STATISTICAL ANALYSIS PLAN (SAP)

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)**

PHASE: **II**

PROTOCOL VERSION and DATE: **Final Version 1.0 - 13/05/2014**

DISEGN: **MULTICENTRE, PROSPECTIVE, RANDOMIZED, PARALLEL ARMS, OPEN-LABEL STUDY**

INVESTIGATIONAL MEDICINAL PRODUCT: **LANREOTIDE AUTOGEL 120 MG**

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

95% C.I.	95% Confidence Interval
AE	Adverse Event/Experience
ANCOVA	ANalysis of COVAriance
ANOVA	ANalysis Of VAriance
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area Under Curve
BMI	Body Mass Index
CA	Competent Authorities
CSR	Clinical Study Report
CT	Computerized Tomography
DUS	Disease Under Study
E	Electronic
ESAS	Edmonton Symptom Assessment System
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	Growth Hormon
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”
IRB	Institutional Review Board
ITT	Intention to Treat
LAN ATG 120 mg	Lanreotide Autogel 120 mg
MBO	Malignant Bowel Obstruction
MRI	Magnetic Resonance Imaging
NET	Neuroendocrine Tumors
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 Porcedures
SSA	Somatostatin Analog
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
WHO	World Health Organization

3 NOTE TO THIS SAP VERSION

The IMBO study SAP was prepared before the decision to prematurely stop the study. Therefore to facilitate the review, any changes, which need to be highlighted, will be presented as notes throughout the SAP.

4 INFORMATION TAKEN FROM THE PROTOCOL

4.1 Study objectives

4.1.1 Primary study objective

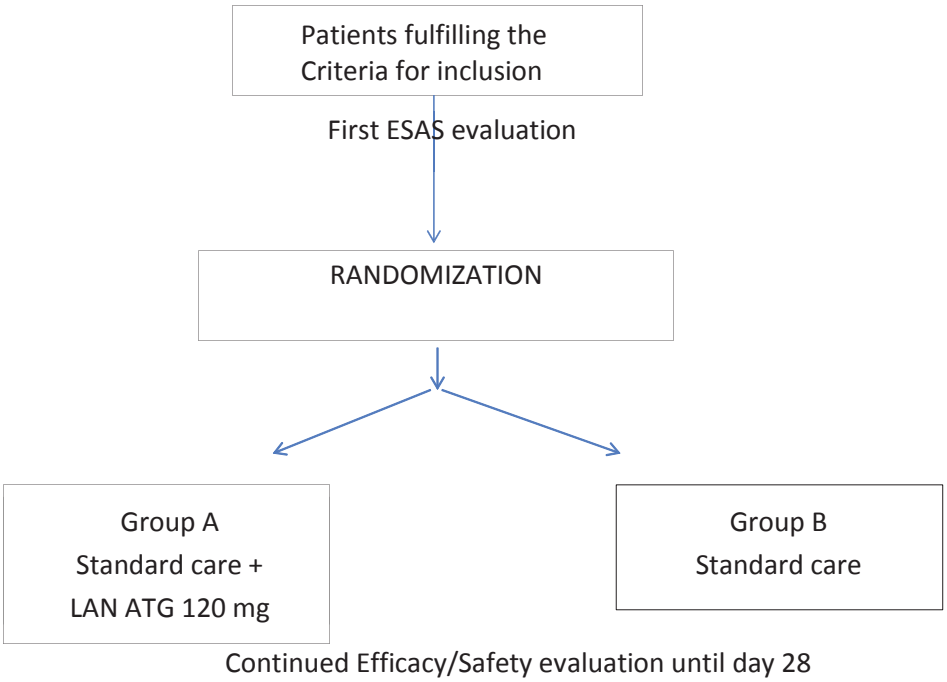
To evaluate the impact on Quality of Life (Edmonton Symptom Assessment System, ESAS total score) of LAN ATG 120 mg in combination with standard care, in comparison to the standard care alone, in subjects affected by inoperable malignant bowel obstruction

4.1.2 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.

4.2 Design

This is a phase II, multicentre, prospective, randomized, parallel arms, open-label study.



4.2.1 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.

Note: given the premature termination of the study, only 43 patients have been included in this study.

4.2.2 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.

Note: the enrollment lasted for 36 months to recruit 43 patients.

4.3 Methods and procedures

4.3.1 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. The enrolment is competitive.

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 4.2.

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.

Note: due to premature termination of the study, recruitment was stopped after 43 evaluable patients have been randomized.

