REPORTING AND ANALYSIS PLAN

CALM-NET: A PHASE IV, MULTICENTRE, OPEN LABEL, SINGLE GROUP EXPLORATORY STUDY TO ASSESS THE CLINICAL VALUE OF ENUMERATION OF CIRCULATING TUMOUR CELLS (CTCs) TO PREDICT CLINICAL SYMPTOMATIC RESPONSE AND PROGRESSION FREE SURVIVAL IN PATIENTS RECEIVING DEEP SUBCUTANEOUS ADMINISTRATIONS OF SOMATULINE® (LANREOTIDE) AUTOGEL® TO TREAT THE SYMPTOMS OF FUNCTIONING MIDGUT NEUROENDOCRINE TUMOURS (NET).

Protocol version and date: Final 6.0 – 27 October 2015

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Draft – Version 0.1	23-JUL-2014
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STUDY NUMBER:	A-97-52030-270
EUDRACT NUMBER	2013-002194-22
PROTOCOL TITLE:	**CALM-NET:** A Phase IV, Multicentre, Open label, Single Group Exploratory Study to Assess the Clinical Value of Enumeration of Circulating Tumour Cells (CTCs) to Predict Clinical Symptomatic Response and Progression Free Survival in Patients receiving Deep Subcutaneous Administrations of Somatuline® (lanreotide) Autogel® to treat the Symptoms of Functioning Midgut NeuroEndocrine Tumours (NET).
RAP VERSION:	Final version 1.0
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Further to your review and agreement to the Reporting and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Reporting and Analysis Plan version became the Final Reporting and Analysis Plan

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
CgA	Chromogranin A
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
CTCs	Circulating Tumour Cells
FITC	Fluorescein Isothiocyanate
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory activities
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NET	Neuroendocrine Tumour
OR	Odds Ratio
PD	Progression Disease
PE	Phycoerythrin
PFS	Progression free survival
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
QoL	Quality of Life
RECIST	Response Evaluation Criteria Solid Tumours
ROC	Receiver Operating Characteristic
SAE	Serious adverse events
SD	Stable Disease
SOC	System Organ Class
SSA	Somatostatin Analogue
SSTR	Somatostatin Receptor

TEAE	Treatment Emergent Adverse Events
ULN	Upper Limit of Normal
5-HIAA	5-Hydroxyindoleacetic acid

1. INFORMATION TAKEN FROM THE PROTOCOL

1.1. Study objectives

1.1.1. Primary objective

To assess the clinical value of enumeration of circulating tumour cells (CTCs) to predict the clinical symptomatic response in subjects receiving Somatuline Autogel. Subjects will provide 24 hour symptom frequency and severity on a daily basis electronically for the first 16 weeks of the study and subsequently, on days 11 to 17 of each subsequent injection interval for the remainder of the study duration. After the final study drug injection at week 49, subjects will provide 24 hour symptom frequency and severity on a daily basis on days 11 to 28. Symptom frequency and severity will be recorded electronically after enrolment for the 7 days preceding the first study treatment. Severity will be classed as mild, moderate and severe for flushing only.

1.1.2. Exploratory Primary objective

To assess the clinical value of enumeration of CTCs to describe progression free survival (PFS) in subjects receiving Somatuline Autogel.

1.1.3. Secondary objectives

To assess the effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in subjects with a functioning Neuroendocrine Tumour (NET).

To assess the effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-G.I.NET 21 and the EORTC QLQ-C30. The questionnaires will be conducted at weeks 1, 13, 25 and 53.

Assessment of PFS at one year. Subjects will undergo a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan at screening, week 25 and week 53 within their local hospital Trust. Progression will be assessed using the Response Evaluation Criteria Solid Tumours (RECIST) criteria.

1.1.4. Exploratory Secondary objectives

To assess the effect of Somatuline Autogel on plasma Chromogranin A (CgA), plasma and urine 5-hydroxyindoleacetic acid (5-HIAA) and neurokinin A, and whether these biomarkers correlate with CTC presence.

To assess whether urinary 5-HIAA and plasma 5-HIAA levels are correlated.

To evaluate the presence of somatostatin receptor (SSTR) subtypes 2 and 5.

1.2. Study design

This is a prospective, pilot, multicentre, open label, single group phase IV study which will be conducted across 14 sites in the United Kingdom.

Eligible subjects will be asked to provide written informed consent for their participation in this study. Subjects who have provided written informed consent will receive Somatuline Autogel injections for a period of one year. Subjects will initially receive Somatuline Autogel 120 mg injections every 28 days for the first 3 injections. Subjects's symptoms will be assessed after three injections, and the dose will be titrated according to clinical judgement for the remaining course of the study.

During the course of the study, 15 clinic visits will be done. Study treatment will be administered at Visit 2 and then at each visit every 4 weeks.

Visit	1 (Screening)	2 (Baseline)	3	4	5	6	7	8	9	10	11	12	13	14	15 (End of study)
Weeks following screening		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**

1.2.1. Study population

Approximately 50 subjects (either sex), who have received a pathological diagnosis of functioning midgut G1 or G2 NET and in the medical opinion of their practitioner will require medical treatment with a somatostatin analogue (SSA) for tumour symptom control will be eligible for this study.

1.2.1.1. Inclusion criteria

Each subject must meet the following criteria:

- 1- Provision of written informed consent prior to any study related procedures,
- 2- Subjects (either sex) must be 18 years or older,
- 3 (after amendment 2) - Subjects must be suffering from symptoms of diarrhoea and/or flushing at the time of study enrolment
- 4 (after amendment 2) / 3 (before amendment 2) - Subjects must have a documented diagnosis of a functioning midgut NET,
- 5 (after amendment 2) / 4 (before amendment 2) - In order to avoid subjects with rapidly progressing tumours, only subjects with well or moderately differentiated tumours and with a Ki67 proliferation index of <20% will be recruited,
- 6 (after amendment 2) - The clinically appropriate treatment for the subject must be therapy with a somatostatin analogue,
- 5 (before amendment 2) - The clinically appropriate treatment for the subject must primarily be monotherapy with a somatostatin analogue,
- 7 (after amendment 2) / 6 (before amendment 2) - Subjects must have had either a positive somatostatin receptor scintigraphy result or a positive 68Gallium-DOTATATE PET imaging result,
- 7 (before amendment) - Subjects must have a documented urinary or plasma 5-HIAA result within the year prior to study entry which is above the laboratory reference range.

1.2.1.2. Exclusion criteria

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

- 1 - Is at risk of pregnancy or is breast feeding, unless treatment with Somatuline Autogel is clearly needed (as determined by the clinician),
- 2 - Is in the opinion of the investigator, unable to comply fully with the protocol and the study instructions, or present any concomitant condition which could compromise the objectives of the study and/or preclude the protocol-defined procedures (e.g. severe medical conditions, brain metastases, psychiatric disorders, active or uncontrolled infection, known pituitary disease),
- 3 - Has been treated with any other unlicensed drug within the last 30 days before study entry or will require a concurrent treatment with any other experimental drugs or treatments,
- 4A (only at V1) - Has been treated with a somatostatin analogue prior to study entry, unless a washout period of at least 2 weeks for subcutaneous octreotide, or at least 6 weeks for a single dose of long acting somatostatin analogue is planned,
- 4B (only at V2) - Has been treated with a somatostatin analogue prior to study entry, unless a washout period of at least 2 weeks for subcutaneous octreotide, or at least 6 weeks for a single dose of long acting somatostatin analogue has occurred,
- 5 (before amendment 2) - Requires medical treatment for the symptoms of the NET other than primarily monotherapy with a somatostatin analogue,
- 6 (before amendment 2) / 5 (after amendment 2) - Has received interferon, chemotherapy, chemoembolisation or radionuclide therapy within 3 months prior to study entry,
- 7 (before amendment 2) / 6 (after amendment 2) - Has a history of hypersensitivity to drugs with a similar chemical structure,
- 8 (before amendment 2) / 7 (after amendment 2) - Females of childbearing potential must be using oral, double barrier or injectable contraception. Non childbearing potential is defined as post-menopause for at least 1 year, surgical sterilisation or hysterectomy at least three months before the start of the study,
- 9 (before amendment 2) / 8 (after amendment 2) - Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subjects' safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.

1.2.1.3. Washout criteria

Any subjects who have previously received either subcutaneous octreotide or one injection of a long acting somatostatin analogue will also be considered for this study following a washout period of 2 weeks after the last subcutaneous octreotide injection or a 6 week washout period after a single long acting somatostatin analogue injection.

