STATISTICAL ANALYSIS PLAN

STUDY A-48-52030-269- IMIO

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

Author: **ITEC Services**
3, avenue Georges Clémenceau
ZI Jean Zay – 33150 CENON
FRAN
CE

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SIGNATURE PAGE

IPSEN
Innovation for patient care

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IPSEN

Name	Position	Date	Signature
LEVEQUE Yannick	Clinical Data Project Manager	15/06/18	PPD
DE RUYTER Vincent	Medical advisor	15/06/2018	PPD
TORKIA Grira	Statistician	15/06/2018	PPD

ITEC Services

Name	Position	Date	Signature
PPD	PPD	15/06/2018	PPD
PPD	PPD	15/06/2018	PPD

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1 ABBREVIATIONS

- **ADS:** Analysis Data Set
- **AE:** Adverse Event
- **ATC:** Anatomical Therapeutic Chemical
- **BMI:** Body Mass Index
- **CI:** Confidence Interval
- **CRF:** Case Report Form
- **CRO:** Contract Research Organisation
- **CS** Clinically significant
- **CT Scan:** Computed Tomography Scan
- **DD:** Derived Data
- **DM:** Data Management
- **DX:** Day X
- **ESAS:** Edmonton Symptoms Assessment Scale
- **GPP:** Good Pharmacoepidemiology Practices
- **HADS:** Hospital Anxiety and Depression Scale
- **IEC:** Independent Ethics Committee
- **IMP** Investigational Medicinal Product
- **ITT:** Intention To Treat
- **KPS:** Karnofsky Performance Scale
- **MedDRA:** Medical Dictionary for Regulatory Activities
- **MRI Scan:** Magnetic Resonance Imaging Scan
- **NCS** Not clinically significant
- **NGT:** Nasogastric Tube
- **PP:** Per Protocol
- **PT:** Preferred Term
- **SAE:** Serious Adverse Event
- **SAP:** Statistical Analysis Plan
- **SAS®:** Statistical Analysis System®
- **SD:** Standard Deviation
- **SOC:** System Organ Class
- **SmPC:** Summary of Product Characteristics
- **SOP:** Standard Operating Procedure
- **VAS:** Visual Analogic Scale
- **WHO-DD:** World Health Organization – Drug Dictionary

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this observational study is to assess the efficacy of Lanreotide Autogel 120 mg for the relief of vomiting due to inoperable malignant intestinal obstruction in patients without nasogastric tube **AND** to assess the efficacy of Lanreotide Autogel 120 mg to remove a nasogastric tube without the recurrence of vomiting in patients with an inoperable malignant intestinal obstruction with a nasogastric tube.

2.2 Secondary objectives

The secondary objectives are as follows:

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

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

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

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

2.3 Safety objectives

To assess the clinical and biological safety of the study treatment

3 STUDY DESIGN

3.1 Type of study

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

3.2 Study Plan

▪ **Phase 1 Initial Injection Lanreotide Autogel 120 mg:**

Patients meeting the selection criteria for participation will need to provide a written informed consent. Patient and caregiver will be asked to complete the Edmonton Symptom Assessment System (ESAS) before any study procedure. Patients will then receive the following treatment: Standard of care + 1 injection of lanreotide Autogel 120 mg.

Response to the treatment will be assessed based on the % of responders in the treatment group at Day 7, Day 14 and Day 28.

Safety of the patients will be followed continuously during the entire study period. A blood sample to assess the serum levels of lanreotide will be taken at Day 0, Day 7 and Day 14 and Day 28

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

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▪ **Phase 2 Second injection Lanreotide Autogel 120 mg:**

Patients completing the 28 days of the first phase and who are responders as defined by this protocol will have the possibility to receive a second injection with lanreotide Autogel 120 mg. Standard of care will be continued for all as described by the protocol.

Response to the treatment will continued to be assessed based on the % of responders at Day 35, Day 42 and Day 56

Safety of the patients will be followed continuously during the entire study period. A blood sample to assess the serum levels of lanreotide will be taken just before the second injection at Day 28 and at Day 35, day 42 and at day 56.