4.3.2 Subjects evaluations

4.3.2.1 Efficacy assessments

Primary efficacy endpoint.

Comparison between the mean of Area Under the Curve (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.

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 ≤ 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.

4.3.2.2 Safety assessments

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

4.3.2.3 Other assessments

Demographic data

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

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.

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.

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.

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.

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.

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.

4.3.2.4 Withdrawal/discontinuation

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.

4.3.2.5 Schedule assessments

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			

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.

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
- AEs and SAEs 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)

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

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

4.3.3 Planned sample size

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.

Note: At the time of study termination, out of planned 84 patients, only 43 patients (51%) have been randomized, where 17 patients (40%) completed the study.

5 SUBJECT POPULATIONS (ANALYSIS SET)

5.1 Efficacy

5.1.1 Intention-To-Treat population (ITT)

The ITT population includes all randomised subjects.

5.1.2 Full Analysis Set (FAS)

In accordance with the Intention To Treat (ITT) principle, the FAS population includes all subjects randomized who received the study drug and who fulfilled the ESAS questionnaire at basal visit and at least at 5 post-treatment assessments during the first seven days of the study.

5.1.3 Per Protocol Population (PP)

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.

IBIS DM will provide the subjects disposition with the attributed analysis population to be reviewed by the study team.

5.2 Safety

The safety population includes all randomised subjects who have received at least one dose of study therapy. The safety population will be analysed using subjects as treated.

5.3 Pharmacokinetics

5.3.1 PK Intent-To-Treat Population

Not applicable.

5.3.2 PK Per Protocol Population

Not applicable.

5.4 Primary population

The primary analysis will be based on the FAS population.

The secondary analysis will be based on the ITT population.

The primary efficacy analysis will be also performed on the Per Protocol Population as confirmatory analysis. If statistical results are different between ITT and PP Population an analysis will be performed in order to give reason of this finding.

The assessment of safety and tolerability will be based on the Safety population.

Note: due to premature termination of the study only FAS, ITT and Safety populations will be considered.

6 STATISTICAL METHODS

6.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline and with the guideline on clinical evaluation of diagnostic agents and they will be based on data from the study sites, unless otherwise stated.

The statistical analysis of efficacy, safety and tolerability will be performed by IBIS Informatica s.r.l. – Milan - Italy

Note: due to premature termination of the study, inferential analysis will be applied only for the analysis of the primary efficacy endpoint. For all other endpoints the statistical analysis will be limited to descriptive summaries to explore any trends or patterns between the two treatment groups.

6.1.1 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.

The AUC is the area under the line which joins the points defined by plotting the ESAS total score on the vertical axis and the time values on the horizontal axis:

The AUC is computed by the trapezoidal rule as follows:

$$AUC=\frac{1}{2}\sum_{i=1}^{6}(T_{i+1}-T_i)(ESAS_{i+1}+ESAS_i).$$

Where T_i is the i[th] time value and $ESAS_i$ is the i[th] ESAS total score value.

Note: due to premature termination of the study, a note will be added to primary endpoint analysis to remind that the results are merely indicative, no conclusion can be drawn

6.1.2 Secondary efficacy endpoints

The secondary endpoints are:

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 ≤ 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.

Note: due to premature termination of the study, secondary endpoint analysis will be limited to descriptive summaries to explore any trends or patterns between the two treatment groups and will be done only if adequate data are available.

6.1.3 Safety Endpoints

Due to the premature termination of the study, adverse events, deaths, laboratory values and vital signs will be carefully analysed, interpreted and reported

6.1.4 Multiplicity

No multiple testing will be performed in this study.

6.1.5 Significance testing and estimation

All the statistical tests will be two-sided at the 5% level of significance. Significance testing will be done only for the primary endpoint.

7 Analysis Methods

7.1 Efficacy

7.1.1 Primary efficacy analysis

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. The comparison between standard therapy and standard therapy + Lanreotide will be performed using the adjusted means if the covariate is statistically significant. The assumptions required for the analysis of covariance will be tested as follows:

- The equality of variances will be verified using the Levene's test. If it is significant AUC values will be properly transformed.
- The linear relationship of AUC with the basal total score within treatment group will be tested by a regression analysis.
- The parallelism of the regression lines between groups and the slope non zero value with the appropriate F tests.