Subjects who have already been on a regimen of long or short acting somatostatin analogue treatment prior to surgery with debulking or curative intent may still be included in the study. These subjects may have received one injection of a long acting somatostatin analogue or subcutaneous octreotide post surgery and must be willing to observe the relevant washout periods documented above.

1.2.2. Study exposure

The overall duration of the study will be approximately 33 months, which is inclusive of an approximate recruitment period of 21 months and a 12 month treatment period. The study will be considered to have started when the first subject has provided signed informed consent to participate in the study. The study will be considered to have finished after the last subject has completed the last treatment period in the study.

1.3. Methods and procedures

1.3.1. Subject identification and allocation to study treatment

All subjects will be automatically allocated a unique subject number when an enrolment visit is created in the Interactive Voice Response System (IVRS). In order to maintain confidentiality, this number in conjunction with the subjects' initials will be used to identify the subjects study data.

As this is an open label, single arm study, no randomisation procedures apply.

1.3.2. Subjects assessments

Methods for derivation of calculated variables are detailed in Section 3.2.11.

1.3.2.1. Efficacy assessments

- **CTCs enumeration**

  Subjects will have blood (10 mL) taken for CTC enumeration at weeks 1 (baseline), 5, 17, 25, and 53. CTC enumeration will be assessed as a continuous variable.

  Subjects with at least a CTC enumeration > 0 in either or both samples will be considered as subjects with CTC presence. CTC presence will be assessed as a qualitative variable (Yes; No).

- **Symptoms frequency (diarrhoea and flushing) and severity (flushing)**

  Episodes of diarrhoea and flushing will be monitored throughout the study by the subject. Subjects will record their symptoms by telephoning the IVRS.

  Symptom frequency and severity will be provided after enrolment for the 7 days preceding the first study treatment (visit 2). For subjects who require a washout period, these 7 days preceding the first study treatment will be during the washout period.

  Subjects who require a washout period due to previous treatment with a somatostatin analogue prior to study entry will require a search of their medical notes to identify NET symptoms upon diagnosis and during prior somatostatin analogue treatment.

  Reporting of 24 hour symptom frequency for diarrhoea and flushing will be made on a daily basis for the first 16 weeks of the study; during this period severity of flushing episodes only will be recorded. Subsequently, subjects will provide 24 hour symptom frequency (diarrhoea and flushing) and severity (flushing only) on days 11 to 17 of each subsequent injection interval until week 49. After the final study drug injection at week 49, subjects will provide 24 hour symptom frequency and severity on a daily basis on days 11 to 28.

Symptom frequency and severity will be recorded by answering pre-determined questions using IVRS:

(1) How many times have you had diarrhoea in the last 24 hours?

(2) How many times have you had flushing events in the last 24 hours?

(3) Overall, how would you rate your flushing events in the last 24 hours? Please give an average rating if more than one flushing event occurred.

Flushing symptom severity will be recorded using a 3 point scoring system: 1.Mild, 2.Moderate and 3.Severe.

Symptom frequency (average number of episodes) and severity (worst and mode) will be calculated on available data:

- at baseline (on the 7 days preceding the first study treatment),
- from visit 2 to visit 5 (on daily basis on day 1 to day before next injection),
- from visit 6 to visit 14 (on daily basis on days 11 to 17)
- at visit 14 (on daily basis on days 11 to 28)

Average number of episodes of diarrhoea and average number of episodes of flushing will be assessed as quantitative variables

Worst severity and mode severity (value that appears the most frequently) of flushing will be assessed as a qualitative variables (Mild; Moderate; Severe)

- **Clinical symptomatic response**

Clinical symptomatic response will be based on 24 hour symptom frequency and severity.

Subject will be considered to have a clinical symptomatic response, between baseline (on the 7 days preceding the first study treatment injection) and last period (on days 11 to 17 after last injection or after theoretical injection if the subject performed the last visit without injection), if:

- the average of number of episodes of diarrhoea decreases by at least 50%,
- or the average of number of episodes of flushing decreases by at least 50%,
- or the mode severity decreases by at least one level.

Clinical symptomatic response will be assessed as a qualitative variable (Yes; No).

- **CT/MRI Scan**

Subjects will undergo a CT or MRI scan at screening, weeks 25 and 53 within their local hospitals. Scans performed within the 6 weeks prior to the screening visit will not need to be repeated. RECIST review from this scan would be sufficient.

To assess PFS at the end of study, progression will be assessed by the investigator using the RECIST criteria version 1.1.

The time point response at week 25 and at week 53 will be assessed as a qualitative and ordinal variable: Complete response (CR), Partial response (PR), Stable disease (SD), Progressive disease (PD) and Non evaluable (NE).

The best overall response to study treatment is the highest time point response achieved by the subject and will be assessed as a qualitative variable (CR; PR; SD; PD; NE).

PFS and PFS time will be assessed.

- **Quality of life (QoL)**

  Subjects will have to complete QoL questionnaires using the EORTC QLQ-G.I.NET 21 and the EORTC QLQ-C30 questionnaires to assess the effect of Somatuline Autogel treatment on QoL. The questionnaires will be administered at weeks 1 (baseline), 13, 25 and 53.

  Scores and subscores of EORTC QLQ-G.I.NET 21 and EORTC QLQ-C30 will be calculated and assessed as continuous variables.

- **Urine 5-HIAA and plasma 5-HIAA Samples**

  Subjects will be required to provide 24 hour urine samples for 5-HIAA analyses. A 5-HIAA test is a urine test that measures the amount of 5-HIAA (a breakdown product of a hormone called serotonin) that is present in the urine.

  A fasting blood sample of 7.5 mL will be drawn to complete plasma 5-HIAA analysis.

  Urine and blood samples will be collected from subjects at weeks 1 (baseline), 5, 17, 25 and 53 weeks. Urine 5-HIAA (µmol/day) and plasma 5-HIAA (nmol/L) will be assessed as continuous variables.

- **Chromogranin A (CgA) and neurokinin A**

  A total blood sample of 7.5 mL will be drawn to complete CgA and neurokinin A analyses. Blood samples will be drawn at weeks 1 (baseline), 5, 17, 25 and 53 weeks. CgA (µg/L and in upper limit of normal [ULN]) and neurokinin A (pg/mL) will be assessed as continuous variables.

- **SSTR 2 and SSTR 5**

  Samples drawn for CTC enumeration for weeks 1, 5, 25 and 53 will also be utilised for SSTR subtype 2 profiling. SSTR subtype 2 will be assessed semi-quantitatively using an immunofluorescent marker specifically directed towards the SSTR2. A Fluorescein Isothiocyanate (FITC) or Phycoerythrin (PE) labelled rabbit monoclonal antibody validated for its specificity for these receptor subtypes will be used for this purpose.

  An additional 10 mL of blood will be drawn at weeks 1, 5, 25 and 53 for SSTR5 profiling. SSTR subtype 5 will be assessed semi-quantitatively using an immunofluorescent marker specifically directed towards the SSTR5. A FITC or PE labelled rabbit monoclonal antibody validated for its specificity for these receptor subtypes will be used for this purpose.

  Samples of previous biopsies or surgical excisions of either primary tumours or liver metastases will be utilised for SSTR subtype 2 and 5 profiling where available using the above methods. Similarly, any biopsies or surgical excisions of either primary tumours or liver metastases conducted during the course of the study according to clinical need will be utilised for SSTR subtype 2 and 5 profiling using the above methods. Samples of previous biopsies or surgical excisions of liver metastases conducted either prior to the study or if clinically required during the study will also be utilised to investigate the genomic profile of this tissue.

Subjects with a SSTR2 > 0 will be considered as subjects with SSTR2 presence. SSTR2 presence will be assessed as a qualitative variable (Yes; No).

Subjects with a SSTR5 > 0 will be considered as subjects with SSTR5 presence. SSTR5 presence will be assessed as a qualitative variable (Yes; No).

For CTC enumeration, Urine 5-HIAA and plasma 5-HIAA Samples, CgA and neurokinin A, all clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor's clinical monitor (or his/her designated representative), or until the abnormality is explained by an appropriate diagnosis.

1.3.2.2. Safety assessments

- **AEs**

  Adverse Events (AEs) will be monitored from the time that the subject gives informed consent to the time when the subjects' participation in the study is considered to have ended. AEs will be elicited by direct, non-leading questioning or by spontaneous reports.

