A PHASE II, MULTICENTRE, RANDOMIZED CONTROLLED STUDY EVALUATING THE QUALITY OF LIFE IN PATIENTS WITH INOPERABLE MALIGNANT BOWEL OBSTRUCTION TREATED WITH LANREOTIDE AUTOGEL 120 MG IN COMBINATION WITH STANDARD CARE VS. STANDARD CARE ALONE (QOL IN IMBO STUDY).

STUDY PROTOCOL

STUDY number: A-93-52030-279
Product Name: Ipstyl
EudraCT number: 2013-003176-12

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Sponsor's Medically Responsible Person:
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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol Number A-93-52030-279 and title "A PHASE II, MULTICENTRE, RANDOMIZED CONTROLLED STUDY EVALUATING THE QUALITY OF LIFE IN PATIENTS WITH INOPERABLE MALIGNANT BOWEL OBSTRUCTION TREATED WITH LANREOTIDE AUTOGEL 120 MG IN COMBINATION WITH STANDARD CARE VS. STANDARD CARE ALONE (QOL IN IMBO STUDY)".

I am aware of my responsibilities as a coordinating 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.

Name & Surname:_____ **Signature:** _____

Title: COORDINATING INVESTIGATOR **Date:** _____

SITE:_____

_____

_____

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

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

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the Protocol Number A-93-52030-279 and title "A PHASE II, MULTICENTRE, RANDOMIZED CONTROLLED STUDY EVALUATING THE QUALITY OF LIFE IN PATIENTS WITH INOPERABLE MALIGNANT BOWEL OBSTRUCTION TREATED WITH LANREOTIDE AUTOGEL 120 MG IN COMBINATION WITH STANDARD CARE VS. STANDARD CARE ALONE (QOL IN IMBO STUDY)".

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[2], 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.

Name & Surname:_____ **Signature:** _____

Title: PRINCIPAL INVESTIGATOR **Date:** _____

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On behalf of the Sponsor:

Name & Surname: PPD **Signature:** _____

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[2] 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	A PHASE II, MULTICENTRE, RANDOMIZED CONTROLLED STUDY EVALUATING THE QUALITY OF LIFE IN PATIENTS WITH INOPERABLE MALIGNANT BOWEL OBSTRUCTION TREATED WITH LANREOTIDE AUTOGEL 120 MG IN COMBINATION WITH STANDARD CARE VS. STANDARD CARE ALONE (QOL IN IMBO STUDY)".
Study Objectives:	**Primary Objective:** To evaluate the impact on Quality of Life (Edmonton Symptom Assessment System, ESAS total score) of LAN ATG 120 mg in combination with standard care, in comparison to the standard care alone. **Secondary Objectives:** 1) To evaluate the impact of LAN ATG 120 mg on each ESAS item and total score; 2) To assess General activity (Karnofsky performance status) and Abdominal Pain (Visual analogue scale); 3) To assess the efficacy of LAN ATG 120 mg for the relief of vomiting in patients without nasogastric tube (NGT); 4) To assess the efficacy of LAN ATG 120 mg on NGT secretion volumes or to remove NGT without recurrence of vomiting in patients with a nasogastric tube; 5) Passage of stools (Yes/No); 6) Descriptive analysis of optional ESAS item 10; 7) To assess the efficacy in reducing concomitant medications/ analgesics intake. **Safety objectives** To assess the clinical and laboratory safety of the study treatment.
Phase of Trial	Phase II
Study Design	This is a phase II, multicentre, prospective, randomized, parallel arms, open-label study. Patients meeting the selection criteria for participation will need to provide a written informed consent. Patients will be asked to complete the Edmonton Symptom Assessment System (ESAS), before any study procedure. Patients will then be randomized in two groups: Group A: Standard care + 1 injection of LAN ATG 120 mg Group B: Standard care ESAS will be assessed at Day 1,2,3,4,5,6, 7, Day 14 and Day 28. Safety will be assessed in both arms continuously during 28 days.

Study Population:	84 patients with inoperable bowel obstruction of malignant origin in Italy. **Inclusion Criteria:** 1) Subjects must demonstrate willingness to participate in the study and to be compliant with any protocol procedure. 2) Provision of written informed consent prior to any study related procedure. 3) Male or female aged ≥ 18 years at the time of enrolment. 4) Diagnosis of an inoperable malignant bowel obstruction, confirmed by appropriate imaging report. 5) In case of peritoneal carcinomatosis, diagnostic confirmation by CT or MRI scan; 6) Confirmed as inoperable after medical advice; 7) Patient with a nasogastric tube or presenting with 3 or more episodes of vomiting every day in the last consecutive 48 hours; 8) Patient life expectancy must be more than 14 days. **Exclusion Criteria:** 1) Operable obstruction or any subobstruction; 2) Bowel obstruction due to a non-malignant cause; (hypokaliaemia, drug side-effects, renal insufficiency, etc) 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) Is likely to require treatment during the study with somatostatin or any analogue other than the study treatment. 7) Is at risk of pregnancy or lactation, or is likely to father a child during the study. Females of childbearing potential must provide a negative pregnancy test at start of study and must be using oral or double barrier contraception. Non childbearing potential is defined as post-menopause for at least 1 year, surgical sterilisation or hysterectomy at least three months before the start of the study. 8) Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude. 9) 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 or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.

Study Treatment:	**Investigational Medicinal Product (IMP):** Patients will be randomized in two groups: Group A: Standard care + 1 injection of LAN ATG 120 mg Group B: Standard care **General Definition of Standard care:** - Oral food or oral liquid intake according to clinical judgement; - Intravenous corticoids - Intravenous H2 antihistaminics - Proton Pump Inhibitors - Antispasmodic - Antipsychotics **Concomitant Medications Authorised for all patients:** - Analgesics - Antiemetic - Gastroprokinetic - Chemotherapy (if already present at study entry) - Venting Gastrostomy **Non Authorised treatments:** Somatostatin or any of its analogues other than the study drug. LAN ATG 120 mg will be administered by deep subcutaneous route, at the maximal scheduled standard dose of 120 mg/28 days, just for 1 administration.
Study Endpoints & Evaluations:	**Primary Efficacy Endpoint and Evaluation:** Comparison between the mean AUC of ESAS Total Scores collected for the first 7 days in patients with Standard care + 1 injection of LAN ATG 120 mg (Group A) and the corresponding mean AUC in patients with standard care alone (Group B). ESAS total score is the sum of nine common symptoms affecting patients with cancer in their terminal phase of life. It consists of nine 0–10 numerical scales: pain, activity, nausea, depression, anxiety, drowsiness, appetite, sense of well-being and shortness of breath. There is an optional tenth scale based on a symptom, which can be added by the patient. Analysis of the primary endpoint will be performed on the first defined 9 items total score. ESAS questionnaire will be assessed by the patient or filled in by the nurse/caregiver in case of patient's physical inability. **Secondary Efficacy Endpoints and Evaluations:** 1) Comparison of single ESAS items symptom score and total score at Day 1,2,3,4,5,6 and 7, Day 14, Day 28, between Group A and Group B;