If the assumptions of linear relationship of AUC with the basal total score or of parallelism of the regression lines between groups are not met then some AUC values transformations (e.g. AUC square root, rank transformation) or non-parametric procedures will be applied (e.g. Mann-Whitnay U-test). The ESAS total score of the first 7 days will be also analyzed by the repeated measures analysis of variance with one group to highlight statistically significant differences between and within groups. Multiple comparisons between and within groups will be adjusted according to Bonferroni's correction. Results will be reported as p-values and 95% Confidence Interval (95% C.I.).

Descriptive statistics will be reported as frequency, mean, standard deviation, median, first and third quartile, minimum and maximum.

Subjects with available basal value and at least 5 post-treatment assessments of ESAS total score will belong to the FAS.

Note: due to premature termination of the study, the results of this analysis should be interpreted cautiously and no conclusions should be made.

7.1.2 Secondary efficacy analysis

The secondary endpoints will be analysed as follows:

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 will be performed by an ANOVA with repeated measures. Multiple comparisons between and within treatment group will be calculated at each assessment time as difference from baseline. The Bonferroni's correction will be applied. If the parametric assumptions of the analysis are not satisfied, then a suitable transformation or/and a non-parametric procedure will be applied.

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. McNemar non-parametric test will be used to test changes between baseline assessment and post-treatment assessments (Day 7, Day 14 and Day 28) within study groups. The distribution of changes from the baseline between treatment groups will be analysed at each time assessment (Day 7, Day 14 and Day 28) by Chi square test.

3) Changes in daily intensity of Abdominal Pain (Visual analogue scale) and comparison between Group A and Group B will be analysed as planned for the ESAS score at point 1.

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). The statistical analysis will be performed as reported at point 2 for Karnofsky performance status.

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. Same analysis as stated at point 2 for Karnofsky performance status.

6) In patients with a NGT, changes in daily NGT secretion volume and comparison between Group A and Group B. This parameter will be analysed as planned for ESAS score. If the distribution is too unbalanced between treatment groups the analysis will be descriptive only.

7) Comparison of number of daily vomiting episodes and number of days without vomiting, between Group A and Group B.

The daily vomiting episodes will be classified as 0 (absent), 1, 2 and more than 2 and they will be reported in a contingency table with treatment arm in columns. The statistical analysis will be performed as reported at point 2 for Karnofsky performance status.

The number of days without vomiting will be analysed performing a Student t test for unpaired data considering the first seven days of treatment and the whole study period (28 days). If the parametric assumptions of the analysis are not satisfied, then a suitable transformation or/and a non-parametric procedure will be applied (Mann-Whitney rank-sum test).

8) Passage of stools (Yes/No) daily assessment and comparison between Group A and Group B. The comparison will be evaluated either between or within study groups and it will be tested as reported at point 2 for Karnofsky performance status.

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 will be compared between and within treatment groups using an ANOVA model with repeated measures as reported at point 1 for ESAS score.

Note: secondary endpoint analyses will be limited to descriptive summaries to explore any trends or patterns between the two group.

7.2 Safety

All safety data will be included in the data listings and summary tables will be based on the safety population.

Note: due to premature termination of the study, any safety signal will be carefully analyzed, interpreted and reported.

7.2.1 Adverse Events

Adverse events will be coded using the latest version available at the time of the start of the study of Medical Dictionary for Regulatory Activities (MedDRA).

Incidence of all reported Adverse Events (AEs)/Treatment Emergent AEs (TEAE) and Serious AEs SAEs) will be tabulated by treatment group and by overall. In addition, summary tables will be presented with the number and percentage of subjects with AEs classified by primary system organ class, preferred term (ordered alphabetically) and by maximum intensity and drug relationship.

A TEAE is defined as any AE that occurs during the active phase of the study (starting after randomization, Visit 1 day 1, until the end of the study, Visit 4 day 28) 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.

The contingency tables will be analysed by the $\chi 2$ test with the Yates correction for 2x2 contingency tables.

Listings will be presented and sorted by treatment group, subject id, start time of AEs, primary system organ class, preferred term for all adverse events recorded during the study.

Listings of serious adverse events (SAE), adverse events leading to withdrawal and listings of deaths will also be presented.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

In the event of multiple adverse events being reported by the same subject, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) will be chosen.

7.2.2 Death

Listings will be presented and sorted by treatment group, subject id, death time reporting narrative of death.

7.2.3 Laboratory data

Not applicable, the study protocol states that all clinical laboratory tests are at the discretion of the investigator and they are not reported in the e-CRF.

7.2.4 Vital signs

Vital signs will be listed at each assessment by treatment group and subject.

