry, as deemed necessary by the treating physician(optional).
- Blood sampling for PK analysis between 2h and 12h after the lanreotide autogel 120 mg injection
- Nutrition procedure (no oral food or oral liquid intake during the first 7 days)
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment (episodes in the last 48 hours) and distribution of diary cards

- Start of compulsory medication (See Section 9.5) and injection of lanreotide Autogel 120 mg
- AEs….

7.2.2 Day 7 and Day 14 (Visit 2-3)

The following procedures will be performed for each subject who received and administration with Lanreotide Autogel 120 mg at Day 1 :

- Physical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 7 and day 14.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- Start of step up medication at Day 7 in case of insufficient efficacy
- AEs and SA

7.2.3a End of Phase 1 Day 28 (Visit 4) or Early Withdrawal Visit Phase 1

The following procedures will be performed for each subject who received an administration of Lanreotide Autogel 120 mg at Day 1 and who stops the study at Day 28 or has an Early Withdrawal Visit Phase I :

- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 28 or at early withdrawal
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Reason for end of phase 1 / early withdrawal
- patient who are not responding or who do not want to be reinjected the EOS visit should be completed

7.2.3b Visit 4 Phase 2 - Day 28 Post injection

The following procedures will be performed for each subject who received and administration with Lanreotide Autogel 120 mg at Day 1 and continues the study at Day 28:

Eligibility Check Phase II : Proven efficacy at Day 28 : ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D28 (for patients without NGT at baseline) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D28 without vomiting recurrence.

- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 28 before the second injection of lanreotide Autogel 120 mg.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.

- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Second injection of Lanreotide Autogel 120 mg

7.2.4 Day 35 and Day 42 (Visit 5-6)

The following procedures will be performed for each subject who received a second administration of Lanreotide Autogel 120 mg at Day 28 :

- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on D35 and D42.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs

7.2.5 Day 56 (Visit 7 End of Study Phase 2) or Early Withdrawal Visit

The following procedures will be performed for each subject who received a second administration with Lanreotide Autogel 120 mg at Day 28 and who ends the study at Day 56 or has an Early Withdrawal Visit Phase II :

- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on D56 or early withdrawal
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Reason for end of study / early withdrawal

8 STUDY EVALUATIONS

For the timing of assessments during the study, refer to the study schedule in Section 7.1.

8.1 Efficacy Endpoints and Evaluations

8.1.1 Primary Efficacy Endpoint and Evaluations

Phase 1 : Initial Injection Lanreotide Autogel 120 mg:

Percentage of responding patients before or at D7. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D7 (for patients without NGT at baseline) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D7 without vomiting recurrence.

- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting

8.1.2 Secondary Efficacy Endpoints and Evaluations

Phase 1 : Initial Injection Lanreotide Autogel 120 mg:

1) Percentage of responding patients before or at D14 (same for D28). A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D14 (D28) **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D14 (D28) without vomiting recurrence.

- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting

2) Time between first injection and clinical response

3) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 7, Day 14 and Day 28 assessed by both the patient and the caregiver.

4) Changes in daily intensity and frequency at Day 7, Day 14 and Day 28 compared to baseline in

- General activity (Karnofsky score)
- Nausea (number of daily episodes)
- Pain (Visual analogue scale)
- Complete/incomplete obstruction: passage of stools

Phase 2 : Second injection Lanreotide Autogel 120 mg :

1) Overall Percentage of patients continuing from Phase I and confirmed as a responder at the end of phase I , showing a continued response at D35, D42 and D56. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day

during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 **or** as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D1 and D35, D42 and D56 without vomiting recurrence.

- Number of daily vomiting episodes recorded on diary cards.
- Number of days without vomiting

2) Changes from baseline in Quality of Life (Edmonton Symptom Assessment System) at Day 35, Day 42 and Day 56 assessed by both the patient and the caregiver.

8.1.3 Pharmacokinetic Endpoints and Evaluations

See 8.4

8.2 Safety Endpoints and Evaluations

8.2.1 Adverse Events

AEs will be monitored from the time that the subject gives informed consent to the time when the subject's participation in the study is considered to have ended (as defined in Section 4.3.2). AEs will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 11.