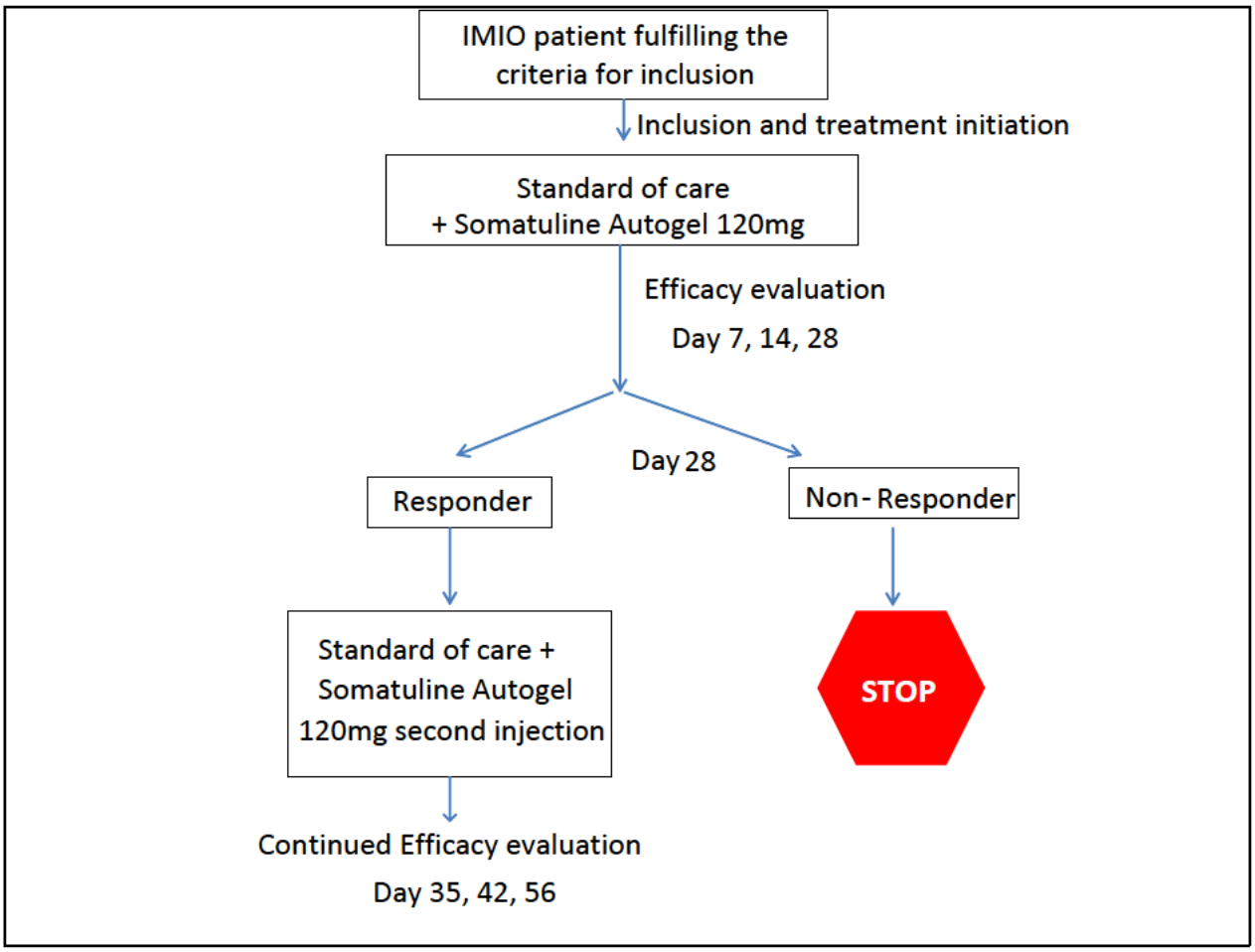

Figure 1 – Study Flow

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

Table 1. Phase I

Visit	V1	V2	V3	V4 Last visit
Day	D0	D7	D14	D 28
Informed consent	●			
Eligibility review	●			
Demography	●			
Medical history	●			
Obstruction history	●			
Clinical examination	●	●	●	●
Nutrition procedure	●	●	●	●
Symptoms and QOL assessment *	●	●	●	●
Vomiting and nausea episodes assessment (diary cards)**	●	●	●	●
Concomitant medications	●	●	●	●
Safety biological assessment (if applicable)	●	●	●	●
Injection Study Treatment Lanreotide Autogel 120 mg	●			
Lanreotide concentrations (PK)	●#	●	●	●
Adverse Events***	●	●	●	●

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

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

***: At Day 0 (baseline) after signature of the informed consent and after clinical examination and medical history

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

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Table 2. Phase II

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

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

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

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

#: Before the second Lanreotide Autogel 120 mg injection

3.3 ***Duration of the study***

The observational study duration for 1 subject will be 56 days as a maximum.

The overall duration of the study will be approximately 3 years; this includes 2 years of recruitment: this period may be extended if needed to allow for the recruitment of the required number of patients.

3.4 ***Enrolment of patients***

Data of 50 patients will be collected.

It is planned to recruit these patients in a 2 year period in approximately 20 centres in Belgium and Luxemburg. Each centre will be required to enrol between 1 and 3 subjects.

Note: Actually, no site in Luxemburg has been included in the study.

Prior to enrolment in this observational study, the subjects will be required to provide written informed consent to confirm that they allow their medical data to be collected and analysed.

The inclusion criteria for the patients are:

- ✓ Written informed consent before any study related procedure
- ✓ Male and female patients age 18 years or older at the time of enrolment
- ✓ Diagnosis of an intestinal obstruction of malignant origin

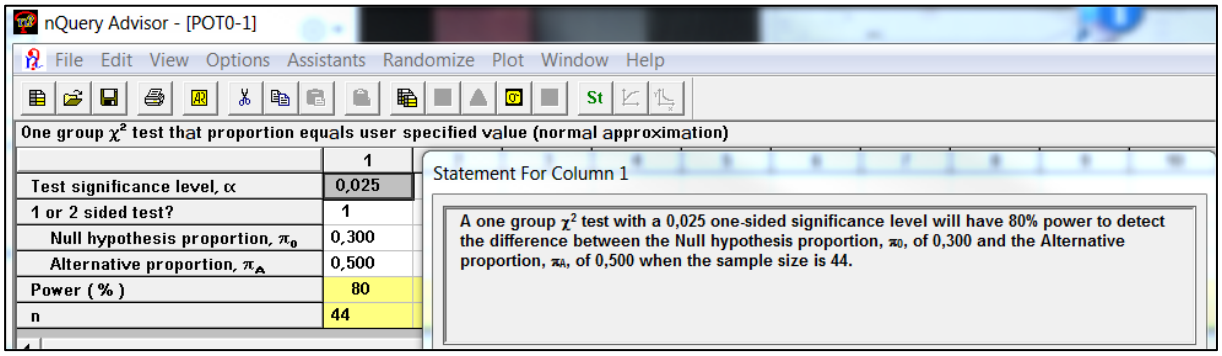
- ✓ In case of peritoneal carcinomatosis, confirmation by CT or MRI scan within the 3 months preceding the inclusion in the study
- ✓ Confirmed as inoperable after surgical advice
- ✓ Patient with a nasogastric tube OR presenting with 3 or more episodes of vomiting / 24h in the last 48 hours
- ✓ Estimated life expectancy 1 month or more

The non-inclusion criteria for the patients are:

- ✓ Operable obstruction or any subobstruction
- ✓ Bowel obstruction due to a non-malignant cause (for example: hypokalaemia, drug side-effects, renal insufficiency, etc.)
- ✓ Signs of bowel perforation
- ✓ Prior treatment with somatostatin or any analogue within the previous 60 days
- ✓ A known hypersensitivity to any of the study treatments or related compounds
- ✓ Previous participation in this study
- ✓ Is likely to require treatment during the study with drugs that are not permitted by the study protocol (see Section 9.5).
- ✓ 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.