	2) Changes in performing General activity (Karnofsky performance status) at Day 7, Day 14 and Day 28 compared to baseline and comparison between Group A and Group B; 3) Changes in daily intensity of Abdominal Pain (Visual analogue scale) and comparison between Group A and Group B; 4) Comparison of number of patients experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D7,14,28, between Group A and Group B, in patients without nasogastric tube (NGT); 5) Comparison of number of patients in whom the NGT has been removed during at least 3 consecutive days at any time point, between the D1 and D7, 14, 28, without vomiting recurrence, between Group A and Group B; 6) In patients with a NGT, changes in daily NGT secretion volume and comparison between Group A and Group B; 7) Comparison of number of daily vomiting episodes and number of days without vomiting, between Group A and Group B; 8) Passage of stools (Yes/No) daily assessment and comparison between Group A and Group B; 9) Descriptive analysis of optional ESAS item 10; 10) Standard care and concomitant medications will be recorded and analysed. In particular changes in analgesic intake. **Safety Endpoints and Evaluations:** Safety will be assessed through the collection of adverse events (AEs) and vital signs and fully described/presented in frequency tables.
Statistical Methods:	**Determination of Sample Size** Since the quality of life is a multidimensional parameter, the AUC of ESAS total scores measured daily and reported on the patient's diary, during the first 7 days, is the primary variable which is calculated on, the sample size. ESAS total score is related to the status of the patient's illness: a low score indicates a good quality of life, a high score indicates a strong discomfort. In the group of patients who have added the injection LAN ATG 120 mg to standard care (Group A), the expected outcome is a lower value of the mean AUC compared to the one detected in the group of patients who were treated with only the standard therapy. In order to determine the sample size, we consider, for each patient, the AUC corrected with the basal ESAS total score by analysis of covariance (ANCOVA). In fact we assume that the AUCs are related to basal values. In this analysis the independent variable (covariate)

	will be the baseline values and the dependent variables will be the AUC of ESAS total scores collected for 7 days. In order to achieve a relevant clinical effect, we can assume an effect size of 0.60 (0.20 indicates a small effect size; 0.50 a medium effect and 0.80 a large effect size). Chosen $\alpha = 0.05$ and $\beta = 0{:}20$ (80% power), a total of 70 evaluable patients are needed: 35 patients in each treatment group. Finally, as literature data show that in this patient population there is drop-out rate of about 20%, the total number of patients to be recruited in the study must be at least 84. **Demographic and other Baseline Characteristics** Descriptive statistics will be used to summarize demographic characteristics, medical history and physical examination abnormalities of all patients included in the study. Concomitant medications will be reported as summary tables. **Analysis of Efficacy** As reported above, the main outcome variable (7 days AUC) will be analysed by the analysis of covariance (ANCOVA), where the AUC is the dependent, and the independent is the basal total score. This variable will be also analysed by the repeated measures analysis of variance with one group to highlight statistically significant differences between and within groups. All recorded variables will be presented in tables using standard procedures depending on the underlying distribution. Descriptive statistics on ordinal and categorical variables will be made reporting numbers and percentages, whereas for continuous variables mean, standard deviation (and standard error) together with range will be showed. To highlight statistically significant differences between and within groups, continuous and normally distributed variables will be analysed by the analysis of variance, with repeated measures (time) and one group (treatment). Discrete or non-normally distributed variables will be analysed by non-parametric tests (Mann-Whitney U test and Wilcoxon test). Nominal and categorical variables will be analysed by the χ^2 test with the Yates correction for 2x2 contingency tables.

	Analysis of Safety Adverse events (AEs), including Treatment Emergent Adverse Events (TEAEs), and vital signs will be fully described and presented in frequency tables. **Statistical Software** Statistical tables and analyses will be conducted using SAS® Version 9.2 statistical software package.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event/Experience
AIFA	Agenzia Italiana del Farmaco
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area Under Curve
BMI	Body Mass Index
CA	Competent Authorities
CRO	Clinical Research Organization
CSR	Clinical Study Report
CT	Computerized Tomography
DUS	Disease under study
e-CRF	Electronic Case Report Form
ESAS	Edmonton Symptom Assessment System
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	Growth Hormone
GI	Gastrointestinal
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor
IMP	Investigational Medicinal Product synonymous with “study drug”
ITT	Intention to Treat
LAN ATG 120 mg	Lanreotide Autogel 120 mg
MBO	Malignant Bowel Obstruction
MeDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NET	Neuroendocrine Tumours
NGT	Nasogastric tube
NOS	Not Otherwise Specified
PI	Package Insert

PP	Per Protocol
PK	Pharmacokinetics
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event/Experience
SAS®	Statistical Analysis System®
SC	Standard Care
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SSA	Somatostatin Analogue
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
WHO	World Health Organization

2 INTRODUCTION

2.1 Disease Review

Bowel obstruction is a common complication in patients with end-stage cancer, particularly in those with an abdominal or pelvic primary cancers. The reported frequency of bowel obstruction ranges from 5% to 42 % in advanced ovarian cancer and from 4% to 24% in 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 (1,2,3).

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. 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) (4,5,6,7).

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 (8,9).

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 (4).

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 (10,11).

Lanreotide is a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin. The compound is characterised by the presence of D-Tryptophan in the amino acid ring, increasing stability, and by the presence of D-beta Nal outside of this ring, which increases its selectivity. The terminal amine function reduces binding to central nervous system receptors. Lanreotide exhibits high affinity for the somatostatin Type 2 (SSTR2) and Type 5 (SSTR5) receptors found in the pituitary gland, GH-secreting pituitary tumours, neuroendocrine tumours, and the digestive tract. The product has a much lower affinity for somatostatin Type 1, 3 and 4 receptors (13).