Summary statistics by treatment group will be presented at each scheduled assessment for actual values and changes from baseline.

Comparison of vital signs at Baseline, Day 7, Day 14 and Day 28 between Group A and Group B will be performed by an ANOVA with repeated measures. Multiple comparisons between and within treatment group will be calculated at each assessment time as difference from baseline. The Bonferroni's correction will be applied. If the parametric assumptions of the analysis are not satisfied, then a suitable transformation or/and a non-parametric procedure will be applied.

Body weight at baseline visit will be tested for homogeneity between treatment groups using Student t test for unpaired data or Mann-Whitney U test in case of unmet parametric assumptions.

Note: due to premature termination of the study, vital signs will be summarized reporting descriptive statistics by treatment groups for each scheduled assessment both actual values and changes from baseline.

7.3 Missing values and outliers

7.3.1 Missing data

Related to the main outcome variable (7 days AUC) subjects will not belong the full analysis set if basal assessment or more than one post treatment assessments result missing. If the analysis population results significant lower than ITT population any eventually sensitivity analysis will be performed replacing post-treatment missing data with the closest non-missing value. The handling of baseline missing data will be

replace applying the most suitable technique (e.g. worst value, group mean, ecc..) after consultation with the sponsor.

For the secondary endpoints parameters if there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to proceed with the statistical analysis.

Any repeat or additional assessments performed will be included in the individual subject data listings.

Note: given the premature termination of the study, the amount of missing data will be assessed and a decision will be made to only report summary statistics based on any available data. Regarding the primary analysis any missing value of ESAS score will not be replace and no one sensitivity analysis will be performed.

7.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it will be assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
- If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

7.3.3 Outliers

A search of outliers by the IBIS DM should be done before performing the statistical analysis and any outlier should be solved through a query issuance. The handling of outliers which cannot be solved contacting the study site will be defined after consultation of the sponsor.

7.4 Subject disposition

A listing of dates of assessments (relative day) and their study exposure will be presented by subject for each treatment group.

A summary table and a flow chart will be presented for each subject population presenting the number of subjects in each treatment group at each assessment and identifying the number of subjects who withdrew over time.

A summary table will present the extent of subject exposure in the study for each treatment group. The definition of the length of exposure is from date of baseline visit (day 1) to the date of the last contact with the study subject.

7.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by treatment group.

Fisher's exact test will be used to compare the proportion of subjects discontinuing within the first 7 days (from Visit 1 to Visit 2) of the study, both overall and for specific reasons, between treatment groups.

A survival analysis according to Kaplan-Meier method will be performed to study discontinuation along the whole study period (from day 1 to day 28) comparing the two treatment groups by means of log-rank test.

Note: due to premature termination of the study no one inferential test will be performed. The 95% Confidence Intervals (95% C.I.) will be reported, overall and for each treatment group, for the percentage of withdrawal patients within the first 7 days of study and for the median time to withdrawal along the whole study period.

7.6 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by treatment group and subject.

Summary statistics will be provided for demographic and baseline characteristics (age, sex, race, age, weight and vital signs), by treatment group, for the ITT and/or Safety population.

No statistical comparison of the treatment groups will be performed and only 95% Confidence Intervals will be reported.

7.7 Medical and surgical history

Medical and surgical history will be coded using MedDRA dictionary according to the latest version available at the time of the start of the study.

Listings will present the preferred term. The listings will be sorted by treatment group, subject, primary system organ class, preferred term.

A frequency table of the number and percentage of subjects will be provided for active medical and surgical history by primary system organ class and preferred term for each treatment group.

7.8 Subject compliance

A listing will be presented for drug administration (dose, quantity, date) by subject for Lanreotide group only. Deviations from observed and scheduled time and dose will be presented.

Descriptive statistics (frequency table for each Standard Care category) will be reported for the Standard Care, generally defined as:

- Oral food or oral liquid intake according to clinical judgement;
- Intravenous corticoids
- Intravenous H2 antihistaminics
- Proton Pump Inhibitors
- Antispasmodic
- Antipsychotics.

for each treatment group.

A listing will be presented for prohibited concomitant medication for any subject who has received this prohibited medication. Subjects excluded from the Per Protocol population due to receiving prohibited concomitant medication (Somatostatin or any of its analogues) will be flagged (+).

All the protocol deviations identified before of the statistical analysis will be also listed by subject for each treatment group/sequence.

The impact of major protocol deviation on the primary efficacy analysis will be investigated by comparing the results of the ITT and PP population analyses.