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

  AEs will be coded according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term (PT) and primary system organ class (SOC).

- **Deaths**

  A death report form will be completed including the primary reason for death (Disease progression; AE; Other).

- **Vital signs**

  Systolic and diastolic blood pressure (mmHg) and heart rate (bpm) (supine after resting for 3 minutes or standing after 1 minute), will be recorded at each study visit. Height (cm) and weight (kg) should be measured at weeks 1 (baseline) and 53.

- **Concomitant medications, Concomitant medications for NET disease / symptoms, Concomitant non-drug therapies and Concomitant surgical procedures**

1.3.2.3. Other assessments

The other assessments will be the following:

- Demography and characteristics at screening / baseline:
  - Age (years and in classes: ≤ 65; > 65) – calculated,
  - Sex (Male; Female),

  - Race (Asian; Black/African American; Caucasian/White; Native Hawaiian/Other Pacific Islander, American Indian/Alaska Native, Multiple),
  - Body mass index (BMI) at baseline (kg/m² and in classes: <18.5; ≥ 18.5 and < 25; ≥ 25 and < 30; ≥ 30) – calculated

- Significant medical or surgical history (excluding the condition(s) of NET), Prior Surgical Procedures for NET, Prior medications, Prior non–drug therapies and Prior medications for NET disease / symptoms

- Primary Disease Diagnosis / Biopsy
  - Time since the NET diagnosis (years and in classes: < 3; ≥ 3) – calculated
  - Location of primary tumour (Jejunum; lleum; Appendix; Second part of the duodenum; Ascending colon, right colon; Transverse colon; Caecum; Unknown; Other)
  - The NET is a functioning NET (Yes; No)
  - Proliferation Index Ki67 (% - in classes: ≤2%; >2% and ≤5%; >5% and <10%; ≥10%)
  - Result obtained is positive for somatostatin receptor scintigraphy and/or 68Gallium-DOTATATE PET imaging (Yes; No)

- TNM staging
  - T-Primary Tumour (TX; T0; T1 [T1 or T1a or T1b]; T2; T3; T4)
  - N-Regional lymph nodes metastasis (NX; N0; N1)
  - M-Distant metastasis (MX; M0; M1)
  - ENETS Staging (Stage 0; Stage I [Stage I or Stage Ia or Stage Ib]; Stage IIa; Stage IIb; Stage IIIa; Stage IIIb; Stage IV and in 5 classes: Stage 0; Stage I; Stage II [Stage IIa or Stage IIb]; Stage III [Stage IIIa or Stage IIIb]; Stage IV)
- Urine Pregnancy Test at screening and baseline visits
  - Urine pregnancy test performed (Yes; No; Not applicable)
    - If Yes, Result (Positive; Negative)

- Diarrhoea frequency, Flushing frequency and severity at diagnosis and during somatostatin analogue treatment prior to the washout (only for subjects with a washout period)
  - Diarrhoea (Yes; No; if Yes, number of episodes per day)
  - Flushing (Yes; No; if Yes, number of episodes per day and intensity [mild; moderate; severe])

1.3.2.4. Withdrawal / discontinuation from the study

The date of early withdrawal and the primary reason for early withdrawal will be recorded (adverse event, protocol violation, consent withdrawn, lost-to follow-up, disease progression, other).

In accordance with the Declaration of Helsinki (in accordance with the applicable UK's acceptance), each subject is free to withdraw from the study at any time.

For subjects who have PD whilst participating in this study, the treating physician will make a clinical decision to continue the subject on the trial or withdraw the subject from the clinical trial. Justification would be recorded on the electronic-Case Report Form and subjects' notes. Subjects who have PD and do continue in the clinical trial will continue with all study procedures, including administration of investigational medicinal product.

1.3.2.5. Compliance

Compliance assessments will be the following:

- Injection (subcutaneous) of Somatuline Autogel performed (Yes; No) for each visit,
- 120 mg Dose Administered (Yes; No) for visits 2 to 4,
- Dose administered (60 mg; 90 mg; 120 mg) for visits 5 to 14,
- Time between each drug intake (days and in classes: < 28; 28; > 28) – calculated.

1.3.3. Schedule of assessments

Table 1: Schedule of Assessments

Visit	Screening period	Washout Period(=)	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ early withdrawal
Screening Period																
Washout Period(=)		**2 to 6 weeks**														
Weeks following screening **			**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Informed Consent	X															
Pregnancy Testing (Urine)	X		X(a)													
Eligibility Criteria Check	X															
Samples of ***previous*** liver biopsy or surgical excision of tumour for storage with report (b).			X													
Samples of ***previous*** primary tumour biopsy or surgical excision for storage with report (b)			X													
Samples of liver biopsy or surgical excision of tumour for storage with report ***during*** study (b).			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Samples of primary tumour biopsy or surgical excision for storage with report ***during*** study (b)			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic Data	X															
Medical History	X															
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height/Weight			X													X
WHO 2010/TNM status	X															
CT/MRI scan with RECIST	X(c)								X							X
Review subjects' notes for NET symptoms at diagnosis and during prior somatostatin analogue treatment (d)	X															
Subject NET symptom reporting (7 days) (e)	X															

Visit	Screening period	Washout Period(=)	2	3	4	5	6	7	8	9	10	11	12	13	14	15/ early withdrawal
Screening Period																
Washout Period(=)		**2 to 6 weeks**														
Weeks following screening **			**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Subject NET symptom reporting			*Daily subject NET symptom reporting IVRS*				*Once monthly (days 11–17) subject NET symptom reporting IVRS*								*Days 11–28 subject NET symptom reporting IVRS*	
Cell free DNA analyses blood sample			X						X							X
CTC blood sample			X	X			X		X							X
CTC genomic profiling blood sample (f)			X						X							X
CTC blood sample for SSTR2 profile (f)			X	X					X							X
CTC blood sample for SSTR5 profile (g)			X	X					X							X
5-HIAA blood sample			X	X			X		X							X
5-HIAA 24 hour urine sample			X	X			X		X							X
Chromogranin A blood sample			X	X			X		X							X
Neurokinin A blood sample (h)			X	X			X		X							X
Liver genomic profiling (i)			X						X							X
Subject Questionnaires of Life			X			X			X							X
Clinician review of subject reported NET symptoms			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Titration review						X	Dose titration decision at each visit based upon clinician review of subject reported NET symptoms									
Administration of investigational medicinal product (120 mg) (j)			X(j)	X	X	X(k)	Administration of 60mg, 90mg or 120mg at each visit after clinician review of subject reported NET symptoms									
Administration of investigational medicinal product (90mg) (j)						X(k)										
Administration of investigational medicinal product (60mg) (j)						X(k)										
Concomitant medication /Non drug therapies/surgical procedures check	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Reporting	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Case Report Form Completion	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

(=) Can run alongside screening visits (only if required)
(**) +/- 3 days
(a) Only for subjects who have had a delay due to CT/MRI scan and/or wash out period
(b) Request sample for storage and report at the UCL Cancer Institute
(c) To be performed only if a CT/MRI scan is not available from within the 6 weeks prior to study entry
(d) Only wash out subjects
(e) Subject symptom reporting for seven days before first dosage of Somatuline Autogel
(f) Same blood sample as that taken for CTC enumeration
(g) Separate blood sample to CTC enumeration sample
(h) Same blood sample as that taken for chromogranin A
(i) Performed using liver samples available prior to study or if clinically required during study (same sample as used for SSTR profiling)
(j) Once all clinical procedures have been completed
(k) First dosage following titration review – 60mg, 90mg or 120mg

If a subject misses a blood sampling visit the sampling may be performed at the next visit

1.3.4. Planned sample size

A sample size of 50 subjects has been chosen for this exploratory study based on practical considerations with the knowledge that there was some statistical power should the relationship between those with measureable CTCs and those without measureable CTCs be a clear one. 50 subjects will give an 80% statistical power to be able to detect a difference in clinical response rates of around 40% (e.g. 55% in subjects with no measureable CTCs versus 15% in subjects with measureable CTCs).

2. SUBJECT POPULATIONS (ANALYSIS SETS)

2.1. Screened population

The screened population is defined as all subjects fully informed about the study who have given written informed consent.

2.2. Enrolled population

The enrolled population is defined as all screened subjects included at the end of the baseline visit.

2.3. Efficacy

2.3.1. Intention-to-treat population

The Intention-to-treat (ITT) population is defined as all enrolled subjects who received at least one injection of study medication.