8.2.2 Physical Examination

A physical examination will be carried out by a physician. If in the opinion of the Investigator there are any clinically significant changes in the physical examination findings (abnormalities) they will be recorded as AEs.

8.2.3 Clinical Laboratory Tests

All clinical laboratory test are at the discretion of the investigator.
Laboratory tests, if clinically relevant will be recorded on the laboratory results pages of the CRF. All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor's clinical monitor (or his/her designated representative), or until the abnormality is explained by an appropriate diagnosis. See Section 10.2.4 for abnormal laboratory tests that should be recorded as AEs in the CRF.

8.3 Total Blood Volume

The total blood during the whole course of the study, taken for serology, biochemistry, haematology, pharmacokinetics (PK) and will not exceed 15 mL per subject.

8.4 Pharmacodynamic Endpoints and Evaluations:NA

8.5 Pharmacokinetic Endpoints and Evaluations

Blood samples will be collected for the assay of lanreotide. The tubes should be centrifuged. The resulting /serum will be collected and split into two equal aliquots. The samples will be frozen and stored until shipment to the central laboratory. Each tube should be labelled with the sample identification, study number, site number, subject number and initials, visit number (when applicable) and the planned time of collection. Full details of required labelling and the shipment process for these samples will be documented in the Study Manual.
On predetermined dates, samples will be shipped in different batches under frozen conditions to the central laboratory. For security reasons, the two aliquots of each sample will be shipped separately. The batch of second aliquot will not be shipped until the first one has arrived.
Upon receipt at the central laboratory, samples will be checked and stored until serum analysis.

The concentration of lanreotide will be analysed using a validated method. All details of samples collection, handling and shipment will be provided in the Study Manual. Details of the methodology and reference ranges will be provided in the TMF.

The PK profile of lanreotide Autogel in patients with IMIO will be assessed using the population approach. The potential effect of the covariates (demographic,pathological) on the PK parameters will be explored.

9 STUDY TREATMENTS

9.1 Study Treatments Administered

It is forbidden to use IMP for purposes other than as defined in this protocol. Administration of the IMP will be supervised by the Investigator, or designee. Each patient who meets the eligibility criteria (inclusion/exclusion criteria) for participation in the study will be given a deep sub cutaneous injection of lanreotide Autogel 120 mg in the upper outer quadrant of the buttock on top of the mandatory medication (Section 9.5). Patients who respond at day 28 and who are willing to participate in the second phase of the study will be given an additional injection of lanreotide Autogel 120 mg on top of the mandatory medication (Section 9.5).

9.2 Subject Identification and Allocation to Study Treatment

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.
Following confirmation of eligibility for the study, subjects will be given a unique patient number and receive the treatment as specified in Section 9.1.

9.3 Study Treatment Supply, Packaging and Labelling

The IMP will be packaged by CTSU Dreux and delivered to the investigational sites. A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form.

The Sponsor's representative will receive; a Certificate of Analysis for which batch of IMP has been used under their study, Material Data Safety Sheet for the active drug, Packaging Order which reflects the product release statement.

The core label texts for all packaging units will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Sponsor name
- Study Number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- Treatment box number
- 'For clinical trial use only'
- 'Keep out of reach of children'
- Name, address and telephone number of the Sponsor, (Reference (3))
- Storage conditions
- Expiry date

The Investigator, or designee, will only dispense IMP to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the CRF.

9.4 Study Treatment Storage and Accountability

The Investigator, or an approved representative (e.g. pharmacist), will ensure that all IMP is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements and will be dispensed by qualified staff members.

All study treatments are to be accounted for on the IMP accountability log provided by the Sponsor. It is essential that all used and unused supplies are retained for verification (by the Sponsor or Sponsor's representative). The Investigator should ensure adequate records are maintained via the IMP accountability log.

9.5 Mandatory and Concomitant Medication/Therapy

MANDATORY concomitant medication for all patients to be started the latest at Day 1:

- No oral food or oral liquid intake during the first 5 days of treatment unless there are signs of resolution of the obstruction (passing stools or gas):

patients can consume oral or liquids at the discretion of the treating physician

- As of Day 1 Intravenous corticoids : Solumedrol 40 mg/day or dexamethasone or methylprednisolone or equivalent at a dose of 1 mg/kg/day or more
- Intravenous H2 antihistaminics : ranitidine 50 mg 3/d or PPI : omeprazole or pantoprazole or equivalent.