Lanreotide has obtained a marketing authorisation in the treatment of acromegaly and neuroendocrine tumours.

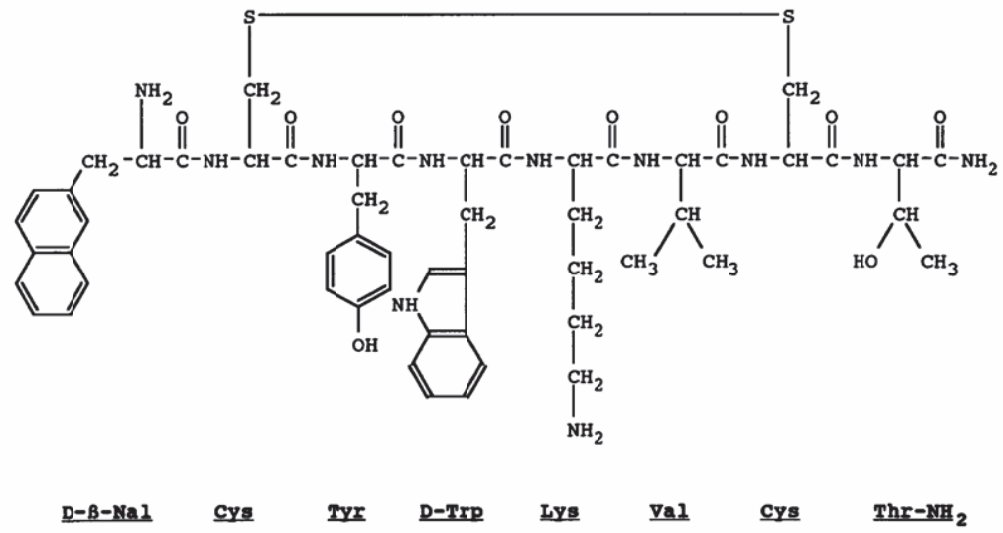
Previous studies have shown that vomiting and pain due to bowel obstruction can be controlled by somatostatin analogues administered daily by subcutaneous injections in patients unresponsive to conventional therapy (4, 5, 6, 12).

A prolonged release of somatostatin analogue would be more convenient for clinical use than discontinued injections. Therefore in this study, the efficacy of lanreotide 120 mg in the

management of symptoms secondary to inoperable intestinal obstruction in terminal cancer patients will be studied.

2.2 Compound 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 action than 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 Investigator's Brochure (IB) represents a summary of the available data. This IB 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 (13).

2.3 Clinical Trial Rationale

Malignant bowel obstruction (MBO) is a challenging complication of advanced cancer and requires a highly individual approach, tailored to the patients. Several pathophysiological mechanisms are responsible for the syndrome, including mechanical compression, motility disorders, accumulation of gastrointestinal secretion and inflammation (1). Its symptoms are challenging to manage since nausea, vomiting, colic and abdominal pain, which are common, cause significant physical distress and demoralization (2).
The medical therapy can palliate symptoms of MBO for most patients. In particular the combination of antisecretive, antiemetic and analgesic drugs has been proved to be effective in controlling gastrointestinal symptoms.
The somatostatin analogs (SSAs) are among the antisecretory drugs recommended in inoperable MBO patients. SSAs inhibit the release of various gastrointestinal secretions, slowing intestinal motility, decreasing splanchnic blood flow and increasing water and electrolyte absorption (3).
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 (4,5,6,12) 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 (14).

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.

Evidence-based evaluation of treatments for the symptomatic management of MBO continues to be an important area of research .The aim of this study is to add data to the body of evidence that establishes a key role for SSAs as a real treatment option for patients with MBO (15, 16).

Palliative cancer patients experience a complex configuration of many physical and emotional symptoms associated with advancing disease. In order to address these complex symptoms experiences, Bruera and colleagues (17) developed The Edmonton Symptom Assessment System (ESAS), a brief and clinically useful bedside tool for self-reporting symptom intensity

by advanced cancer patients. The ESAS was designed to enable repeated quantitative measurement of symptom intensity with minimal patient burden. (18).
ESAS is designed to assist in the assessment of nine symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath. There is an optional tenth symptom, which can be added by the patient. The severity of each symptom is rated from 0 to 10 on visual numeric scale.
Since its inception in 1991, the ESAS has been adopted and widely used internationally for clinical and research purposes. The Italian version of ESAS has been validate in two different palliative care settings of patient with advanced cancer: home care patients and in-patients (19).

3 STUDY OBJECTIVES

3.1 Primary Study Objective

To evaluate the impact on Quality of Life (Edmonton Symptom Assessment System, ESAS total score) of LAN ATG 120 mg in combination with standard care, in comparison to the standard care alone, in subjects affected by inoperable malignant bowel obstruction.

3.2 Secondary Study Objectives

1) To evaluate the impact of LAN ATG 120 mg on each ESAS item and total score;
2) To assess General activity (Karnofsky performance status) and Abdominal Pain (Visual analogue scale);
3) To assess the efficacy of LAN ATG 120 mg for the relief of vomiting in patients without nasogastric tube (NGT);
4) To assess the efficacy of LAN ATG 120 mg on NGT secretion volumes or to remove NGT without recurrence of vomiting in patients with a nasogastric tube;
5) Passage of stools (Yes/No);
6) Descriptive analysis of optional ESAS item 10;
7) To assess the efficacy in reducing concomitant medications/ analgesics intake;
8) To assess the safety of the study treatment.

4 STUDY DESIGN

4.1 Overview

4.1.1 Population Characteristics

It is planned to include 84 patients in this study. Male or female patients of 18 years of age or older, diagnosed with bowel obstruction due to malignant origin, confirmed by appropriate imaging report, who are unsuitable candidates for surgery.

4.1.2 Design

This is a phase II, multicentre, prospective, randomized, parallel arms, open-label study to be conducted in Italian sites.