2.3.2. Per Protocol population

The Per Protocol (PP) population is defined as all subjects in the ITT population for whom no major protocol violations/deviations occurred during the trial.

Definition of protocol deviations will be managed in a separate document.

The final status of deviations (minor/major) will be finalized during a blind data review meeting.

Listings of subjects regarding inclusion in each population (i.e. satisfying the population definition) and associated data will be reviewed by the study team. Data will be excluded from the PP population on a subject basis and not on a visit basis. Reasons for exclusion from PP population will be presented in a summary table.

2.4. Safety

The safety population is defined as all enrolled subjects who received at least one injection of study medication

2.5. Primary populations

The primary analysis based on the primary efficacy endpoint will be performed on the ITT population. In addition a supportive analysis will be performed on the PP population.

The exploratory primary efficacy endpoint and the secondary efficacy endpoints will be analysed on the ITT population and on the PP population if there is a difference of at least 10% between both populations.

The analyses of safety data will be performed based on the safety population.

For all demographic data and other parameters at baseline, if there is a difference of at least 10% between ITT population and PP population, these tables will be repeated on the PP population.

3. STATISTICAL METHODS

3.1. Statistical analysis strategy

All statistical analyses will be performed by the biostatistics unit of LINCOLN managed by the sponsor, using the Statistical Analysis System® (SAS®) software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The statistical analyses will be performed in accordance with International Conference on Harmonisation E9 guideline.

3.1.1. Primary efficacy endpoint

The primary efficacy endpoint is the assessment of the clinical value of enumerating CTCs to predict clinical symptomatic response in subjects receiving Somatuline Autogel.

3.1.2. Exploratory primary efficacy endpoint

The exploratory primary efficacy endpoint is the assessment of the clinical value of enumerations of CTCs to describe PFS in subjects receiving Somatuline Autogel.

3.1.3. Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- Symptoms frequency of diarrhoea and flushing, severity of flushing,
- QoL domain scores (via the EORTC QLQ-G.I.NET 21 and EORTC QLQ-C30),
- PFS at end of study

3.1.4. Exploratory Secondary efficacy endpoint(s)

The exploratory secondary efficacy endpoints are:

- Plasma CgA, urinary and plasma 5-HIAA and plasma neurokinin A levels,
- Correlation between urinary and plasma 5-HIAA levels,
- The presence of SSTR2 and SSTR5.

3.1.5. Safety endpoint(s)

The safety endpoints are:

- AEs,
- Deaths,
- Vital signs,
- Concomitant medications,
- Concomitant medications for NET disease/symptoms,
- Concomitant non-drug therapies,
- Concomitant surgical procedures.

3.1.6. Multiplicity

No adjustment for multiplicity will be performed.

3.1.7. Significance testing and estimation

As this is an exploratory study, statistical testing will only be carried out for exploratory purposes. Unless otherwise stated, testing will be performed two-sided with a type I error rate set at 5%.

Quantitative variables will be summarised in statistical tables indicating the number of non missing observations (n), the number of missing data, the mean and standard deviation, the median, the quartiles (Q1 and Q3), the minimum and maximum. 95% confidence intervals (CI) of the mean and of the median will be presented.

- 95% CI of the mean will be calculated as follows:

$$\text{Lower Limit} = \bar{x} - z \times \frac{s}{\sqrt{n}} \qquad \text{Upper limit} = \bar{x} + z \times \frac{s}{\sqrt{n}}$$

with n = number of non-missing observations $\bar{x}$ = mean
z = 1.96 for two-sided 95%CI s = standard deviation

- 95% CI of the median will be calculated using option CIPCTLDF in the PROC UNIVARIATE:

```
PROC UNIVARIATE data=… CIPCTLDF alpha=0.05;
VAR variable;
RUN;
```

Qualitative variables will be summarised in statistical tables indicating the number of non missing observations (n), frequency and percentage of each modality. Where appropriate, 95% CI of the proportion will be presented.

- 95% CI of a proportion will be calculated using the method of Wilson's score without continuity correction [(1)]:

$$\text{Lower Limit} = \frac{2np + z^2 - z\sqrt{z^2 + 4npq}}{2\left(n + z^2\right)} \qquad \text{Upper limit} = \frac{2np + z^2 + z\sqrt{z^2 + 4npq}}{2\left(n + z^2\right)}$$

with n = number of non-missing observations
p = percentage q = 1 – p z = 1.96 for two-sided 95% CI

For all parameters, the number of missing values will also be reported in the tables, but they will not be counted for the percentage calculation (qualitative data).

3.2. Analysis methods

3.2.1. Efficacy

3.2.1.1. Primary efficacy analysis

The primary efficacy analysis of the clinical symptomatic response and its relationship with CTC presence at baseline will be performed on the ITT population (cf. Section 3.2.11 for derived CTC presence and clinical symptomatic response).

A supportive analysis will be performed on the PP population.

Clinical symptomatic response will be described according to CTC presence at baseline and overall using descriptive qualitative statistics including 95% CIs.

Clinical symptomatic response will also be described according to CTC presence at baseline and overall for each category of concomitant medications potentially impacting symptoms taken (Full, Partial, No - cf Section 3.2.11 for the derivation) using descriptive qualitative statistics including 95% CIs.

To assess the relationship between CTC presence at baseline and clinical symptomatic response, a logistic regression with clinical symptomatic response as dependent variable and CTC presence at baseline as explanatory variable (reference level = Yes [presence]) will be used. The presence of washout period (reference level = No [subjects without washout period]) will be taken into account as explanatory variable, if there is at least 20% of subjects with a washout period. Results will be presented in terms of odds ratio (OR) associated with 95% CI and p-value for CTC presence.

The relationship between CTC presence at baseline and clinical symptomatic response will also be assessed adjusted for the presence of other potentially influential subject characteristics using multivariate logistic regression. These subject characteristics are presented in the Table 2.

The potentially influential variables will be selected initially on the basis of univariate logistic regressions. Only variables with a $p<0.2$ will be retained for the next step.

In a second step, each pre-selected characteristic will be tested with the other retained characteristics at the 0.001 level to confirm that there is no strong link between them. The association between two categorical or binary variables will be tested using
Chi-square or Fisher's exact test. If independence is not met for two characteristics ($p<0.001$), the choice will be made according to clinical and statistical relevance.

Using an appropriate stepwise procedure (entry of variable at a 20% significance level and retention of variable at a 5%-level), a final multivariate logistic regression model will be derived that includes CTC presence at baseline along with any still influential characteristics. From the final model the odds ratio for the effect of CTC presence at baseline on response, adjusted for any influential characteristics will be estimated and the associated 95% confidence interval calculated.

```
PROC LOGISTIC data=Tab;
Class CTCpresence FactorQuali1
MODEL Response = CTCpresence FactorQuali1/ include=1 selection=stepwise slstay=0.05 slentry=0.2;
run;
```

Table 2: List of variables tested in the logistic regression model

Factors	*Coding*
DEMOGRAPHICS	
Age (years)	1 if ≤ 65 years (reference) 2 if > 65 years
Sex	1 if Male (reference) 2 if Female
BMI (kg/m²)	1 if < 18.5 2 if >= 18.5 - < 25 (reference) 3 if >= 25 - < 30 4 if >= 30
PRIMARY DISEASE DIAGNOSIS / BIOPSY	
Time since the NET diagnosis (months)	1 if < 3 years (reference) 2 if ≥ 3 years
Location of primary tumour	1 if Jejunum (reference) 2 if Ileum 3 if Appendix 4 if Unknown 5 if Other (Second part of the duodenum, ascending colon, right colon, Transverse colon, Caecum, other)
ENETS Staging	1 if Stage 0 (reference) 2 if Stage I (Stage I or Stage Ia or Stage Ib) 3 if Stage II (Stage IIa or Stage IIb) 4 if Stage III (Stage IIIa or Stage IIIb) 5 if Stage IV
Prior medications for NET	0 if No (reference) 1 if Yes
CONCOMITANT TREATMENTS POTENTIALLY IMPACTING THE SYMPTOMS	
Full concomitant medications potentially impacting the symptoms taken	0 if No (Partial concomitant treatment or non concomitant treatment potentially impacting the symptoms - Reference) 1 if Yes

3.2.1.2. Exploratory primary efficacy analysis

The exploratory primary efficacy analysis will be performed on the ITT population and on the PP population if there is a difference of at least 10% between both populations.