4 DETERMINATION OF SAMPLE SIZE

Sample size is calculated using nQuery to test if the proportion responders at day 7 using Lanreotide 120 mg is larger than the reference proportion of 30%. The following assumption underlie the sample size calculation: expected proportion responders using Lanreotide is 50%, 1-sided test, 2.5 % significance level alpha and power of 80 % using Z-test for binomial proportion. The required sample size is 44 subjects. However, taken into account a certain margin for drop outs (15-20%), 50 patients will be recruited for this study.



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5 CRF VARIABLES

Data collection will be done through a paper based Case Report Form (CRF).

• ***Day 0 (Visit 1)***

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

- Eligibility check (inclusion/exclusion criteria)
- Demographics (sex, age, race,)
- Medical history, including ongoing medical history and physical examination
- Prior and concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician (optional).
- Blood sampling for PK analysis between 2h and 12h after the lanreotide autogel 120mg injection
- Nutrition procedure (no oral food or oral liquid intake during the first 5 days)
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment (episodes in the last 48 hours) and distribution of diary cards
- Start of compulsory medication and injection of lanreotide Autogel 120 mg
- AEs

• ***Day 7 and Day 14 (Visit 2-3)***

The following procedures will be performed for each subject who received an administration with Lanreotide Autogel 120 mg at Day 0:
- Physical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 7 and day 14.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- Start of step up medication at Day 7 in case of insufficient efficacy
- AEs and SAEs

• ***End of Phase 1 Day 28 (Visit 4) or Early Withdrawal Visit Phase 1***

The following procedures will be performed for each subject who received an administration of Lanreotide Autogel 120 mg at Day 0 and who stops the study at Day 28 or has an Early Withdrawal Visit Phase I:
- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 28 or at early withdrawal
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Reason for end of phase 1 / early withdrawal

Patient who are not responding or who do not want to be reinjected the EOS visit should be completed

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• ***Visit 4 Phase 2 - Day 28 Post injection***

The following procedures will be performed for each subject who received and administration with Lanreotide Autogel 120 mg at Day 0 and continues the study at Day 28:

Eligibility Check Phase II: Proven efficacy at Day 28: ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D0 and D28 (for patients without NGT at baseline) or as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D0 and D28 without vomiting recurrence.

- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on Day 28 before the second injection of lanreotide Autogel 120 mg.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Second injection of Lanreotide Autogel 120 mg

• ***Day 35 and Day 42 (Visit 5-6)***

The following procedures will be performed for each subject who received a second administration of Lanreotide Autogel 120 mg at Day 28:
- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Blood sampling for PK analysis on D35 and D42.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment- diary cards AND/OR removal of nasogastric tube
- AEs and SAEs

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

The following procedures will be performed for each subject who received a second administration with Lanreotide Autogel 120 mg at Day 28 and who ends the study at Day 56 or has an Early Withdrawal Visit Phase II:
- Clinical examination
- Changes and initiations of concomitant medications/therapies
- Blood sampling for haematology and biochemistry, and urinalysis as deemed necessary by the treating physician.
- Nutrition procedure and changes in nutrition procedure
- Symptom and quality of life assessment (Edmonton Symptom Assessment System) by both patient and caregiver. Visual analog scale for abdominal pain and Karnofsky for daily activities.
- Vomiting and nausea episodes assessment - diary cards AND/OR removal of nasogastric tube
- AEs and SAEs
- Reason for end of study / early withdrawal

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6 EFFICACY PARAMETERS

6.1 Primary Efficacy Endpoint and Evaluations

✓ ***Phase 1: Initial Injection Lanreotide Autogel 120 mg:***

Percentage of responding patients before or at D7. A responder is defined as a patient experiencing ≤2 vomiting episodes/day during at least 3 consecutive days at any time point between the D0 and D7 (for patients without NGT at baseline)

or

as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D0 and D7 without vomiting recurrence.

Number of daily vomiting episodes and number of days without vomiting recorded on diaries will be used to calculate this endpoint.

6.2 Secondary Efficacy Endpoints and Evaluations

✓***Phase 1: Initial Injection Lanreotide Autogel 120 mg:***

1) Percentage of responding patients before or at D14 (same for D28). A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D0 and D14 (D28)

or

as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D0 and D14 (D28) without vomiting recurrence.

Number of daily vomiting episodes and number of days without vomiting recorded on diaries will be used to calculate this endpoint.

2) Time between first injection and clinical response

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

The Edmonton Symptom Assessment System provided is the revised system by Watanabe. This tool is designed to assist in the assessment of nine symptoms common in cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath, (there is also a line labelled “Other Problem”). The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that the symptom is absent and 10 that it is of the worst possible severity.