4.1.3 Structure

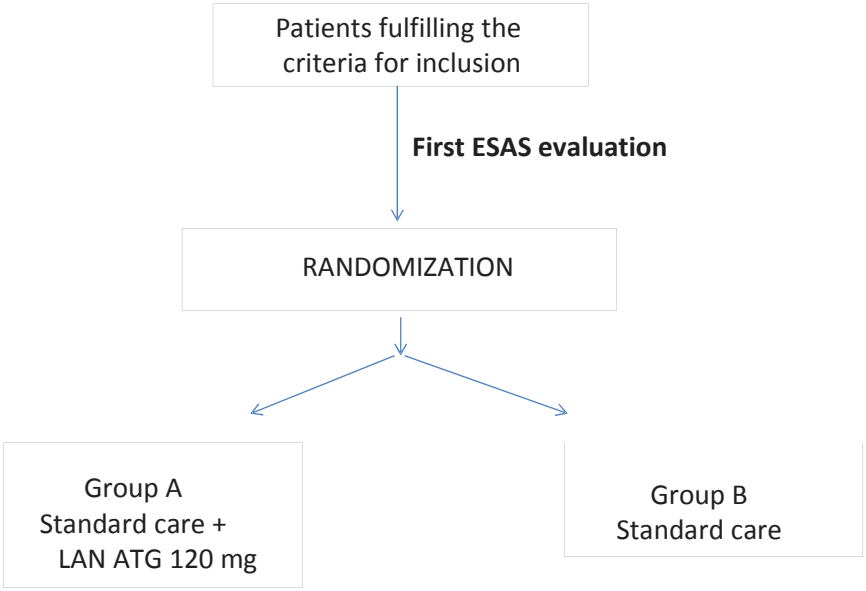


Figure 2 Study flow

Patients meeting the selection criteria for participation will need to provide a written informed consent before any study related procedure.
Patient will be asked to complete the **first** Edmonton Symptom Assessment System (ESAS) before randomization. Patients will then be randomized in two groups:

- Group A will receive standard care + 1 injection of LAN ATG 120 mg.
- Group B will receive standard care alone.

The efficacy and safety will be evaluated until 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 treatment.

4.2 Endpoints

4.2.1 Primary Efficacy Endpoint

Comparison between the mean AUC of ESAS Total Scores collected daily for the first 7 days in patients with standard care + 1 injection of LAN ATG 120 mg (Group A) and the corresponding mean AUC in patients with standard care alone (Group B).

ESAS total score is the sum of nine common symptoms affecting patients with cancer in their terminal phase of life. It consists of nine 0–10 numerical scales: pain, activity, nausea, depression, anxiety, drowsiness, appetite, sense of well-being and shortness of breath. There is an optional tenth scale based on a symptom, which can be added by the patient. Analysis of the primary endpoint will be performed on the first defined 9 items total score.

ESAS questionnaire will be assessed by the patient or filled in by the nurse/caregiver in case of patient's physical inability.

4.2.2 Secondary Efficacy Endpoints

1) Comparison of single ESAS items symptom score and total score at Day 1,2,3,4,5,6 and 7, Day 14, Day 28, between Group A and Group B.
2) Changes in intensity at Day 7, Day 14 and Day 28 compared to baseline in General activity (Karnofsky performance status) and comparison between Group A and Group B.
3) Changes in daily intensity of Abdominal Pain (Visual analogue scale) and comparison between Group A and Group B.
4) Comparison of number of patients experiencing $\leq$ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D1 and D7,14,28, between Group A and Group B, in patients without nasogastric tube (NGT).
5) Comparison of number of patients in whom the NGT has been removed during at least 3 consecutive days at any time point, between the D1 and D7, 14, 28, without vomiting recurrence, between Group A and Group B.
6) In patients with a NGT, changes in daily NGT secretion volume and comparison between Group A and Group B.
7) Comparison of number of daily vomiting episodes and number of days without vomiting, between Group A and Group B.
8) Passage of stools (Yes/No) daily assessment and comparison between Group A and Group B.
9) Descriptive analysis of optional ESAS item 10.
10) Standard care and concomitant medications will be recorded and analysed. In particular changes in analgesic score intake.

4.2.3 Safety Endpoints

Safety will be assessed through the collection of adverse events (AEs) and vital signs and fully described and presented in frequency tables.

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 every day in the last consecutive 48 hours or who have a nasogastric tube and candidate to receive symptoms supportive (standard) care, are eligible to be included in this study.

This study aims to recruit a total of 84 patients, 42 per group – male or female of 18 years or older who fulfil the eligibility criteria (see Section 6.2 – 6.3).

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 2 years.

The study will be considered to have started at first patient Informed Consent signature. The study will be considered to have finished when last patient last visit will be performed.

Study enrolment will last about 18 months. The subjects participation in the study is considered to have ended at 28th day after randomization.

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) (21) and Good Clinical Practice (GCP) Guidelines, Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures (22) and FDA Guidance for Industry: Computerized Systems Used in Clinical Trials (23). In addition, this study will adhere to all local regulatory requirements.

Before initiating a trial, the Investigator/institution should have written and dated approval/favourable opinion from the IEC for the trial protocol/amendment(s), written informed consent form, any consent form updates, 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 (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 84 subjects at approximately 12 sites.

The enrolment is competitive. Section 11.3 provides a discussion of sample size.

6.2 Inclusion criteria

All subjects must fulfil the following:

a) Subjects must demonstrate willingness to participate in the study and to be compliant with any protocol procedure.
b) Provision of written informed consent prior to any study related procedure.
c) Male or female aged ≥ 18 years at the time of enrolment.
d) Diagnosis of an inoperable malignant bowel obstruction, confirmed by appropriate imaging report.
e) In case of peritoneal carcinomatosis, diagnostic confirmation by CT or MRI scan.
f) Confirmed as inoperable after medical advice.
g) Patient with a nasogastric tube or presenting with 3 or more episodes of vomiting every day in the last consecutive 48 hours.
h) Patient life expectancy must be more than 14 days.

6.3 Exclusion Criteria

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

(a) Has operable obstruction or any sub-obstruction.

(b) Has bowel obstruction due to a non-malignant cause; (hypokaliaemia, drug side-effects, renal insufficiency, etc).

(c) Has signs of bowel perforation.

(d) Has prior treatment with somatostatin or any analogue within the previous 60 days.

(e) Has a known hypersensitivity to any of the study treatments or related compounds.

(f) Is likely to require treatment during the study with somatostatin or any analogue other than the study treatment.

(g) Is at risk of pregnancy or lactation, or is likely to father a child during the study. Females of childbearing potential must provide a negative pregnancy test at start of study and must be using oral or double barrier contraception. Non childbearing potential is defined as post-menopause for at least 1 year, surgical sterilisation or hysterectomy at least three months before the start of the study.

(h) Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

(i) 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 or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.