Time point response at week 25 and at week 53 will be described by CTC presence at baseline and overall, using descriptive qualitative statistics including 95% CIs.

Best Overall Response will be described by CTC presence at baseline and overall, using descriptive qualitative statistics including 95% CIs (cf. Section 3.2.11 for derived data).

For PFS, event dates are assigned to:

- The first time when progressive disease was noted, or
- Date of death.

In case of progressive disease followed by death, the first event will be considered in the analysis.

The progressive disease date is assigned to the first time at which progressive disease can be declared.

- For progressive disease based on a new lesion, the progressive disease date is the date of the first radiological assessment when the new lesion was detected.

- For progressive disease based on an increase in the sum of the target lesion measurements, the progressive disease date is the date of the last radiological assessment of target lesions that shows the predefined increase in the sum of the target lesion measurements.

Censoring dates are defined in subjects with no progressive disease or death before end of study. In these subjects, the censoring date is defined as the last date on which progression status was 'adequately' assessed. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated by local review:

Table 3: Censoring Rules for PFS

Reason for censoring	Rule
No screening evaluable* assessment	Date of first treatment administration
One or more not evaluable (NE) assessments before progressive disease or death	Date of last evaluable disease assessment before the NE assessment
No progressive disease	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment

* An assessment is considered NE when no imaging/measurement is done at all at a particular time point, or only a subset of lesion measurements are made at the time point. The subject is considered NE at that time point.

PFS time (in months) = [(Date of event – date of first injection of study drug) + 1] / 30.4375

Completely missing tumour data:

When tumour assessment visits are completely missing, FDA Guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" [(3)] states that "events occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate assessment'.

The following table shows the event status for various scenarios with missing data:

Table 4: Event status

Scan Time	W25	W52	Event status
Scenario 1	missing	missing	Censored at screening
Scenario 2	missing	SD	Censored at W52
Scenario 3	SD	SD	Censored at W52
Scenario 4	SD	missing	Censored at W25
Scenario 5	missing	PD	Censored at W25

PFS time will be analysed by CTC presence at baseline and overall using Kaplan-Meier method to obtain the estimates of survival median, Q1 and Q3, the associated 95% CI, survival curves for each group and log-rank test p-value will be provided for group comparison (cf. Section 3.2.11 for derived data).

The syntax with SAS using the LIFETEST procedure will be:

```
Proc lifetest data=… method=km outsurv=t graphics plot=(s);
Time time*cens(1);
Strata CTCpresence;
Run;
```

The Cox Proportional hazard model will be fitted to compute hazard ratios and the corresponding 95% CI with CTC presence at baseline as fixed factors.

The syntax with SAS using the PHREG procedure will be:

```
Proc phreg data=...;
Class CTCpresence;
Model time*cens(1) = CTCpresence / risklimits;
Run;
```

The Cox Proportional hazard model will be also fitted to compute hazard ratios and the corresponding 95% CI with CTC presence at baseline as fixed factors, adjusted for the presence of other potentially influential subject characteristics. These subject characteristics are presented in the Table 2.

The potentially influential variables will be selected initially on the basis of univariate analysis. Only variables with a Wald test $p<0.2$ will be retained for the next step.

In a second step, each pre-selected characteristic will be tested with the other retained characteristics at the 0.001 level to confirm that there is no strong link between them. The association between two categorical or binary variables will be tested using Chi-square or Fisher's exact test. If independence is not met for two characteristics ($p <0.001$), the choice will be made according to clinical and statistical relevance.

Using an appropriate stepwise procedure (entry of variable at a 20% significance level and retention of variable at a 5%-level), a final model will be derived that includes CTC presence at baseline along with any still influential characteristics.

The maximum likelihood estimates of model coefficients (with associated standard error, Wald Chi–square statistic and p-value) will be presented for the final model along with the hazard ratios and 95% CIs.

The check of the proportional hazard assumption will be performed graphically for each categorical or ordinal factor using the LOG of the negative LOG of survival curve.

The syntax with SAS using the PHREG procedure is:

```
Proc phreg data=…;
Class CTCpresence FactorsQuali;
Model time*Cens(1)=CTCpresence FactorsQuali/ include=1 rl selection=stepwise
slstay=0.05 slentry=0.2;
Run;
```

3.2.1.3. Secondary efficacy analyses

The secondary efficacy analyses will be performed on the ITT population and on the PP population if there is a difference of at least 10% between both populations.

- **Description of CTC enumeration over time**

  The CTC enumeration and CTC presence will be described at week 1 (baseline), 5, 17, 25 and 53.

  For CTC enumeration, raw and change from baseline values will be described at each time point by sample (cf. Section 3.2.11 for calculation).

  For CTC presence, raw values will be described at each time point by sample, using descriptive qualitative statistics including 95% CIs. Shift table from baseline will be also described at each time point by sample.

- **Effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in subjects with a functioning NET**

  Symptoms frequency of diarrhoea and flushing (average number of episodes), severity of flushing (worst intensity and mode) will be described at each time point.

  For symptoms frequency of diarrhoea and flushing (average number of episodes), raw and change from baseline values will be described at each time point by CTC presence at baseline and overall, for all subjects, for subjects with a washout period and for subjects without washout period (cf. Section 3.2.11 for calculation).

  For severity of flushing (worst intensity and mode), raw values will be described at each time point by CTC presence at baseline and overall, for all subjects, for subjects with a washout period and for subjects without washout period, using descriptive qualitative statistics including 95% CIs. Shift table from baseline will be also described at each time by CTC presence at baseline and overall, for all subjects, for subjects with a washout period and for subjects without washout period.

- **Effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-G.I.NET 21 and EORTC QLQ-C30**

  The scores and subscores of EORTC QLQ-G.I.NET 21 and EORTC QLQ-C30 will be described at week 1 (baseline), 13, 25 and 53. Raw and change from baseline values will be described at each time point (cf. Section 3.2.11 for calculation).

- **PFS at the end of study**

  PFS rate at the end of study will be estimated by CTC presence and overall at baseline using Kaplan-Meier method (cf. Section 3.2.1.2 for definition of PFS).

3.2.1.4. Exploratory secondary analyses

The exploratory secondary efficacy analyses will be performed on the ITT population.

- **Effect of Somatuline Autogel on plasma CgA, urinary and plasma 5-HIAA and plasma neurokinin A, and whether these biomarkers correlate with CTC presence**

  Plasma CgA, urinary and plasma 5-HIAA and plasma neurokinin A levels will be described at week 1 (baseline), 5, 17, 25 and 53.. Raw and change from baseline values will be described at each time point (cf. Section 3.2.11 for calculation).

  For each biomarker, the correlation with CTC presence will be tested at each time point using analysis of variance. In the event that normality is revealed to be unreasonable, Wilcoxon test will be performed.

- **Correlation between urinary 5-HIAA and plasma 5-HIAA**

  The correlation between urinary and plasma 5-HIAA levels will be tested at each time point using Pearson correlation coefficients, as well as p-values, if the normality of the distribution of parameters (p-value of Shapiro-Wilk test ≥ 5%) can be assumed. In case of strong violation of normality, Spearman coefficients of correlation will be provided.

- **Presence of SSTR subtypes 2 and 5**

  The the presence of SSTR2 and SSTR5 will be described at week 1 (baseline), 5, 25 and 53.

  For presence of SSTR2 and SSTR5 (cf. Section 3.2.11 for calculation), raw values will be described at each time point, using descriptive qualitative statistics including 95% CIs. Shift table from baseline will be also described at each time point.

3.2.2. Safety

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

3.2.2.1. Adverse events

AEs will be coded according to the MedDRA (version 18.0) and will be classified by SOC and PT.

Listings will be presented and sorted by subject id, primary SOC, PT and verbatim text for all AEs recorded during the study.

Listings of serious AEs (SAE), AE leading to study drug discontinuation, drug related AEs and listings of deaths will also be presented.

Treatment Emergent AEs (TEAE) will be flagged (*) in the AEs listing and will be summarised.

A TEAE is defined as any AE that occurs from the first study drug injection until 28 days after the last study drug injection if:

- it was not present prior to receiving the first dose of study drug, or
- it was present prior to receiving the first dose of study drug but the intensity increased during the active phase of the study, or
- it was present prior to receiving the first dose of study drug, the intensity is the same but the drug relationship became related during the active phase of the study.

An overall summary table of all AEs will be presented.