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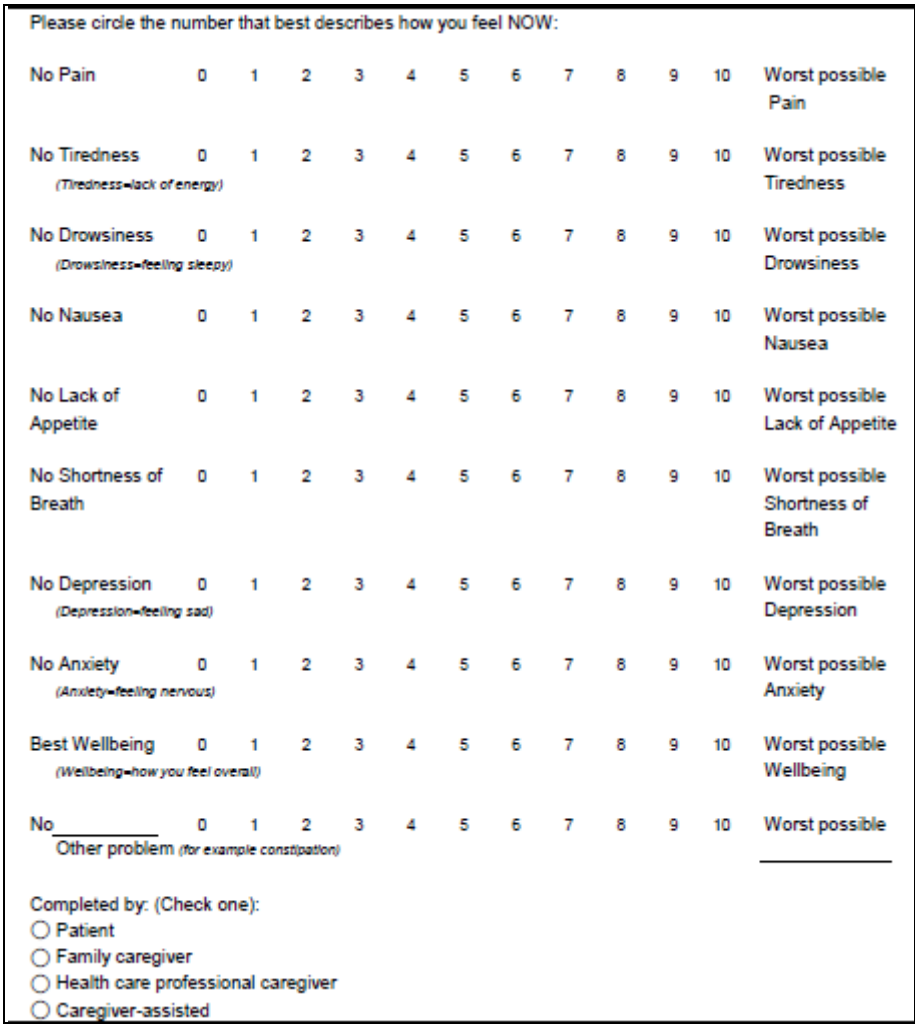

Please circle the number that best describes how you feel NOW:

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

Completed by: (Check one):
- ○ Patient
- ○ Family caregiver
- ○ Health care professional caregiver
- ○ Caregiver-assisted

Figure 2 – Edmonton Symptom Assessment System

Each symptom rating is interpreted independently and a total symptom distress score will be calculated (see section 8.4.2.3).

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

▪ **General activity (Karnofsky score)**

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

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Figure 3 – Karnofsky Performance Scale (KPS)

▪ **Nausea (number of daily episodes)**
The episodes are recorded using the patient diary.

▪ **Pain (Visual analogue scale)**
The pain is evaluated by the patient using a 100 mm Visual Analogue Scale (VAS) from "No pain" (=0) to "Unbearable pain" (=100).

▪ **Complete/incomplete obstruction: passage of stools**
No data are collected on this point so this analysis will not be done. See section 8.6 "Changes from protocol"

✓***Phase 2: Second injection Lanreotide Autogel 120 mg:***
1) Overall Percentage of patients continuing from Phase I and confirmed as a responder at the end of phase I, showing a continued response at D35, D42 and D56. A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D0 and D35, D42 and D56
or
as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D0 and D35, D42 and D56 without vomiting recurrence.

⇨ Number of daily vomiting episodes
⇨ Number of days without vomiting

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

7 DATA SETS ANALYSED

7.1 Subject Classification and Definitions

✓ **Enrolled subject:**
Subject fully informed about the study who has given written informed consent to participate (before any occurrence of trial related procedure).

✓ **Treated subject:**
Enrolled subject who is treated with at least one dose of study medication.

✓ **Treatment Completed subject:**
Treated subject who has completed all specified assessments after the first and second IMP injections .

✓ **Study Completed subject:**
Treated subject who has completed all specific assessments of each phase of the study

✓ **Drop-out:**
Treated subject who did not complete the study and or discontinued IMP administration.

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7.2 Analyses Populations Definitions

✓ **Safety population:**
All subjects who received at least one dose of study medication.

✓ **Intention-to-treat (ITT) population:**
Enrolled subjects with at least one dose of study medication.

✓ **Per protocol (PP) population:**
All subjects from the ITT population for whom no major protocol violations/deviations occurred.

✓ **PK Population:**
All subjects with at least one measurable lanreotide concentration.

The primary analysis based on the primary endpoint will be performed on the ITT population. In addition, per protocol (PP) analysis will be performed. All secondary efficacy endpoints will be analysed on the ITT population. Safety will be analysed using safety population which is identical to the ITT population.

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

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8 STATISTICAL METHODOLOGY

The statistical analysis will be performed by ITEC Services - 3 Avenue Georges Clemenceau - 33150 CENON – FRANCE (except pharmacokinetic analyses that will be performed by IPSEN).

8.1 Descriptive statistics

Each modality of qualitative data will be presented with their number and percentage.

For quantitative data, mean, median, minimum and maximum as well as standard deviation and interquartile range will be described.

For all the variables, number of available and missing observations will be specified. If necessary, 95 % CI will also be presented.

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: same number of decimal as collected,
- Derived data: 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),
- Mean, median and standard deviation: reported to one decimal place greater than the raw/derived data that they summarize,
- Minimum and maximum : same precision as the raw data,
- Percentage: one decimal place,
- P-values: four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

8.2 Management of missing values

8.2.1 Missing data

If necessary, specifications for handling missing data are provided in Appendix A. Without precision in this section missing data will not be replaced.