6.4 Subject Withdrawal Criteria

Under no circumstances will subjects be enrolled more than once. As this is a single treatment study, subjects cannot be withdrawn from study treatment after the administration of IMP. However, subjects can be discontinued from study participation for the following reasons:

- Withdrawal of informed consent.
- Investigator's and/or Sponsor's decision to withdraw the subject if it is considered to be in the subject's best interest.
- Continuous failure to comply with the provisions of the study protocol which is likely to have an adverse impact on the safety or wellbeing of the subject, or could jeopardise the scientific value of the study.
- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.

Every effort should be made to follow up all subjects within the framework of the study, especially with regard to safety assessments. See Section 10.7 for further details.

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 patient's medical file and in the electronic case report form (eCRF).

In case of discontinuation, the patient will be asked to attend a final visit, performing all assessments required by the End of Study visit.

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

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

Table 1 Schedule of Assessments

Visit	V1 Baseline	V2	V3	V4 EoS/ Early withdrawal
Day	**1**	**7**	**14 ± 2 days**	**28 ± 2 days**
Informed Consent	X			
Demographic data	X			
Medical history	X			
Physical examination	X	X	X	X
Vital signs	X	X	X	X
Body weight	X			
Pregnancy test (If applicable)	X			
Eligibility Criteria evaluation	X			
Patient's Diary (Delivery and review)	X	X	X	X
Concomitant medications/ SC/nutrition	X	X	X	X
Karnofsky performance status	X	X	X	X
ESAS questionnaire	X (*)	X	X	X
Abdominal pain assessment (VAS)	X (*)	X	X	X
Vomiting episodes assessment	X	X	X	X
NGT presence secretion volume or NGT removal recording	X	X	X	X
Passage of stools recording	X	X	X	X
Safety assessment and recording (AE & SAE)	X	X	X	X
IF ALL INCLUSION & ESCLUSION CRITERIA ARE MET:				
Randomisation	X			
Injection of LAN 120 mg (if randomized in Group A)	X			

7.2 Study Visits

Allowed time deviation for the visits :

Visit 1/Baseline (Day1) : Not applicable

Visit 2 (Day 7): No deviations allowed

Visit 3 (Day 14) : ± 2 days

Visit 4/End of Study- Withdrawal visit (Day 28) : ± 2 days

Written informed consent must be obtained prior to any study procedure implementation, even before the Visit 1.

(*): Prior to randomization, the Investigator must administer the first ESAS questionnaire and VAS to the patient. They have been arranged in a separated/specific form (Patient Diary pre-treatment), which must then be filed in the clinical records as source document.

Investigators and patients should do their best to comply with study visits schedule to be performed at the site. If the patient is resigned from the Hospital after Visit 2 (Day 7) and he/she is physically unable (e.g. bedridden) to reach the site for the next control visits, these will be replaced by a phone call: the investigator or study staff have to collect as many information as possible, according to the scheduled visit.
In any case, the patient diary and ESAS questionnaires, fully completed, must be delivered to the investigator or study staff the day of the scheduled visit for the appropriate revision.

7.2.1 Visit 1 (Baseline)

- Demographics data (sex, age, ethnic origin)
- Medical history, including obstruction history
- Physical examination
- Vital signs
- Body weight
- Karnofsky Performance Status
- Pregnancy test (if applicable)
- Concomitant medications/SC therapy/Nutrition procedures
- Vomiting episodes assessment (episodes in the last 48 hours)
- NGT presence and related secretion volume
- **Eligibility criteria evaluation**
- Quality of life assessment, using the ESAS questionnaire (*)
- Abdominal pain assessed using the VAS (*)
- Passage of stools (Yes or No)
- Patient's Diary delivery and explanations
- AE's and SAE's will be collected after signature of the informed consent and again after clinical examination and medical history evaluation
- **Randomisation** (see section 9.3)
- **Treatment administration** (LAN ATG 120mg and/or SC therapy)

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

- Vital signs
- Physical examination
- Karnofsky Performance Status

- Changes in concomitant medications/ SC therapy/Nutrition procedures
- Quality of life assessment using the ESAS questionnaire
- Patient's Diary data review:
  - Abdominal pain
  - N. of Vomiting episodes
  - NGT presence and secretion volume
  - Passage of stools (Yes or No)
- Collection of AEs and SAEs

7.2.3 Visit 4 - End of study/Withdrawal visit (Day 28)

The following procedures will be performed for each subject who has completed the study at Day 28 or is an Early Withdrawal.

- Vital signs
- Physical examination
- Karnofsky Performance Status
  Changes in concomitant medications/ SC therapy/Nutrition procedures
- Quality of life assessment using the ESAS questionnaire
- Patient's Diary data review
  - Abdominal pain
  - N. of Vomiting episodes
  - NGT presence and secretion volume
  - Passage of stools (Yes or No)
- Collection of AEs and SAEs
- Reason for end of study/early withdrawal

8 STUDY EVALUATIONS

8.1 Demographic data

The subject's demographic profile will include sex, age and ethnic origin. The data has to be collected at the Baseline Visit and recorded on the patient's medical file.

8.2 Medical History

The medical history, including on-going medical history and obstruction history, will be recorded on the patient's medical file. They will be collected at the Baseline Visit.

8.3 Physical Examination

The physical examination will include inspection of the following areas: general appearance, head, eyes, ears, nose, throat, neck, lymph nodes, skin, lungs, heart, abdomen, extremities/musculoskeletal evaluation, and neurological evaluation. It will be carried out by a physician and has to be recorded on the patient's medical file, at each patient's visit on site. If in the opinion of the Investigator there are any clinically significant changes in the physical examination (abnormalities), they will be recorded as AEs.

8.4 Vital Signs and body weight

Blood pressure and heart rate will be recorded on the patient's medical file, at each patient's visit on site.

Body weight only at baseline visit.

8.5 Pregnancy Test

A pregnancy test will be performed for all female subjects of child bearing potential. The test will be performed on site before randomization procedure.

8.6 Karnofsky performance status

The Karnofsky Performance Status (24) allows patients to be classified as to their functional impairment. The lower the Karnofsky Performance Status, the worse the survival for most serious illnesses.

The first Karnofsky Performance Status has to be assessed **prior the patient randomization** (Day 1). The Karnofsky Performance Status will be then assessed also at Visit 2 (Day 7), Visit 3 (Day 14) and Visit 4 (Day 28). The total score will be recorded on the patient's medical file, at each patient's visit.