Note: given the premature termination of the study, the impact of major protocol deviation on the primary efficacy analysis will not be performed because the analysis will be performed on the ITT population.

7.9 Prior and concomitant therapies

Concomitant therapies will be coded using the WHO-Drug Dictionary according to the latest version available at the time of the start of the study. The therapeutic class will correspond to the second level of ATC code, that is, corresponding to the first 3 figures.

Listings will be presented for the therapeutic class, preferred term and verbatim text. The listings will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant therapies by therapeutic class and preferred name for each treatment group.

Prohibited concomitant medication (Somatostatin or any of its analogues) will be flagged (+).

7.10 Pharmacokinetics & antibodies

Not applicable.

7.11 Pharmacodynamics

Not applicable.

7.12 Derived data

The derived data are variables which are calculated from the raw data in the CRF/eCRF and not included in the database (e.g.: AUC, total score, duration, summary value from repeated observations, study exposure, study drug exposure, study drug cumulative dose, …).

The following derived data will be calculated and included in the listings:

Age: Subject age (years) will be derived as (screening date – birth date)/365.25 and truncated to the largest integer that is less than or equal to the calculated result.

ESAS AUC over the first seven days (Visit 1 to Visit 2): AUC of the total score of the first nine items of the ESAS questionnaire will be calculated via the trapezoidal rule.

Changes from baseline: Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

Number of Vomiting episodes: For each diary page filled in (fill in with date and other items), the number of vomiting episodes will be set to 0 if none box related to the vomiting episodes has been filled in.

7.13 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Study phase	Scheduled visit	Time interval (days)
Active phase	Baseline	1 (prior to first dose)
	Week 1	7
	Week 2	12 to 16
	Week 8	26 to 30

7.14 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented n, number of missing values, arithmetic mean, standard deviation, median and the range (minimum, maximum).

Mean, median, standard deviation and standard errors of the mean (SE) values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one/two decimal place(s) and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary.

Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).

Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

However, the ways these values will be taken into account for any analyses should be described.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm]. The format for presentation of other data types should be specified.

7.15 Pooling of Centres

The method for handling centres with small sample sizes will be described and determined prior to proceed with the statistical analysis (e.g.: combining centres with small sample sizes, geographical location, centre type etc)..

7.16 Interim analysis

No interim analysis will be performed.

7.17 Role of independent data monitoring committee (DMC)/interim data review committee

Neither a data monitoring committee nor an interim data review committee will be set up for the study conduction.

7.18 Covariates and analysis of subgroups

The ESAS total score will be used as covariate for the primary efficacy analysis as described in the statistical methods.

8 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

8.1 Hardware

The statistical analysis will be performed using SONY VAIO personal computer with Windows 7 professional as operating system.

8.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS version 9.3. All output will be in Microsoft Word Format.

8.3 Validation programs

IBIS will provide a Validation Plan to Ipsen identifying the methods of validation.

The Program Reviewer is responsible for reviewing each project program and output associated with the deliverable product. Program logs are reviewed for logical, syntax and fatal errors. The review in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The Reviewing/QC Statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g., SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the reporting and analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further changes are required to produce the deliverable, the Program Reviewer and Reviewing/QC Statistician need to complete and sign the CRO's Validation Checklist/Sign-off Sheet, to indicate that they have successfully performed all of their responsibilities.

Copies of the internal QC forms produced for the validation process and the CRO's sign-off forms will be provided to the sponsor to support the validation.

8.4 Restitution of the programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

9 CHANGES FROM PROTOCOL

Due to the low accrual rate despite the extension of the planned enrollment period (from 18 to 36 months) the study has come to a premature termination.

43 patients have been recruited from the planned 84 patients.

The statistical analysis will be performed only on ITT and Safety population. The inferential tests will be performed only for the primary endpoint on the FAS population. A note will be added to primary endpoint analysis to remind that the results are merely indicative, no conclusion can be drawn

For all other endpoints, the statistical analysis will be mainly descriptive in nature with the aim to explore any trend or patterns between the two treatment groups

10 REFERENCES

11 DATA PRESENTATION

Data listings are presented for all screened subjects.

Footnotes should be used to clarify ambiguities (e.g.: the denominator used to calculate a percentage or for notes for the programmer). If the number of footnotes is high, they could be presented only in the last page,

with on each page the following footnote “See last page for listing notes”. The order of the footnotes for key symbols (*, ~) will be in the order that they appear in the listing.