Missing data handling for efficacy parameter is detailed in section 8.4.1.

8.2.2 Missing or incomplete dates

For partial dates, if the day is missing, the convention is to use "15" (middle of the month). If the day and the month are missing and it's a former date (for example date of birth), the convention is to use the value "1" for the day and "7" for the month (middle of the year). This convention is useful to estimate some time intervals and/or duration.

8.2.3 Outliers

Any outlier identified prior to database lock which is impossible/implausible will be excluded from the analysis. A search of outliers should be performed during the data review meeting and actions with the sponsor should be defined.

8.3 Baseline description

8.3.1 Subject disposition

A summary table and a flow chart of subjects enrolled and included in each population will be presented overall and according to NGT use. The reasons for exclusion from each population will be presented in the same table. A listing of excluded patients from each population will also be presented.

The number of patients by centre will be presented.

Follow-up duration[DD] (days) corresponds to the time between baseline visit (Visit 1 / D0) and last visit recorded and will be calculated overall and a summary of the number of subjects at each assessment will also be provided.

The number and percentage of subjects who withdrew from the study (overall and during each phase) and the primary reason for early withdrawal will be presented overall and according to NGT use. Time between inclusion and early withdrawal[DD] (days) will also be presented overall and during each phase.

8.3.2 Baseline characteristics

Summary statistics will be provided for data at baseline for the ITT Population.

▪ Demographic characteristics

The following characteristics will be presented overall and according to NGT use:
- Age at inclusion[DD] (years) in quantitative and in classes (<40 / [40;50[/ [50;60[/ [60;70[, >70)
- Sex (Male/Female)
- Race (Asian/Black-African American/Caucasian-White/Native Hawaiian-Other Pacific Islander/ American Indian/Alaska Native/Multiple)

▪ Malignancy history causing obstruction

The following characteristics will be presented overall and according to NGT use:
- Time between initial diagnosis and inclusion visit[DD] (months)
- Previous intestinal obstruction (No/Yes)
- If yes, has it resolved? (No/Yes)
- If Yes, Specify (Spontaneously/Medical Treatment/Surgical Treatment)
- Time between current intestinal obstruction and inclusion visit[DD] (days)
- Malignancy origin causing intestinal obstruction (Digestive/Ovarian/Other, specify)
- Presence of ascites (No/Yes)

▪ Vital signs

The following characteristics will be presented:
- Height (cm) in quantitative
- Weight (kg) in quantitative
- Body Mass Index (kg/m²)[DD] in quantitative and in classes (<18.5 / [18.5;25[/ ≥ 25)
- Supin Blood pressures
  - Systolic (mmHg) in quantitative
  - Diastolic (mmHg) in quantitative
- Heart rate (bpm) in quantitative

▪ Local laboratory data

The following parameters will be presented as quantitative variables

- Haematology
  - Blood sample collected (No/Yes)

o If no, a listing of reasons why vital signs measurements were not done will be presented
o If yes :
  - Red blood cells count (10^{12}/L)
  - Hemoglobin (g/L)
  - Haematocrit (RATIO)
  - MCV (fL)
  - MCH (pg)
  - MCHC (g/dL)
  - White blood cells count (10^9/L)
  - Neutrophils (10^9/L)
  - Lymphocytes (10^9/L)
  - Monocytes (10^9/L)
  - Eosinophils (10^9/L)
  - Basophils (10^9/L)
  - Other differentials (10^9/L)
  - Platelets (10^9/L)

- Biochemistry
  - Blood sample collected (No/Yes)

o If no, a listing of reasons why vital signs measurements were not done will be presented
o If yes :
  - Subject fasting (No/Yes)
  - Urea (mmol/L)
  - Total bilirubin (µmol/L)
  - Sodium (mmol/L)
  - Potassium (mmol/L)
  - Calcium (mmol/L)
  - Chloride (mmol/L)
  - Bicarbonate (mmol/L)
  - Alkaline phosphatase (IU/L)
  - Albumin (g/L)
  - Total protein (g/L)
  - Total cholesterol (mmol/L)
  - Triglycerides (mmol/L)
  - Glucose (mmol/L)
  - Creatinine (µmol/L)
  - ASAT (IU/L)
  - ALAT (IU/L)
  - GGT (IU/L)

in quantitative and in classes (Normal/Abnormal NCS/Abnormal CS/Not evaluable).
NCS=Not Clinically Significant / CS=Clinically Significant

Note: Baseline laboratory parameters are discussed in Section 8.5.9 with the post baseline laboratory data.
If a laboratory parameter was retested, the most recent value will be used for the description.

▪ Significant medical and surgical history

Significant medical and surgical history data will be coded using MedDRA dictionary version 19.0.

Two frequency tables of the number and percentage of subjects and of events will be provided by primary system organ class (Primary SOC) and preferred term (PT). The first table will present medical

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and surgical history ongoing at inclusion^{DD}, and the second table will present only events ended at the time of inclusion^{DD}.

▪ Concomitant medications started prior inclusion

Concomitant medications started prior inclusion will be coded using ATC code of the WHO-Drug Dictionary Version of December 2015.

A table presenting number and percentage of subjects and concomitant medication started prior inclusion^{DD} by ATC2 and Drug Name will be tabulated.

▪ Non drug therapies started prior inclusion

Non drug therapies started prior inclusion will be coded using MedDRA dictionary version 19.0.

A table presenting number and percentage of subjects and concomitant non drug therapies started prior inclusion^{DD} by PT will be tabulated.

▪ Concomitant medications for Inoperable Malignant Intestinal Obstructions started prior inclusion

Concomitant medications for Inoperable Malignant Intestinal Obstructions started prior inclusion will be coded using ATC code of the WHO-Drug Dictionary Version of December 2015.