8.7 Edmonton Symptom Assessment System *(*ESAS)

The ESAS (17-19) will be assessed by the patient or filled in by the nurse/caregiver in case of patient's physical inability (see the Appendix n. 1). The data recording/symptoms evaluation should be referred to the last 24 hours (20).

The first ESAS has to be completed sooner after the written informed consent has been obtained and **prior the patient randomization** (Day 1). For the filling of this questionnaire at baseline (Day 1), a **separated/specific baseline form** "Pre-treatment ESAS & VAS evaluations" has been arranged and must then be filed in the clinical records as source document.

The ESAS will be then performed also at day 2,3,4,5,6,7, 14 and 28 and recorded in a dedicated "Post-treatment ESAS Questionnaire".

All ESAS copies needed during the study period will be arranged in book and each ESAS will be in double copy: one will be kept in the patient's medical file as source document at the site; the second one will be sent to the CRO, delegated for the data management.

8.8 Abdominal Pain assessment, vomiting episodes, NGT and Passage of stools

The abdominal pain, the vomiting episodes, the NGT secretion volume or NGT removal and passage of stools assessments have to be evaluated and recorded on Patient Diary daily (possibly at the same time of day) until the end of study (Day 28), by the patient or filled in by the nurse/caregiver in case of patient's physical inability.

The first assessment of the above parameters has to occur **prior the patient randomization** (Day 1).

In particular, the abdominal pain will be evaluated through a visual analogue scale (VAS) (26). For the filling of VAS at baseline (Day 1), a **separated/specific**

baseline form "Pre-treatment ESAS & VAS evaluations" has been arranged and must then be filed in the clinical records as source document.

8.9 Concomitant medications/therapies including standard care therapy

All concomitant medications, including the standard care therapy and nutrition procedures, have to be recorded on the patient's medical file at the Baseline Visit and all changes at all patient's visit on site. If the patient will be followed at home, all concomitant medications and therapies used as needed, will have to be recorded on the patient diary (See Section 9.6).

8.10 Safety assessment/Adverse Events

AEs will be monitored from the time that the subject gives informed consent to the end of the study (see 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 10. Safety of the patients will be followed continuously during the entire study period**. If the patient will be followed up at home, all adverse events must be recorded in the patient diary.**

8.11 Clinical Laboratory Tests

All clinical laboratory tests are not mandatory; they are at the discretion of the investigator.

Clinical chemistry, haematological and urinalysis tests will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

8.12 Patient diary

A patient diary will be arranged and all pages will be in double copy: one will be kept in the patient's medical file as source document at the site; the second one will be sent to the CRO, delegated for the data management.

The patient diary will be divided in two parts:

- Patient diary pre-treatment: it will be delivered to the patients at the baseline visit with the related user instructions, prior the randomization. It has to be filled in by the patient **or by the nurse/caregiver in case of patient's physical inability** for recording the following data:

- Baseline Abdominal Pain
- Baseline ESAS questionnaire

- Patient diary post-treatment: it will be delivered to the patients at the baseline visit with the related user instructions, after the randomization. It has to be filled in daily, since the second day after the drug administration, by the patient **or by the nurse/caregiver in case of patient's physical inability,** for recording the following data:

- Abdominal Pain
- Vomiting episodes
- NGT secretion volume or NGT removal
- Passage of stools
- Concomitant Medications and Therapies used at Home, as needed
- AE occurred at Home

The Investigator or qualified designee has to review the patient diary at each patient visit on site, checking the completeness and accuracy of the reported data.

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, according to a centralised randomisation list, will be given standard care therapy in combination with Lanreotide Autogel 120 mg (group A) or standard care therapy (group B).

Lanreotide Autogel 120 mg administration, deep sub-cutaneous injection in the upper outer quadrant of the buttock, Administration of the Lanreotide Autogel 120 mg will occur in conjunction with or on the same day of standard care therapy administration. The administrations will be supervised by the Investigator, or designee.

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.

9.3 Randomisation

Following confirmation of eligibility for the study, subjects will be given a randomisation/treatment allocation number and allocated to one of the treatment groups specified in Section 9.1.

The Sponsor's Randomisation Manager, a statistician independent from the study, will prepare and keep the master randomisation list. It will be produced in blocks by using an internal validated randomisation software and will be generated with a balance ratio [1 'Standard care + LAN ATG 120 mg' versus 1 'Standard care alone'].

Patients meeting the randomisation criteria will be allocated to a randomisation number through the eCRF (WEB server) in the order in which they enter the randomised study period. Authorized Users at sites will open the eCRF, fill in all the mandatory items and then if the requirements are satisfied he can press the randomization button. The eCRF automatically send via Internet a request to the WEB server (using secure, encrypted protocols). The WEB server assigns patients to one of two treatment groups based on a pre-defined randomisation list. The Investigator can read the assigned treatment directly in the eCRF (additional details may be found in the study eCRF manual provided to each site).

Recruitment will stop once 84 evaluable patients have been randomised. Patients who leave the study early will not be replaced. Randomised patients who terminate their study participation for any reason before starting the treatment period will retain their randomisation number, i.e. the randomisation number will not be reused. The next patient will be given the next randomisation number.

No centre will randomise more than approximately 20 patients. The subjects enrolled will be monitored using the remote study monitoring system.

The Sponsor's Randomisation Manager will keep the master list, and a copy of the randomisation list will be confidentially supplied to the CRO in charge of central randomisation allocation / eCRF. The master list and the copy supplied to the CRO in charge of central randomisation allocation / eCRF will be kept confidential in a secure location. Access to the randomisation lists must be restricted until authorisation is given for its release.

9.4 Study Treatment Supply, Packaging and Labelling

The IMP will be packaged by Supply Chain CMC&E (Beaufour IPSEN Industrie, 20 rue Ethe Virton, 28100 Dreux, France) 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 and Compliance for which batch of IMP has been used under their study, Material Data Safety Sheet for LAN ATG 120 mg, 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 (25), national laws in force and in accordance with the local languages. A description of the core text of the IMP labels is displayed below:

- Name, address and telephone number of the Sponsor
- Name of the product with strength and potency
- Study Number
- Pharmaceutical dosage form
- Route of administration
- Quantity of dose units
- Batch number
- Treatment number
- Randomisation number with specific blank space to enter the subject ID
- The statement 'For clinical trial use only'
- The statement 'Keep out of reach of children'
- 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 patients' medical file and in the eCRF.