TEAEs will be summarised overall with the number and percentage of subjects with AEs classified by primary SOC, PT (ordered alphabetically). The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for AEs, SAEs, non SAEs, TEAEs leading to study drug discontinuation, TEAE leading the study withdrawal, drug–related TEAE, TEAE leading to drug interruption, TEAEs per decreasing frequency and TEAEs by maximum intensity and causality.

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

In the event of multiple adverse events (corresponding to different PTs) being reported by the same subject, each subject is counted for each intensity level, each causality level or each intensity and causality combined level. That means that the total of subjects for all levels of intensity / causality might be higher than the overall number of subjects with at least one AE.

Note: For intensity*causality combined description, missing causalities are taken into account only in the related level / missing intensities are taken into account only in the severe level

Moreover, the number of deaths and primary reason for death will be described.

3.2.2.2. Laboratory data

All laboratory data (Section 8.3.4 of the protocol) are regarded as efficacy assessments in this study and therefore analyses as part of the efficacy endpoints (See Section 3.2.1).

3.2.2.3. Vital signs

Baseline values will be defined as the last vital signs measurement collected prior to the first injection of study drug i.e. at week 1 (Baseline visit).

Vital signs (systolic and diastolic blood pressure, heart rate, height and weight) will be described for raw values and changes from baseline at each time point for systolic and diastolic blood pressure and heart rate and at weeks 1 and 53 for height and weight.

3.2.3. Missing data and outliers

3.2.3.1. Missing data

Missing data will not be imputed and dropouts will not be replaced.

If a value requires a retest (for laboratory values, vital signs), the closest non–missing reliable value to the scheduled visit is used in the summary tables. An assessment is considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

For adverse events with missing information for the intensity and causality, the value will not be replaced and will be summarized as a separate category.

Rules for missing data for PFS are addressed in Section 3.2.1.2.

Rules for missing data for the clinical symptomatic response and for the frequency and severity of symptoms will be addressed in Section 3.2.11.

Rules for missing data imputation for QoL scores calculation will be addressed in Section 3.2.11.

3.2.3.2. 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 concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase 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 the study inclusion.
- 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 (i.e.: a medication with partial start and stop dates could be considered as prior and concomitant treatment).
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e. for a medication started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing medication will be"≥xx" according to the start and last visit dates).

For partially missing dates for efficacy endpoints derived, adverse event and death, the following imputation rules will be used:

- If the day is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before the first injection of study treatment, then the date of start of study treatment is used.
- If the day and month is missing, but year is known (UN-UN-YYYY), it will be imputed by the 1st of January (01-JAN-YYYY). If this implementation rule produces a date before the first injection of study treatment, then the date of start of study treatment is used.

3.2.3.3. Outliers

Any outlier identified prior to data base lock which is impossible/implausible will be excluded from the analysis.

For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

If any outliers are identified after the database lock, the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.

A search of outliers for the CTC enumeration will be performed before the database lock and actions with the sponsor will be defined during data review meeting.

3.2.4. Subject disposition

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

A summary table will present the number and percentages of subjects enrolled included in each analysis set, overall and by centre.

The reason for subjects' exclusion from each of the analysis set will also be tabulated.

The numbers of subjects who received the study drug, discontinued and completed the study will be tabulated. A subject is considered as having completed the study when "Completed the study" is ticked in the Case Report Form at visit 15 (Week 53). The primary reason for early study withdrawal will be provided (adverse event, protocol violation, consent withdrawn, lost-to follow-up, disease progression, other).

A summary table (and a flow chart) will be performed for each analysis set (Safety population, ITT and PP population) presenting the number and proportion of subjects overall at each visit.

A summary table will present the duration of study drug exposure and the extent of subject exposure in the study (weeks). The length of exposure is defined as the number of days between the date of consent and the last study visit date.

A listing of dates of visit and calculated time interval since the baseline visit (days) will be presented by subject.

3.2.5. 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 overall.

3.2.6. Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by subject.

Descriptive summary statistics will be provided by subgroup (subjects with a washout period versus subjects without washout period) and overall for demographic and baseline characteristics, for the ITT population. It includes assessments as detailed in the Section 1.3.2.3 (Demography and characteristics at screening, , Primary Disease Diagnosis / Biopsy, TNM staging, Urine Pregnancy Test at screening and baseline visits, Diarrhoea frequency, Flushing frequency and severity at diagnosis and during somatostatin analogue treatment prior to the washout (only for subjects with a washout period)).

3.2.7. Medical and surgical history

Significant medical or surgical history will be coded using the MedDRA version 18.0.

Listings will present the PT and verbatim text. The listings will be sorted by subject, primary SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by SOC class and PT for the ITT population.

3.2.8. Prior surgical procedures for NET

Prior surgical procedures will be coded using the MedDRA version 18.0.

Listings will present the PT and verbatim text. The listings will be sorted by subject, primary SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all prior surgical procedures for NET by SOC class and PT for the ITT population.

3.2.9. Compliance

A listing will be presented for drug administration by subject, on the ITT population. Deviations from observed and scheduled times will be presented.

The number of injections will be presented on the ITT population, as well as the number of subjects with a dose of 120 mg throughout the study, those who switched for a dose of 60 mg, those who switched for a dose of 90 mg and those with a combination of 60/90/120 mg dose.

The cumulative dose will be also presented on the ITT population.

The compliance (%) will be calculated as the ratio of the actual number of injections over the planned number of injections, then multiplied by 100 (cf. Section 3.2.11 for calculation).

A summary table of compliance will be presented on the ITT population. Additionally, the number and percentage of subjects with compliance ≤ 80% will be described using descriptive qualitative statistics including 95% CIs.

Descriptive summary statistics will be provided including assessments as detailed in the Section 1.3.2.5 'Compliance' on the ITT Population.

The number and % of subjects who took concomitant treatment potentially impacting the symptoms (Full, Partial, No) will be described using descriptive qualitative statistics including 95% CIs (cf. Section 3.2.11 for derivation).

3.2.10. Prior and concomitant therapies

Descriptive summary statistics will be provided on the ITT population for prior therapies and on the Safety population for concomitant therapies.

<u>Prior and concomitant medications / Prior medications for NET / Concomitant medications for NET disease/symptoms:</u>

Prior and concomitant medications will be coded using WHO-Drug Dictionnary Enhanced B2 format of March 2015. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code.

A concomitant medication will be defined as a medication started prior to the baseline visit date and ongoing at the baseline visit date, or started the day of the baseline visit or after. A prior medication will be defined as a medication started prior to the baseline visit date and stopped prior or the day of the baseline visit date.

Listings containing prior and concomitant medications will be presented for the therapeutic class, preferred name and verbatim text, and will be sorted by centre, subject, chronological start date, therapeutic class, preferred name and verbatim text.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant medications only by therapeutic class and preferred name.

<u>Prior and concomitant non-drug therapies and concomitant surgical procedures:</u>

Prior and concomitant non-drug therapies and concomitant surgical procedures will be coded using MedDRA version 18 and will be classified by PT and SOC.

A concomitant therapy will be defined as a therapy started prior to the baseline visit date and ongoing at the baseline visit date, or started the day of the baseline visit or after. A prior therapy will be defined as a therapy started prior to the baseline visit date and stopped prior or the day of the baseline visit date.

Listings containing prior and concomitant non-drug therapies and concomitant surgical procedures will be presented for the SOC, PT and verbatim text, and will be sorted by centre, subject, chronological start date, SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant non-drug therapies and concomitant surgical procedures only by SOC and PT.

3.2.11. Derived data

The derived data are variables which are calculated from the raw data and not included in the database.

Date of withdrawal

If the subject performed an early withdrawal visit, the date of withdrawal will be equal to the date of this visit. Else the date of withdrawal will be equal to:

- The date of withdrawal consent if the subject withdrew his consent,
- The start date of AE if the subject withdrew for AE,
- The date of death if the subject died,
- The date of withdrawal if the subject withdrew for "Other reason".

Age

Age will be derived as (Date of screening – Date of birth) / 365.25.

The result will be truncated to the largest integer that is less than or equal to the calculated result.

Following classes will be defined: ≤ 65 years, > 65 years.

BMI at baseline

BMI (kg/m²) at baseline will be derived as [Weight (kg) at baseline / (Height (cm) at baseline/ 100)²]

Following classes will be defined:< 18.5 kg/m², ≥ 18.5 - < 25 kg/m², ≥ 25 - < 30 kg/m², ≥ 30 kg/m².