A table presenting number and percentage of subjects and concomitant medications for Inoperable Malignant Intestinal Obstructions started prior inclusion^{DD} by ATC2 and Drug Name will be tabulated.

▪ Nutrition procedure started prior inclusion

Nutrition procedures started prior inclusion will be described according to route of administration (enteral / intravenous / oral):

- Number and percentage of patients with at least one nutrition procedure
- Number and percentage of nutrition procedures
- Type of food (solid / liquid)

8.4 Efficacy analysis

8.4.1 Main analysis

▪ **Primary endpoint**

The primary endpoint is the percentage of responding patients before or at D7.
A responder is defined as a patient experiencing ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point between the D0 and D7 (for patients without NGT at baseline) based on diary cards

or

as a patient in whom the NGT has been removed during at least 3 consecutive days at any time point between the D0 and D7 without vomiting recurrence.

Number of daily vomiting episodes and number of days without vomiting recorded on diaries will be used to calculate this endpoint. If diary cards are not available, then the assessment of vomiting reported in the CRF will be taken into account.

A day with a missing number of vomiting on diary cards will be imputed by the worst case (For patients without NGT: >2 vomiting episodes and for patients with NGT: ≥ 1 vomiting episodes).

Hypotheses: H_0 : p = 30% versus H_1 : $p > 30\%$ where p is the probability of responder and p_0 = 30% is the reference proportion. If $\bar{p}$ is the observed sample proportion of responders, E($\bar{p}$) and V($\bar{p}$)=p(1-p)/n; the Central Limit Theorem then gives the z-statistic,

$$z = \frac{\bar{p} - p_0}{\sqrt{p_0(1-p_0)/n}}$$

SAS code

```
Proc freq data=dataset;
  table responder/binomial(level=1 p=0.3) alpha= 0.025
  exact binomial; * Exact p-values;
run;
```

The one-sided binomial test will indicate if a statistically significant difference exists between the observed proportion of responders and the theoretical proportion. We will conclude that the proportion of responders in our study is significantly superior to 30% if p-value<0.025.

Primary analysis will be based on the ITT population. Analyses based on the PP population will be used as supportive.

▪ **Sensitivity analyses**

The following sensitivity analysis for the primary endpoint will be performed:

- Same analysis with “best case” scenario, which means that all missing or unknown daily vomiting episodes will be imputed for patients without NGT by ≤2 vomiting episodes and for patients with NGT by < 1 vomiting episode

8.4.2 Secondary analyses

Secondary analyses will be performed only on the ITT population.

✓ ***Phase 1: Initial Injection Lanreotide Autogel 120 mg:***

8.4.2.1 Responder proportions at D14 and D28

The same rules as for the main analysis described in 8.4.1 will be used, except that no formal test will be done.

8.4.2.2 Time between first injection and clinical response

Clinical response is defined (like the primary endpoint) as the occurrence of:

- ≤ 2 vomiting episodes/day during at least 3 consecutive days at any time point (for patients without NGT at baseline)

- the removal of NGT during at least 3 consecutive days at any time point between the D0 and D7 without vomiting recurrence (for patients with NGT at baseline)

The time for clinical response in phase 1 will be defined as the time from inclusion (D0) to the date of clinical response defined above.

Non-responder patients will be censored at their last collection data date. Withdrawal patients will be censored at their withdrawal date.

Kaplan-Meier (K-M) estimates of the time to clinical response and the respective K-M curves will be provided by NGT status at baseline and overall.

8.4.2.3 Changes from baseline in Quality of Life (Edmonton Symptom Assessment System (ESAS))

For each symptom from Edmonton Symptom Assessment System (ESAS) and for total symptom distress score[DD], the statistics will be provided at baseline and at D7, as well as for the absolute change from baseline[DD].

The significance of the difference between baseline and studied visit will be assessed using the paired Student t test. In case of non-normality of the data, usual transformation will be applied to normalize the

data. If the usual transformation does not end up with normal data, the Wilcoxon signed-rank test will be used to test the significance of the difference.

This analysis will be done for ESAS assessed by both the patient and the investigator, at D7, D14 and D28, overall and according to NGT use. Associated figures (boxplots) will be presented for each dimensions and total at each visit, for ITT and by NGT status at baseline.

ESAS completed by the "patient", the "family caregiver" or "caregiver – assisted" will be considered as assessment by the patient. ESAS completed by "Health care professional caregiver" will be considered as assessment by the investigator. If 2 questionnaires are filled at the same visits by both the patient and the family caregiver, or both the patient and caregiver – assisted, then the patient questionnaire will be used in the following order of priority: 1-patient / 2-Family caregiver / 3-Caregiver-assisted.

Only patients with data of ESAS at baseline and at Day X (DX) will be used for this analysis.

8.4.2.4 Changes in daily intensity and frequency at D7, D14 and D28 compared to baseline

▪ **General activity (Karnofsky score)**

Karnofsky Performance Status (KPS) score will be presented as a continuous variable (/100) and in classes ([0;40] / [50;70] / [80;100]). The statistics will be provided at baseline and at D7 (respectively D14 and D28), as well as for the absolute change from baseline[DD].Associated figures (boxplots) will be presented at each visit.

The significance of the difference between baseline and studied visit will be assessed using paired Student t test. In case of non-normality of the data, usual transformation will be applied to normalize the data. If the usual transformation does not end up with normal data, the Wilcoxon signed-rank test will be used to test the significance of the difference.

Only patients with data of KPS at baseline and at DX will be used for this analysis.

▪ **Nausea (number of daily episodes)**

The number of daily episodes at DX will be calculated as the sum of episodes of nausea reported the last 3 days before DX divided by 3.

The statistics will be provided at baseline and at D7 (respectively D14 and D28), as well as for the absolute change from baseline[DD].