9.5 Compliance

If a patient after signing the IC and undergoing all entry study evaluations refuses to have IMP administered, this must be regarded as a major protocol violation and patient is automatically withdrawn.

9.6 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 (2°C – 8°C), 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. Any deviation/problems in either storage or shipping conditions must be notified to the Sponsor via IMP Incident Form.

9.7 Reporting of Investigational Medicinal Product Quality Complaints

Any defect or possible defect in the IMP (defined as a pharmaceutical form of an active substance being tested) must be reported by the Investigator or qualified designee to the Sponsor (study clinical monitor, designated complain officer or safety officer) via the Complaint Form who should report the details of the incident. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol (see Section 10.4), and the SAE report should mention the product quality complaint.

9.8 Concomitant Medication/SC therapy/Nutrition Procedures

This protocol foresees a standard care defined by each hospital according to its best supportive standard SC and generally defined below.

- General definition of Standard care :
  - Oral food or oral liquid intake according to clinical judgement;
  - Intravenous corticoids
  - Intravenous H2 antihistaminics
  - Proton Pump Inhibitors
  - Antispasmodic

- Antipsychotics

➢ Concomitant Medication Authorised for all patients on request:

- Analgesics
- Antiemetic
- Gastroprokinetic
- Chemotherapy (if already present at study entry)
- Venting Gastrostomy

9.9 Non authorized treatments

Somatostatin or any of its analogues, other than the study treatment are not permitted during the study.

9.10 Treatment of Overdose of IMP

As this is a single dose administration, overdose of IMP is unexpected. In any case the pre-clinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

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 eCRF. 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 ASSESSMENT OF SAFETY

10.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study duration and will be elicited by direct, non-leading questioning or by spontaneous reports.

10.1.1 Definition of an Adverse Event

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 IMP has been administered.

This definition includes events occurring from the time of the subject giving written informed consent until the end of the study (as defined in Section 4.3.2).

Natural progression or deterioration of the disease or related signs and symptoms, which are part of the efficacy evaluation, should not be recorded as an AE/SAE.

Otherwise, signs and symptoms of the disease should be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or accelerated disease/symptoms or
- if the investigator considers the deterioration of disease/symptoms signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to the disease/symptoms under study, it should be reported as an AE/SAE as appropriate.

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

AEs will be classified according to The Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (26) or higher, as:

Grade 1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 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 eCRF. 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 eCRF. 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 a 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/eCRF and the Standard Pregnancy Outcome Report Form, including pregnancies with normal progress and outcome. . A Standard Pregnancy Outcome Report Form must be completed by the Investigator and provided to the Sponsor Pharmacovigilance Contact within 24 hours of the knowledge of the pregnancy in any study subject.

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 Death

All AEs resulting in death either during the study period or within 28 days after the IMP administration, 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, grade 5 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 will be recorded on the eCRF page.

The investigator must ensure the subject receives appropriate medical follow up (see Section 6.5).

10.8 Reporting to Competent Authorities/IECs/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 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).
- **Screened failure subject:** Enrolled subject who fails to fulfil one or more entry criteria and thus does not proceed to the treatment phase of the study. Although not exposed to study medication, they may have been exposed to some study related procedures. Records up to the time of premature termination should be completed including the reason for termination.
- **Treated subject/ Treatment Completed subject:** Enrolled subject who received the IMP (one single dose).
- **Randomised subject:** Enrolled subject who is allocated to a treatment group at random.

- **Study Completed subject:** Randomised subject who has completed all specified assessments of the study.
- **Drop-out:** Randomised subject who did not complete the study.

11.2 Analyses Populations Definitions

- **Screened population**: All subjects who signed the informed consent.
- **Randomised population:** All subjects randomly assigned to one of the treatment required by the protocol.
- **Safety population:** All subjects who received the dose of study medication.
- **Intention-to-treat (ITT) population:** All randomised subjects.
- **Per protocol (PP) population:** All subjects in the ITT population for whom no major protocol violations/deviations occurred and have carefully filled in the patient diary and ESAS questionnaire for the first seven days of study.

11.2.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint will be performed on the ITT subjects having the ESAS questionnaire duly filled in at baseline (before the randomization) and at least five out of six duly filled in ESAS questionnaires related to the first 6 days post baseline visit. 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 estimation was based on the mean AUC of ESAS total score collected for 7 days after basal visit. Based on following assumptions:

- expected standardised difference (effect size) between mean AUC of group A and group B equal to 0.60.
- expected common standard deviation of the primary efficacy variable is equal to 1.
- type I error 0.05, two sided test, 80% power.

the number of subjects to be randomized/treated per group is 35. By taking into consideration an invalidity rate of 20% for multiple centre design/premature withdrawals and other invalidity reasons, a total of 42 per group will be needed.

Since the quality of life is a multidimensional parameter, the AUC of ESAS total scores measured daily and reported on the patient's diary, during the first 7 days, is the primary variable which is calculated on, the sample size.

ESAS total score is related to the status of the patient's illness: a low score indicates a good quality of life, a high score indicates a strong discomfort.

In the group of patients who have added the injection LAN ATG 120 mg to standard care (Group A), the expected outcome is a lower value of the mean AUC compared to the one detected in the group of patients who were treated with only the standard therapy.

In order to determine the sample size, we consider, for each patient, the AUC corrected with the basal ESAS total score by analysis of covariance (ANCOVA). In fact we assume that the AUCs are related to basal values. In this analysis the independent variable (covariate) will be the baseline values and the dependent variables will be the AUC of ESAS total scores collected for 7 days.

Without preliminary data of the distribution of AUCs in the study population, we must assume the data have a normal distribution. Thus, in order to achieve a relevant clinical effect, we can assume an effect size of 0.60 (0.20 indicates a small effect size; 0.50 a medium effect and 0.80 a large effect size).

We state

$$d = \frac{|\mu_A - \mu_B|}{\sigma'} = 0.60$$

Where

- d is the effect size index and σ' the standard deviation of the dependent corrected by the basal values (covariates);

- μ_A is the mean AUC recorded for 7 days, adjusted for the respective baseline, in the group receiving standard care + Lanreotide injection;
- μ_B is the AUC recorded for 7 days adjusted mean, in the group treated with standard care alone;
- σ' is defined as: $\sigma' = \sigma \sqrt{(1 - r^2)}$
  Where, σ is the standard deviation of the dependent variable, and r (r=0.50) is the correlation coefficient between basal total scores and AUC values. We set r =0.50 because we suppose a correlation between the basal score and AUC.