Step up medication if not enough efficacy at Day 7:

- butylhyoscine bromide (Buscopan): 40-120 mg SC or IV
  AND
- Haloperidol : 5 mg / 2 x day IV

Authorised for all patients :

- Analgesics on request

- Metoclopramide 10 mg/4h or Domperidone 10 mg qid or Odansetron 8mg/4ml at the discretion of the investigator
- Chemotherapy (if already present at study entry)
- Venting Gastrostomy after Day 7

The following concomitant medications are not permitted during this study (see also Section 6.2):

- Somatostatin or any of its analogues other than the study drug

9.6 Treatment of Overdose of IMP

Any appropriate treatment of overdose of IMP will be determined by the Investigator according to the characteristics of the events and will be recorded in the subject's CRF. An event resulting from an overdose of the trial medication is not considered as serious unless it meets the definition of a Serious Adverse Event (SAE) and consequently should be reported on the SAE form (see Section 10.4).

10 ADVERSE EVENT REPORTING

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.
This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 4.3.2).

10.1 Disease Progression

Symptoms of expected disease progression do not need to be recorded as AEs.

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

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

Mild: symptoms do not alter the subject's normal functioning

Moderate: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject

Severe: symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

10.2.2 Causality Classification

The relationship of an AE to the IMP will be classified according to the following:

Related: reports including 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 IMP in the sense that it is plausible, conceivable or likely.

Not related: reports including 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 IMP.

10.2.3 Assessment of expectedness

The expectedness of an AE/reaction shall be determined by the Sponsor according to the Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SmPC) or Package Insert (PI) for an authorised medicinal product which is being used according to the terms and conditions of the marketing authorisation. If the IMP has marketing authorisations in several countries with different SmPCs or PIs, one will be selected as the reference document for assessing expectedness.

The reference document for assessing expectedness of AEs/reactions in this study will be: the current Investigator's Brochure

10.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- they result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- they require intervention or a diagnosis evaluation to assess the risk to the subject,
- they are considered as clinically significant by the Investigator.

10.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

10.2.6 Other Investigation Abnormal Findings

Abnormal objective test findings as judged by the Investigator as clinically significant (e.g., electrocardiogram changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs

10.3 Recording and Follow-up of Adverse Events

At each visit the subject should be asked a non-leading question such as: "Do you feel different in any way since starting the new treatment/the last assessment?"
All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the CRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation's of pre-existing illnesses should be recorded
AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.
For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e., IMP or other illness). The Investigator is required to assess causality and record that assessment on the CRF. Follow-up of the AE, after the date of therapy discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

10.4 Serious Adverse Events

10.4.1 Definitions

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the Investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.
A SAE is any AE occurring at any dose that:

(1) results in death;

(2) is life threatening, that is any event that places the subject at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death;

(3) results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further);

(4) results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;

(5) results in congenital anomaly/birth defect in the offspring of a subject who received the IMP;

(6) is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional AE that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system.

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the Investigator or treating physician**. For protocol-specified hospitalisation in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.
- Pre-planned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

10.4.2 Reporting Requirements

Any SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period.

Any SAE with a suspected causal relationship to the IMP occurring at any other time after completion of the study must be promptly reported.

10.4.3 Mandatory Information for Reporting an SAE

The following information is the minimum that must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Trial number
- Centre number

- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

10.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected post-study and it may be necessary to discontinue treatment with the IMP. Information regarding pregnancies must be collected on the AE page of the CRF and reported to the sponsor as an SAE. The Sponsor will request further information from the Investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

Investigators must instruct all female subjects to inform them immediately should they become pregnant during the study. The Investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the fœtus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.

Pregnancies with a conception date within 90 days after subject's last dose of IMP or completion of the study must also be reported to the Investigator for onward reporting to the Sponsor.