The significance of the difference between baseline and studied visit will be assessed using the paired Student t test. In case of non-normality of the data, usual transformation will be applied to normalize the data. If the usual transformation do not end up with normal data, the Wilcoxon signed-rank test will be used to test the significance of the difference.

Only patients with data of episodes of nausea at baseline and at DX will be used for this analysis.

▪ **Pain (Visual Analogue Scale)**

The score of the Visual Analogue Scale (VAS) will be presented at baseline and at D7 (respectively D14 and D28), as well as for the absolute change from baseline[DD].Associated figures (boxplots) will be presented at each visit.

The significance of the difference between baseline and studied visit will be assessed using the paired Student t test. In case of non-normality of the data, usual transformation will be applied to normalize the data. If the usual transformation do not end up with normal data, the Wilcoxon signed-rank test will be used to test the significance of the difference.

Only patients with data of VAS at baseline and at DX will be used for this analysis.

▪ **Complete/Incomplete obstruction: passage of stools**

No data are collected on this point so this analysis will not be done. See section 8.6 "Changes from protocol"

✓ ***Phase 2: Second injection Lanreotide Autogel 120 mg:***

8.4.2.5 Responder proportions at D35, D42 and D56

The same rules as for the main analysis described in 8.4.1 will be used, except that no formal test will be done.

8.4.2.6 Changes from baseline in Quality of Life (Edmonton Symptom Assessment System)

The same analysis as described in 8.4.2.3 will be done for D35, D42 and D56.

8.5 Safety analysis

8.5.1 Study drug exposure

For 1st injection (SC) of Lanreotide Autogel 120 mg at D0 and 2nd injection at D28, a table will present if the administration was performed (No/Yes) and if planned dose was administered (No/Yes).

A listing of difficulties during drug administration will also be presented.

8.5.2 Adverse events

The number and percentage of patients with at least one:

- ✓ Adverse event (AE)
- ✓ Serious Adverse Event (SAE)
- ✓ SAE with outcome=fatal
- ✓ Non serious AE
- ✓ AE of mild intensity
- ✓ AE of moderate intensity
- ✓ AE of severe intensity
- ✓ AE leading to drug withdrawn
- ✓ SAE leading to drug withdrawn
- ✓ AE related to study treatment
- ✓ SAE related to study treatment
- ✓ AE leading to patient withdrawal
- ✓ SAE leading to patient withdrawal

will be presented. For each category listed, the number of AEs will be presented in another table.

Adverse events (AE) will be coded using MedDRA dictionary version 19.0. Detailed description of all Adverse Events in terms of Preferred Term (PT) and Primary System Organ Class (SOC) per patient and by episode of Adverse Event will be done. In the description per patient, a given patient presenting several Adverse Events in the same SOC is counted only once in this System Organ Class. Moreover, a patient presenting several episodes of the same Adverse Event is counted only once in the corresponding PT. All the percentages correspond to the number of patients presenting one type of Adverse Event for each treatment group. This analysis will be conducted on the following types of AEs:

- ✓ All the AEs
- ✓ SAE
- ✓ SAE with outcome=fatal
- ✓ Non serious AE
- ✓ AE leading to drug withdrawal
- ✓ SAE leading to drug withdrawal
- ✓ AE related to study treatment
- ✓ SAE related to study treatment

The total number of deaths will be given and a listing of dead patients will be provided.

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8.5.3 Concomitant surgical procedures

Concomitant surgical procedures data will be coded using MedDRA dictionary version 19.0.

A table presenting number and percentage of subjects and concomitant surgical procedures by PT will be tabulated.

8.5.4 Concomitant medications

Concomitant medications data will be coded using ATC code of the WHO-Drug Dictionary Version of December 2015.

A table presenting number and percentage of subjects and concomitant medication by ATC2 and Drug Name will be tabulated.

8.5.5 Concomitant non drug therapies

Concomitant non drug therapies data will be coded using MedDRA dictionary version 19.0.

A table presenting number and percentage of subjects and concomitant non drug therapies on by PT will be tabulated.

8.5.6 Concomitant medications for Inoperable Malignant Intestinal Obstructions

Concomitant medications for Inoperable Malignant Intestinal Obstructions data will be coded using ATC code of the WHO-Drug Dictionary Version of December 2015.

A table presenting number and percentage of subjects and concomitant medications for Inoperable Malignant Intestinal Obstructions by ATC2 and Drug Name will be tabulated.

8.5.7 Nutrition procedure

Nutrition procedures will be described according to route of administration (enteral / intravenous / oral):

- Number and percentage of patients with at least one nutrition procedure
- Number and percentage of nutrition procedures
- Type of food (solid / liquid)

8.5.8 Vital signs

The vital signs (weight, Systolic blood pressure, Diastolic blood pressure and Heart rate) will be described quantitatively at each visit. Percentage change from baseline will be also calculated in quantitative and in classes (<20% vs ≥20%).

8.5.9 Local laboratory data

▪ ***Haematology***

The haematology parameters will be described quantitatively at each visit and percentage change from baseline will be also calculated.

The clinical evaluation in classes (Normal/Abnormal NCS/Abnormal CS/Not evaluable) between baseline and each visit will be described with shift tables.

The following haematology parameters will be described:

- Red blood cells count (10^{12}/L)

- Haemoglobin (g/L)
- Haematocrit (RATIO)
- MCV (fL)
- MCH (pg)
- MCHC (g/dL)
- White blood cells count (10^9/L)
- Neutrophils (10^9/L)
- Lymphocytes (10^9/L)
- Monocytes (10^9/L)
- Eosinophils (10^9/L)
- Basophils (10^9/L)
- Other differentials (10^9/L)
- Platelets (10^9/L)

▪ ***Biochemistry***

The biochemistry parameters will be described at each visit in quantitative and percentage change from baseline will be also calculated.