The null hypothesis can therefore be as follow:

H_0: $| \mu_A - \mu_B | \leq 0.60$
While the alternative hypothesis:

H_A: $| \mu_A - \mu_B | > 0.60$
So chosen $\alpha = 0.05$ and $\beta = 0{:}20$ (80% power), a total of 70 evaluable patients are needed: 35 patients in each treatment group.

Finally, as literature data show in this patient population there is a drop-out rate of about 20%, the total number of patients to be included in the study must be at least 84 patients, 42 per group.

11.3.1 Significance Testing and Estimations

All statistical tests will be performed two sided with a type I error rate set at 5% .

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.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.3 or higher).

11.4.1 Demographic and Other Baseline Characteristics

In order to ensure balance of treatment groups, descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease (pre-treatment AEs and on-going medical history, prior medications and therapies, baseline symptoms etc) will be presented by treatment group and overall for the ITT and PP/safety population(s).

11.4.1.1 Homogeneity of Treatment Groups

In order to assess the homogeneity of treatment groups at baseline, statistical significant testing may be carried out in selected parameters such as age, sex, body mass index, risk factors etc. Appropriate methods based on analysis of variance approach or on the Mantel –Haenszel chi-squared test will be used. Positive findings ($p<0.05$) will be discussed regarding their potential influence on the analyses of the primary efficacy endpoint(s).

11.4.1.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the ITT /PP and safety populations will be tabulated by centre. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were randomized, discontinued and completed at each visit. Primary reasons for discontinuation of study treatment will be tabulated.

11.4.1.3 Efficacy evaluation

The main outcome variable (7 days AUC) will be analysed by the analysis of covariance (ANCOVA), where the AUC is the dependent, and the independent is the basal total score. This variable will be also analysed by the repeated measures analysis of variance with one group to highlight statistically significant differences between and within groups

The secondary efficacy variables are Karnofsky performance status, abdominal pain (VAS) vomiting episodes (≤2) for 3 days, daily vomiting episodes, days without vomiting, removal of NGT for 3 days, NGT secretion volume, passage of stools, ESAS optional item 10 assessed daily and concomitant medications/analgesic intake. The analgesic score will be calculated given 1 to each intake of non-opioids analgesics and 2 to opioids analgesics.

The basal ESAS score will be used as covariates in the primary model.

If the parametric assumptions of the analysis are not satisfied, then a suitable transformation or a non-parametric procedure will be sought.

All recorded variables will be presented in tables using standard procedures depending on the underlying distribution. Descriptive statistics on ordinal and categorical variables will be made reporting numbers and percentages, whereas for continuous variables mean, standard deviation (and standard error) together with range will be showed.

To highlight statistically significant differences between and within groups, continuous and normally distributed variables will be analysed by the analysis of variance, with repeated measures (time) and one group (treatment). Discrete or non-normally distributed variables will be analysed by non-parametric tests (Mann-Whitney U test and Wilcoxon test). Nominal and categorical variables will be analyzed by the χ^2 test with the Yates correction for 2x2 contingency tables.

11.4.1.4 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.

Incidence of all reported AEs/treatment emergent AEs (TEAE) and SAEs will be tabulated by treatment group and by overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

it was not present prior to receiving the first dose of IMP, or

it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study, or

it was present prior to receiving the first dose of IMP, the intensity is the same but the drug relationship became related during the active phase of the study.

Treatment emergent AEs will be flagged (*) in the AEs listings.

Concomitant medications will be coded by using Prontuario Farmeceutico Italiano Farmadati (available at the URL www.prontuariofarmaceutico.it/), which includes the same ATC codes of those in WHO Drug Dictionary, but limited to the drug on the Italian market. They will be summarised by treatment group and by overall with the number and percentage of subjects receiving concomitant medication by <drug class and preferred drug name>.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and by overall will be presented for vital signs, blood pressure, heart rate, ECG parameters, clinical laboratory tests etc at each assessment with change from baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

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 regulatory requirements and local laws.

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 electronic Case Report Form (eCRF), 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 eCRFs within 5 days after the patient's visit and on an on-going 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 eCRFs, 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 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 patient's medical file/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 eCRFs provided for the study. The Investigator, by completing the signature log, may formally designate the qualified sub-investigators to complete eCRF. They have to be registered as eCRF operators into the system, though personal credentials.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each "visit status" eCRF page to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the Investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

The study foresees the Patient Diary (pre and post-treatment) and the ESAS questionnaire: they will be in paper and printed. Each page will be in double copy: the original will send to the CRO in charge of the statistical analysis and it will be responsible also for the data entry in the eCRF/database of the data collected from the patients and the copy will kept at the site as source document.

13.3 Source Data Verification

The FDA 21 CFR Part 11, is a regulation which provides criteria for acceptance by the FDA, under certain circumstances, of electronic records, e-signatures and hand-written signatures executed to electronic records as equivalent to paper records and hand-written signatures on paper.

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 eCRF.

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 eCRFs 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 eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13.5 Data Management

eCRF will be utilized for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only Sponsor authorized users will get access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO. 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, (see Section 12). eCRF and other data documentation removed from the Investigator site(s) will be tracked by the CRO and the monitor.

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The Investigator will receive their data, from the clinical trial, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference. Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the eCRF. It is the Sponsor's responsibility to ensure that all queries are resolved by the relevant parties. The Sponsor will also ensure that SAE data collected in the eCRF 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 Prontuario Farmeceutico Italiano Farmadati (available at the URL www.prontuariofarmaceutico.it/) and AEs/medical history terms will be coded using MedDRA (version 16.1 or higher).

13.6 Study Management Committees

No Committees foreseen for study management.

13.7 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 must be retained according to the applicable regulatory requirements and national laws. 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.

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.

Financial Disclosure Statements will need to be completed, as requested by FDA 21 CFR Part 54 and local regulation.

14.5 Insurance, Indemnity and Compensation

The Sponsor will provide Product Liability insurance for all subjects included in the clinical study.

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 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 and Italian central CA (AIFA). Prior to implementation, documented approval must be received from the IECs. In the case AIFA has raised no grounds for non-acceptance during an allocated time period, following acknowledgment of receipt of a valid application, the substantial amendment could be considered approved.
- ***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 and CA notification, forthwith.

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17 LIST OF APPENDICES