10.6 Deaths

All AEs resulting in death either during the study period or within 28 days after the last dose of IMP, must be reported as an SAE within 24 hours of the Investigator's knowledge of the event.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.

For AEs leading to death, severe is the only appropriate grade (see Section 10.2.1).

Deaths that cannot be attributed to a specific cause have to be reported as one of these four AE options:

- Death NOS
- Disease progression NOS
- Multi-organ failure

- Sudden death

10.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Sections 6.4 and 6.5).

If the IMP is discontinued due to a SAE it must be reported immediately to the Sponsor's designated representative (see Section 10.4).

In all cases the Investigator must ensure the subject receives appropriate medical follow-up (see Section 10.3).

10.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs, IRBs and other Investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

11 STATISTICAL CONSIDERATIONS

11.1 Subject Classification and Definitions

- **Enrolled subject:** Subject fully informed about the study who has given written informed consent to participate (before any occurrence of trial related procedure)
- **Treated subject :** Enrolled subject who is treated with at least one dose of study medication
- **Treatment Completed subject:** Treated subject who has completed all specified phases of the first injection of the active treatment.
- **Study Completed subject:** Treated subject who has completed all specified phases/assessments of the study.(day 28 or day 56)
- **Drop-out:** Treated subject who did not complete the study and or discontinued treatment.

11.2 Analyses Populations Definitions

- **Safety population**: All subjects who received at least one dose of study medication
- **Intention-to-treat (ITT) population**: Enrolled subjects with at least one dose of study medication
- **Per protocol (PP) population**: All subjects in the ITT population for whom no major protocol violations/deviations occurred
- **PK Population** All subjects with at least one measurable lanreotide concentration

11.2.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the ITT population. In addition, PP analysis may be performed as secondary.
The analyses of safety data will be performed based on the Safety population.

11.2.2 Subject Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of subjects to each of the analysis populations will be defined and documented during a "data" review meeting held prior to database lock. During the data review meeting, based on minor or major protocol violations/deviations, subjects may be excluded from the Safety/ITT/PP population. Subjects may be excluded from the analyses if one or more of the following violations/deviations occur.

- inclusion/exclusion criteria violations
- did not receive any study medication
- prohibited medication intake
- deviations from time windows
- deviations from IMP administration

- no baseline evaluation of primary efficacy criterion
- no valid post baseline evaluation of primary efficacy criterion
- other protocol violation/deviations

11.3 Sample Size Determination

Sample size is calculated to test if the proportion responders at day 7 using Lanreotide 120 mg is larger than the reference proportion of 30% (18). The following assumption underlie the sample size calculation: expected proportion responders using lanreotide is 50%, 1-sided test, 2.5 % significance level alpha and power of 80 % using Z-test for binomial proportion. The required sample size is 44 subjects. However, taken into account a certain margin for drop outs (15-20%), 50 patients will be recruited for this study. It is planned to recruit these patients in a 2 year period in approximately 20 centres in Belgium and Luxemburg. Each centre will be required to enrol between 1 and 3 subjects.

11.3.1 Significance Testing and Estimations

Formal significance testing will be performed 1-sided at 2.5% significance level alpha using z-test for binomial proportion, for the primary efficacy endpoint (ie percentage of responders at day 7). This method tests if the proportion responders using Lanreotide 120 mg is larger than the reference proportion of 30% (18).

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the Sponsor's Clinical Development Data Sciences Department.
A Reporting and Analysis plan (RAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.
The pharmacokinetic analyses will be performed independently, by IPSEN or a designated contract organisation
Statistical evaluation will be performed using Statistical Analysis Software (SAS)® (version 8 or higher).

11.5 Subgroup Analyses

It will also be detailed in the RAP if and what subgroup analyses are to be performed. All subgroup analyses will be performed by means of descriptive statistics for exploratory purposes

11.6 Interim Analyses

No interim analysis will be performed.

12 MONITORING PROCEDURES

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and well being of subjects are protected, that trial data are accurate (complete and verifiable

to source data) and that the trial is conducted in compliance with the protocol, GCP and regulatory requirements.