The clinical evaluation in classes (Normal/Abnormal NCS/Abnormal CS/Not evaluable) between baseline and each visit will be described with shift tables.

The following biochemistry parameters will be described:

- Urea (mmol/L)
- Total bilirubin (µmol/L)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mmol/L)
- Chloride (mmol/L)
- Bicarbonate (mmol/L)
- Alkaline phosphatase (IU/L)
- Albumin (g/L)
- Total protein (g/L)
- Total cholesterol (mmol/L)
- Triglycerides (mmol/L)
- Glucose (mmol/L)
- Creatinine (mmol/L)
- ASAT (UI/L)
- ALAT (UI/L)
- GGT (UI/L)

If a laboratory parameter was retested, the most recent value will be used for the description.

8.6 Changes from protocol

- The secondary efficacy endpoint concerning complete/incomplete obstruction (passage of stools) cannot be analysed as no data are collected on this point.

- The definitions of “Treatment Completed subject”, “Study Completed subject” and “Drop-out” (see section 7.1) have been readjusted.

- In the protocol, the mentioning of “caregiver” in the first secondary objective as well as the QOL analysis, is represented by the health care professional caregiver. Therefore, a clarification is made in this SAP to indicate this fact.

- If the patient evaluation is missing due to his/her inability to complete the QOL questionnaire, then we will replace this missing data by using family caregiver/caregiver assisted evaluation, whichever is available.

9 SUBGROUPS

Some subgroup analyses will be done on primary endpoint using the following baseline characteristics:

- Age (≤65 / >65)
- Gender (Male / Female)
- Time between initial diagnosis and inclusion visit (≤ median / > median)
- Previous intestinal obstruction (No / Yes)
- Time between current intestinal obstruction and inclusion visit (≤ median / > median)
- Malignancy origin causing intestinal obstruction (Digestive / Ovarian / Other)
- Presence of ascites (No / Yes)
- Body Mass Index (kg/m²) in classes (< 25 / ≥ 25)

10 INTERIM ANALYSIS

No interim analysis will be performed for this study.

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11 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

11.1 Hardware

The statistical analysis will be performed using Windows 7 professional and a 64-bit operating system.

11.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.3 or above. All outputs will be edited in Microsoft Word Format.

11.3 Validation of programs

Validations will be done according to the procedure of the CRO ITEC Services.

The program reviewer is responsible for reviewing each project program and output provided to the sponsor. 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 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 statistical 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 the statistician in charge of the study need to complete and sign a validation checklist, to indicate that they have successfully performed all of their responsibilities.

Copies of the internal quality control forms produced for the validation process and the sign-off forms will be provided to the sponsor to support the validation if asked.

11.4 Restitution of the programs

All programs (including Macros and SAS® analysis datasets) producing the tables, listings and statistical output along with associated logs will be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised and the clinical study report is approved.

12 REFERENCES

13 STATISTICAL APPENDICES

APPENDIX A: Derived data (DD)

The derived data are variables which are calculated from the raw data in the eCRF and not included in the database (e.g.: age, total score, duration, summary value from repeated observations, follow-up duration, study drug exposure, study drug cumulative dose, etc.).

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

(1) ***Follow-up duration (days)***
(Last visit date recorded - date of visit 1+ 1)

(2) ***Time between inclusion and early withdrawal (days)***
(Date of withdrawal - date of visit 1+ 1) only for patients who prematurely withdrew

(3) ***Age at inclusion (years)***
Year of inclusion visit - Year of birth

(4) ***Time between initial diagnosis and inclusion visit (months)***
(Date of inclusion visit - Date of initial diagnosis + 1)/ 30.4375

(5) ***Time between current intestinal obstruction and inclusion visit (days)***
(Date of inclusion visit – Start date of current intestinal obstruction + 1)

(6) ***Body Mass Index (kg/m²)***
(Weight in kg) / (Height in m)²

(7) ***Medical and surgical history ongoing at inclusion***
Any medical or surgical event still continuing at inclusion and without resolution date or a resolution date ≥ date of inclusion visit

(8) ***Medical and surgical history ended at time of inclusion***
Any medical or surgical event not continuing at inclusion and/or with a reported resolution date < date of inclusion visit

(9) ***Concomitant medication / concomitant non drug therapies / Concomitant medications for Inoperable Malignant Intestinal Obstructions / Nutrition procedure/ started prior inclusion***
Any medication or procedure with (start date < date of inclusion visit or started prior to study early is ticked) and (end date ≥ date of inclusion visit or continuing at the end of the study is ticked)

(10) ***Edmonton Symptom Assessment System (ESAS) total symptom distress score***
Represents the sum of all ESAS symptoms (→ from 0 to 100)
Total symptom distress score will be calculated only when all of the 9th dimensions (except the optional one) will be reported. If one of the dimension is missing then the total distress score will be considered as missing.

(11) ***Absolute change from baseline***
Absolute change from baseline will be calculated as: post baseline assessment at Dx – baseline assessment at D0.

(12) ***Percentage change from baseline (%)***
Percentage change from baseline will be calculated as: [post baseline assessment at Dx – baseline assessment at D0] * 100 %/ baseline assessment at D0 * 100).

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APPENDIX B: Algorithm to categorize patient in subgroup of nasogastric tube at baseline

NGT group	Algorithm
Patient with NGT at baseline	If NGT was inserted before or at baseline and is ongoing at baseline: Date tube inserted ≤ date of baseline visit < date tube removed
Patient without NGT at baseline	If "Was a Nasogastric tube inserted" is ticked "No"
	If NGT was inserted and removed before or at baseline: date tube inserted ≤ date tube removed ≤ Date of baseline
	If NGT was inserted after baseline: Date of baseline < date tube inserted

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