Time since the NET diagnosis

Time since the NET diagnosis (years) will be derived as (Date of screening visit – Date of NET diagnosis +1)/ 365.25

If the day is missing, it will be imputed by '01'.

Following classes will be defined: < 3 years, ≥ 3 years.

Time between each drug intake

Time between each drug intake (days) will be derived as (Date of drug intake at $Visit_t$ – Date of drug intake at $Visit_{t-1}$ +1).

No imputation for partial missing dates will be done.

Following classes will be defined: <28, 28, >28.

Compliance

Compliance (%) will be derived as Actual number of injections / Planned number of injections * 100

Following classes will be defined: ≤ 80%, > 80%.

For medical and surgical history, prior and concomitant medication, prior and concomitant non-drug therapy:

Duration of events (days) will be derived as (Date of stop – date of start or diagnosis) + 1

Type of concomitant medications potentially impacting symptoms

A concomitant medication potentially impacting symptoms will be considered as "Full" if :

- The medication is "ANTIPROPULSIVES", "SOMATOSTATIN AND ANALOGUES" or "OTHER INTESTINAL ANTIINFECTIVES"
- And the medication was started before the start of the last period of symptoms collection (on days 11 to 17 after last injection)
- And the medication was ongoing during the last period of symptoms collection (i.e. ongoing at the end of study or stopped after the end of the last period of symptoms).

A concomitant medication potentially impacting symptoms will be considered as "Partial" if :

- The medication is "ANTIPROPULSIVES", "SOMATOSTATIN AND ANALOGUES" or "OTHER INTESTINAL ANTIINFECTIVES"
- And the medication was not started before the start of the last period of symptoms collection (on days 11 to 17 after last injection) or the medication was not ongoing during the last period of symptoms collection

Any other concomitant medications will be considered as "No".

If a subject meets both the "Full" and the "Partial" definition, the subjects will be classified in the "Full" category.

Changes from baseline

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

Length of subject exposure in the study

Length of subject exposure in the study (weeks) will be calculated as [(Date of last visit attended – informed consent date) +1] / 7.

Duration of study drug exposure

Duration of study drug exposure (weeks) will be calculated as [(Date of last study drug administration – Date of first study drug administration) +1] /7.

Adverse event

Time to onset of AE (days) = AE start date – date of first study drug administration.

Duration of AE (days) = (AE resolution date – AE start date) + 1.

CTC presence

CTC presence will be defined as:

CTC presence = Yes if subject has at least CTC enumeration > 0 in either or both samples

CTC presence = No if subject has CTC enumeration = 0 in both samples

In case of missing value, if both (CTC for sample 1 and sample 2) are missing, the CTC will be considered as missing.

In case of missing value for one CTC and the second one is equal to 0, the CTC will be considered as absent.

In case of missing value for one CTC and the second one is larger than 0, the CTC will be considered as present.

CTC - Sample 1	CTC - Sample 2	CTC present
>0	>0	Yes
0	>0	Yes
0	0	No
>0	0	Yes
.	0	No
0	.	No
.	>0	Yes
>0	.	Yes
.	.	Missing

Clinical symptomatic response

Clinical symptomatic response will be defined as:

Clinical symptomatic response = Yes if between baseline (on the 7 days preceding the first study treatment) and last period (on days 11 to 17 after last injection or after theoretical injection if the subject performed the last visit without injection), there is

- a reduction of at least 50% of the average number of episodes of diarrhoea = percent change from baseline to last period ≥ -50%
- OR a reduction of at least 50% of the average number of episodes of flushing = percent change from baseline to last period ≥ -50%
- OR a reduction of at least one level of mode severity = mode severity at last period < mode severity at baseline

Clinical symptomatic response = No if between baseline (on the 7 days preceding the first study treatment) and last period (on days 11 to 17 after last injection), there is

- No reduction of at least 50% of the average number of episodes of diarrhoea
- AND no reduction of at least 50% of the average number of episodes of flushing
- AND no reduction of at least one level of mode severity

If more than 50% of the 7 days are missing, no imputation will be performed for the concerned parameter.

The clinical symptomatic response will be defined as soon as one parameter is available.

Frequency and severity of symptoms

Average number of episodes (for diarrhoea or flushing) = Sum of number of episodes / Number of days with available data.

Worst severity (for flushing) = Highest severity

Mode severity (for flushing) = Most frequent severity. In case of ties (ie 2 modes within the period) the highest mode (ie conservative method) will be kept.

If more than 50% of the days are missing, the average number of episodes (for diarrhoea or flushing) and the mode severity (for flushing) will be missing.

Nadir

Nadir is defined as the smallest sum longest diameter recorded since the treatment started.

Best overall response (RECIST version 1.1):

The best overall response to study treatment is the highest time point response achieved by the subject and will be classified as CR, PR, SD, PD and not evaluable (NE)

PFS

See in Section 3.2.1.2.

Quality of life

- Questionnaire EORTC QLQ-C30 score and subscores

  The scale is made of 30 items that can be divided in nine multi-item scales (including five functional scales (15 items), one global health status / quality of life scale (2 items) and three general symptom scales (7 items)) and six single items. The Table below presents the conceptual structure of QLQ-C30.

  Possible answers to the first 28 items (all items except the two concerning global quality of life) go from 1 (“Not at all”) to 4 (“Very much”). No inversion is necessary to calculate the different corresponding scores. The answers for the two last questions (29, 30) go from 1 (“Very poor”) to 7 (“Excellent”).

Table 5: Conceptual structure of QLQ-C30

Dimension	Sub-scales	Number of items	Item numbers
FUNCTION	Physical functioning	5	1 to 5
	Role functioning	2	6, 7
	Emotional functioning	4	21, 22, 23, 24
	Cognitive functioning	2	20, 25
	Social functioning	2	26, 27
GLOBAL HEALTH STATUS	Global quality of life	2	29, 30
GENERAL SYMPTOMS	Fatigue	3	10, 12, 18
	Nausea and vomiting	2	14, 15
	Pain	2	9, 19
SPECIFIC SYMPTOMS	Dyspnoea	1	8
	Insomnia	1	11
	Appetite loss	1	13
	Constipation	1	16
	Diarrhea	1	17
	Financial difficulties	1	28

Scores will be calculated in agreement with the scoring manual [(2)]. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / quality of life represents a high quality of life, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

For multi-item scales, the raw score will be calculated by the addition of item responses divided by the number of items. Then a linear transformation will be used to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Raw score (RS):

RS = sum of item responses / number of items.

Standardised score (S):

Functional scales: $S = 100 - [(RS - 1) / 3] \times 100$.

Global health status: $S = (RS - 1) / 6 \times 100$.

Symptom scales / items: $S = (RS - 1) / 3 \times 100$.

Missing data

For multi-item scales, if at least 50% of the items from the scale have been answered then raw score will be calculated by the addition of available responses divided by the number of not missing items. If less than 50% of the items from the scale have been answered then the raw score will be set to missing.

- EORTC QLQ-G.I.NET 21 score and subscores

The scale is made of 21 items that can be divided in five multi-item scales and four single items. The following table presents the conceptual structure of G.I.NET 21.

Table 6 : Conceptual structure of G.I.NET 21

		Number of items	Item numbers
Multi-item scales	Endocrine	3	31, 32, 33
	Gastro Intestinal	5	34, 35, 36, 37, 38
	Treatment	3	39, 40, 46
	Social function	3	42, 44, 49
	Disease related worries	3	41, 43, 47
Single items	Muscle/Bone pain	1	48
	Sexual function	1	51
	Information/communication function	1	50
	Body image	1	45

Possible answers go from 1 ("Not at all") to 4 ("Very much"). A high score is equivalent to worse or more problems. The subject can also answer "N.A" to items 39, 40, 47 and 51. No inversion is necessary to calculate the different scores.

For each scale, the raw score will be calculated by the addition of item responses divided by the number of items. Then a linear transformation will be used to standardise the raw score, so that scores range from 0 to 100.

Raw score = sum of item responses / number of items.

Standardised score = (raw score – 1) / 3 x 100.

Single items will be treated individually. They will be linearly transformed to a 0-100 scale.

Standardised score = (raw score – 1) / 3 x 100.

Missing data

For multi-item scales, if at least 50% of the items from the scale have been answered then raw score will be calculated by the addition of available responses divided by the number of not missing items.

Not applicable box

For calculations N/A data should be managed as for missing data.

CgA (ULN)

CgA will be derived in ULN as CgA (µg/L) / ULN (µg/L).