12.1 Routine Monitoring

Sponsor-assigned monitors will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all subjects) and clinical trial supplies (dispensing and storage areas) for the purpose of verifying entries made in the CRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the CRFs within 5 days after the patient's visit and on an ongoing basis to allow regular review by the study monitor. This time period may be changed at some specific stages of the study (e.g., end of study or for interim analysis purposes).During the study the monitor will visit the site regularly to check the completeness of patient's records, the accuracy of the entries on CRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

Whenever a subject name is revealed on a document required by the Sponsor (e.g., laboratory print-outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

13 STUDY MANAGEMENT

13.1 Inspections and Auditing Procedures

Authorised personnel from external CAs and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in section 12.1, and to any other locations used for the purpose of the study in question (e.g., laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

13.2 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical trial.

The Investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the CRFs provided for the study. The Investigator must, as a minimum, sign each "visit status" CRF page to attest to the accuracy and completeness of all the data.

All corrections on a CRF and on source documents must be made in a way, which does not obscure the original entry. The correct data must be inserted, dated and initialled/authorised by study site personnel. If it is not obvious why a change has been made, a reason must be provided.

13.3 Source Data Verification

As required by GCP, the Sponsor assigned monitor must verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the CRF.

As required by ICH GCP §6.4.9, the following items will be recorded directly on the CRF and will be considered as source data:

- *Case and visit notes(hospital medical records) containing demographic and medical information, laboratory data,and the results of any tests or assessments*

The source documents must, as a minimum, contain the following; a statement that the subject is included in a clinical trial, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration, and any AEs and associated concomitant medication.

Definition for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH GCP Section 1.51]
- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). [ICH GCP Section 1.52]

The subject must have consented to their medical records being viewed by Sponsor-authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

13.4 Data Quality

Monitored CRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant CRF page for any missing data and other protocol deviations, where space has been provided. Any data management queries and items not adequately explained will be returned to the Investigator by the monitor for clarification/correction. The Investigator must ensure that data queries are dealt with promptly. Copies of all data changes and clarifications must be retained by the Investigator and filed with the CRFs.

13.5 Data Management

Data management will be conducted either by a CRO, directed by the Sponsor's Clinical Development Data Sciences (CDDS) Group or by the Sponsor's CDDS Group. All data management procedures will be completed in accordance with Ipsen and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the Investigator site, (for further details please see section 12 Monitoring Procedures). CRF and other data documentation removed from the Investigator site(s) will be tracked by the CRO and the monitor.

The Sponsor will ensure that appropriate data entry methods are used (e.g., double data entry) and suitable queries are raised to resolve any missing or inconsistent data.

Any queries generated during the data management process will also be tracked by the contracted data management CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The Sponsor will also ensure that SAE data collected in the CRF are consistent with information provided to the Sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the contracted CRO, and reviewed and approved by the Sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

13.6 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

14 ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

As required by local regulations, the Sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

14.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

14.3 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on structure and contents of clinical study reports. A final clinical study report will be prepared where any subject has signed informed consent, regardless of whether the trial is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

14.4 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

14.5 Insurance, Indemnity and Compensation

The Sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

15 PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required (see section 5.1), is will be classified into one of the following three categories:

- ***Non-Substantial Amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs/IRBs or Competent Authorities (CA) for information purposes.
- ***Substantial Amendments*** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the trial;
  - the conduct or management of the trial; or
  - the quality or safety of the IMP used in the trial.

  Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the EU member states, approval or 'favourable opinion' can be assumed if the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.
- ***Urgent Amendments*** are those that require urgent safety measures to protect the trial subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

16 REFERENCES

(1) Investigators Brochure Lanreotide

(2) International Conference on Harmonisation (ICH) E9 and Federal register Vol 63, No. 179 (September 1998).

(3) GMP, Annex 13.

(4) Food and Drug Administration (FDA) 21 CFR Part 11, Electronic Records, Electronic Signatures

(5) FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials

(6) Ripamonti C.: Management of bowel obstruction in advanced cancer. *Current Opinion in Oncology* 1994; 6: 351-357.

(7) Baines M., Oliver D.J., Carter R.L.: Medical management of intestinal obstruction in patients with advanced malignant disease: a clinical and pathological study. *Lancet* 1985; 2: 990-993.