SSTR presence

SSTR presence will be defined as:

SSTR presence = Yes if subject has SSTR enumeration > 0

SSTR presence = No if subject has SSTR enumeration = 0

3.2.12. 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 after the baseline visit 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 only one record is expected and corresponds to the baseline visit; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

	Scheduled visit		**Time interval (days) used for analysis (Consecutive intervals)**
Treatment period	Baseline - Week 1 [V2]	Day 1	1
	Week 5 [V3]	Day 29	2 to 42
	Week 9 [V4]	Day 57	43 to 70
	Week 13 [V5]	Day 85	71 to 98
	Week 17 [V6]	Day 113	99 to 126
	Week 21 [V7]	Day 141	127 to 154
	Week 25 [V8]	Day 169	155 to 182
	Week 29 [V9]	Day 197	183 to 210
	Week 33 [V10]	Day 225	211 to 238
	Week 37 [V11]	Day 253	239 to 266
	Week 41 [V12]	Day 281	267 to 294
	Week 45 [V13]	Day 309	295 to 322
	Week 49 [V14]	Day 337	323 to 350
After study treatment	End of Study (V15) / Early withdrawal		Four weeks after the subject's last treatment visit
Note: Any subjects who have previously received either subcutaneous octreotide or one injection of a long acting somatostatin analogue will also be considered for this study following a washout period of 2 weeks after the last subcutaneous octreotide injection or a 6 week washout period after a single long acting somatostatin analogue injection. Time interval (days) = Date of visit – date of first study drug intake +1			

3.2.13. 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 data, arithmetic mean, standard deviation, median, first quartile, third quartile, minimum and maximum. 95% CI of the mean and of the median will be presented.

Mean, median, quartiles and standard deviation 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.

Lower and upper CI 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.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population with non-missing observations. The denominator will be specified in a footnote to the tables for clarification if necessary.

P-values will be reported to three decimal places (e.g.: p=0.037), after rounding.
P-values which are less than 0.001 will be presented as '<0.001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. In summaries of data values below limit of detection will be set to the limit of detection. Values above limit of detection will be set to limit of detection.

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 and times will be presented in the format as defined in the data-base, i.e. [ddmmmyyyy] and [hh:mm] respectively.

3.2.14. Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.15. Interim analysis

No interim analysis will be performed.

3.2.16. Covariates and analysis of subgroups

For the primary efficacy analysis, to assess the relationship between CTC presence at baseline and clinical symptomatic response, a logistic regression with clinical symptomatic response as dependent variable and CTC presence at baseline as explanatory variable (reference level = Yes [presence]) will be used. The presence of washout period (reference level = No [subjects without washout period]) will be taken into account as explanatory variable, if there is at least 20% of subjects with a washout period.

The relationship between CTC presence at baseline and clinical symptomatic response will also be assessed adjusted for the presence of other potentially influential subject characteristics using multivariate logistic regression. These subject characteristics are: Age, Sex and BMI, Time since diagnosis, Location of primary tumour, ENETs staging and prior medication for NET.

For the exploratory primary efficacy, to assess the relationship between CTC presence at baseline and PFS, a Cox Proportional hazard model will be used with the same variables as for the primary efficacy analysis.

Clinical symptomatic response, PFS rate and PFS will be described according to CTC presence (Section 3.2.1).

Symptoms frequency of diarrhoea and flushing (average number of episodes), severity of flushing (worst intensity and mode) will be described according to CTC presence, for all subjects, for subjects with a washout period and for subjects without washout period.

Demographic and baseline characteristics will be described by subgroup (subjects with a washout period versus subjects without washout period).

4. COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1. Hardware

The statistical analysis will be performed using Windows 7 or XP Pro and PCs will be used to run the SAS® programs.

4.2. Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.2. All outputs will be in Microsoft Word Format.

4.3. Validation programs

Validation of SAS programs will be performed by Lincoln as described in Lincoln Standard Operating Procedure "Analyse statistique".

The CRO 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 Lincoln's sign-off forms will be provided to the sponsor to support the validation.

4.4. Restitution of the programs

All programs (including Macros specifically written for this study 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.

5. CHANGES FROM PROTOCOL

Genomic profile of CTCs, genomic profile of liver metastases and density of SSTR2 and SSTR5 were not collected. Therefore, the following exploratory secondary objectives on these criteria will be not investigated:

- To investigate the genomic profile of CTCs at baseline and at the time of any observed progression (RECIST review).
- To investigate the genomic profile of liver metastases at the time of any observed progression (RECIST review) in appropriate subjects.
- To evaluate the density of SSTR2 and SSTR5, and compare the density with subjects' clinical symptomatic response and PFS during Somatuline Autogel treatment.
- To compare the density of SSTR2 and SSTR5 with the density on primary tumour and liver metastasis in patients where the primary tumour or liver metastasis samples are available.

More precisely, density analyses planned in the protocol will not be performed and are therefore not detailed in this RAP. The density/intensity of staining was not validated at the time of the genomic analyses by UCL. In order to validate density of staining, UCL would have required several cell lines with various expression levels and these were not available.

The correlation of biomarkers (CgA, plasma and urine 5-HIAA and neurokinin A) will be explored with CTC presence instead of CTC number and no plot will be performed.

Before 24APR2015, SSTR2 and SSTR5 were not analysed. Therefore only one sample was taken for CTC dosage.

After 24APR2015, SSTR2 and SSTR5 were analysed. Therefore two samples were taken and CTC dosage were performed for both samples, except for Visit 6 (as per protocol, only CTC dosage were planned).

The definition of the safety population has been modified and defined as all enrolled subjects who received at least one injection of study medication instead of all enrolled subjects who received at least one dose of study medication and have at least one post-baseline safety assessment (AE, vital signs).

For subjects with a washout period, symptom frequency and severity are provided during the washout period for the 7 days preceding the first study treatment. Therefore, as the baseline data could be different between subjects:

- Demographic and baseline characteristics will be described by subgroup (subgroup (subjects with a washout period versus subjects without washout period).
- For the primary endpoint, the washout period presence (Yes / No) will be taken into account in the model if there is at least 20% of patients with a washout.
- The effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in subjects with a functioning NET will be analysed by subgroup (subjects with a washout period versus subjects without washout period) and overall.

Medications potentially impacting symptoms (eg loperamide, nifuroxazide, octreotide infusion) were not forbidden for ethical reasons. Subjects having taken these treatments were identified (Full, Partial, No - cf. Section 3.2.11 for derivation) and the following analyses were added:

- Clinical symptomatic response will be described according to CTC presence at baseline and overall for each category of concomitant medications potentially impacting symptoms taken (Full, Partial, No),

- The status of full concomitant medications potentially impacting symptoms will be added as a potentially influential variable in the logistic regression (primary endpoint),
- Presence and type of concomitant medications potentially impacting symptoms will be presented by subject.

6. REFERENCES

(1) NewCombe R.G. (1998) Two sided confidence intervals for the single proportion: comparison of seven methods in Medicine; 17,857-872.

(2) Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

(3) FDA guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", May 2007:

(4) http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

7. DATA PRESENTATION

Data listings are presented for all enrolled and treated 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.

The title of each generated table, listing and figure should appear bookmarked within Word (one single bookmark per table/listing/figure) to allow document publishing by Ipsen.

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Listing 16.2.1.3.2: Inclusion Criteria – Screened Population

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Listing 16.2.8.2: Physical Examination – Screened Population

7.2. Listing templates

Listing templates are provided in Appendix 8.1. The listings will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size as 8 and according to the standard margins defined in SOP GEN014.

The page number of each listing shell (n of N) represent n=page number of the listing and N=total number of pages for that specific listing.

7.3. Tables index

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7.4. Table templates

Table templates are provided for each unique table in Appendix 8.2. The tables will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size as 8 and according to the standard margins defined in SOP GEN014.

7.5. Figure templates

Figure templates are provided for each unique figure in Appendix 8.3. The figures will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size as 8 and according to the standard margins defined in SOP GEN014.

7.6. Statistical Appendix

A Statistical Appendix for inclusion in the study report will be provided. All the methods used in checking the assumptions of the analyses and conclusions should be included and explained. Transformation of the data or other methods used for the statistical analysis other than the ones detailed in the RAP will be described and the change will be justified. All the SAS output will be included without reworking the data (raw output).

This output should contain the study number, the date, the number of pages printed by SAS and the table number to which it refers. Any other relevant information (e.g. statistical references…) will be added in the Statistical Appendix.

8. APPENDICES