(8) Ripamonti C., Twycross R., Baines M., and al.: Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. *Support Care Cancer* 2001; 9 (4): 223-233.

(9) Ripamonti C. Panzeri C., Groff L. and al.: The role of somatostatin and octreotide in bowel obstruction: pre-clinical and clinical results. *Tumori* 2001; 87: 1-9.

(10) Fainsinger R.L., Pisani A., Bruera E.: Use of somatostatin analogues in terminal cancer patients. *J. Palliat. Care* 1993; 9/1: 56-57.

(11) Mercadante S., Spoldi E., Caraceni A., Maddaloni S., Simonetti M.T.: Octreotide in relieving gastrointestinal symptoms due to bowel obstruction. *Palliat. Med*. 1993; 7: 295-299.

(12) Laval G. and al.: The use of steroids in the management of inoperable obstruction. *Palliative Medicine* 200; 14: 3-10.

(13) Raptis S., Schlegel W., Lehmann E., Dollinger H.C., Zoupas C.: Effects of somatostatin on the exocrine pancreas and the release of duodenal hormones. *Metabolism* 1978; 27: 1321-1328.

(14) Tulassay Z.: Somatostatin and the gastrointestinal tract. *Scand. J. Gastroenterol* 1998; 33 Suppl 228: 115-121.

(15) Lansden F.T., Adams D.B., Anderson M.C.: Treatment of external pancreatic fistulas with somatostatin. *Am. Surg*. 1989; 55: 695-698.

(16) Barnes S., Kontny B., and Prinz R. Somatostatin analog treatment of pancreatic fistulas. *International Journal of Pancreatology* 1993; 14 (2): 181-188.

(17) Mystakidou K.,Tsilika E., Kalaidopoulou O. and al.: Comparison of Octreotide administration versus conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Research* 2002; 22: 1187-1192.

(18) P. Mariani, J. Blumberg, L. Chauvenet : Efficacy of Lanreotide 30 mg as Symptomatic Treatment in Patients with Inoperable Bowel Obstruction Due to Peritoneal Carcinomatosis: A Randomized, Double-blind, Placebo-controlled Study

17 LIST OF APPENDICES

No table of figures entries found.

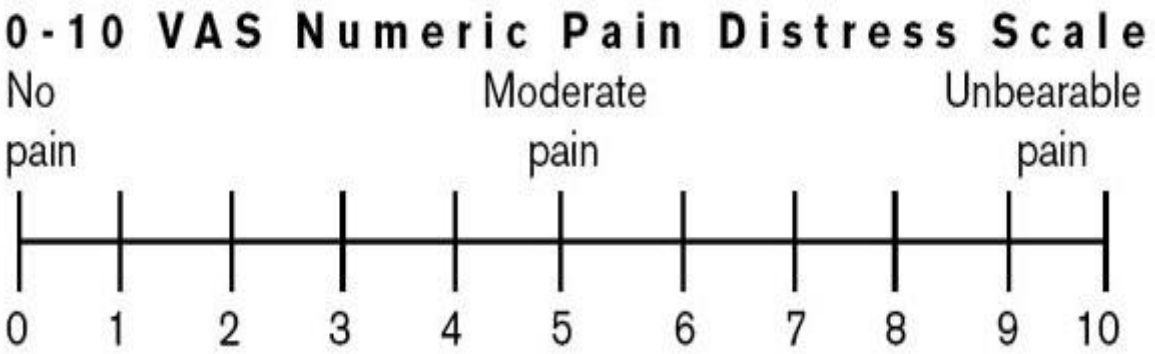
IMIO - STUDY

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Appendix 2: Visual Analogue Scale



Appendix 3: Karnofsky performance status scale (%)

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 4: Patient's diary

IPSEN Innovation for patient care	DIARY	STUDY A-48-52030-269	PERIOD DAY 1 TOT DAY 28	SITE N° 0560	PATIENT N° 000

EXAMPLE **Please fill in.**

07 / 01 / 2013	V	V	N	N											Remarks:
_08 / 01 / 2013	N	N	V	N											Remarks:
___/___/20____															Remarks:
___/___/20____															Remarks:
___/___/20____															Remarks:
___/___/20____															Remarks:
___/___/20____															Remarks: