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).

STUDY PROTOCOL

Study Number: A-97-52030-270

SOMATULINE® AUTOGEL®

EudraCT Number: 2013-002194-22

Protocol Version: 6.0 incorporating Protocol Amendment 03

Date: **27 October 2015**

Sponsor's Medically Responsible Person:
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PROTOCOL SIGNATURES

Investigator Signature:
I have read and agree to the A-97-52030-270 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).

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

NAME: PROFESSOR TIM MEYER

TITLE: CHIEF INVESTIGATOR

SIGNATURE: PPD DATE: PPD

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

On behalf of the Sponsor:

NAME: PPD

TITLE: UK MEDICAL DIRECTOR

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Note: For IND studies, a Form 1572 will also be completed

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

SUMMARY OF CHANGES

The current version of the protocol was released on 27 October 2015 and includes Amendment 03. For all protocol amendments, amendment forms were prepared and are provided in Appendices1 and 2 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	22 May 2015	N/A – no permanent amendment to protocol – temporary suspension of SSTR2 and SSTR5 blood sampling until validation approved.
2	19 December 2014	Appendix 1
3	27 October 2015	Appendix 2

SYNOPSIS

Study Title:	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). **Short title**: **Circulating Tumour Cells in Somatuline Autogel treated NET patients**
Study Objectives:	**Primary Study Objective:** To assess the clinical value of enumeration of circulating tumour cells (CTCs) to predict clinical symptomatic response in patients receiving Somatuline Autogel. **Exploratory Primary Study Objective:** To assess the clinical value of enumeration of CTCs to describe progression free survival in patients receiving Somatuline Autogel. **Secondary Study Objectives:** To assess the effect of Somatuline Autogel on clinical symptoms in patients with a functioning NET. To assess the effect of Somatuline Autogel treatment on quality of life via a specific NET questionnaire (EORTC QLQ-NET21) in addition to EORTC QLQ-C30. To assess progression free survival (measured using RECIST criteria) after one year of first study treatment. To assess the safety of Somatuline Autogel in this group. **Exploratory Secondary Objectives:** To assess the effect of Somatuline Autogel on plasma chromogranin A, urinary 5-hydroxyindoleacetic acid (5-HIAA), plasma 5-HIAA and neurokinin A, and whether these biomarkers correlate with CTC numbers. To assess whether urinary 5-HIAA and plasma 5-HIAA levels are correlated.

	To investigate the genomic profile of CTCs at week 1 (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) via analysis of liver biopsies in appropriate patients. To evaluate the presence and density of somatostatin receptor (SSTR) subtypes 2 and 5 on CTCs, and compare the density with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment. To compare the density of SSTR2 and SSTR5 on CTCs with the density on primary tumour and liver metastasis in patients where the primary tumour or liver metastasis samples are available.
Phase of Trial:	IV
Study Design:	This is a multicentre, open label, single group study. Patients who have given prior written informed consent and who are eligible for the study will receive Somatuline Autogel injections for a period of one year. One Somatuline Autogel 120mg injection will be administered every 28 days (± 3 days) for the first 3 injections. Patients' symptoms will be assessed after three injections, and the dose will be titrated according to clinical judgement. CTCs will be enumerated at weeks 1, 5, 17, 25 and 53. Recruitment will be approximately 21 months; therefore study duration is expected to be 33 months. There will be approximately 14 centres in the UK.
Study Population:	The study will recruit 50 patients who will receive one deep subcutaneous injection of Somatuline Autogel 120mg every 28 days (± 3 days) for the first 3 injections and then receive further Somatuline Autogel injections (titrated according to symptoms) for the remaining course of the one year study. Patients will have received a recent, pathologically confirmed diagnosis of a functioning midgut G1 or G2 NET and will require medical treatment with a somatostatin analogue for tumour symptom control. Patients may have undergone surgery with curative or debulking intent but have residual NET tumour and symptoms.

Patients may have previously received either subcutaneous octreotide or one injection of a long acting somatostatin analogue prior to study entry. A washout period of 2 weeks after the last subcutaneous octreotide dose or of 6 weeks after a single long acting somatostatin analogue dose is required prior to enrolment.

Patients 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 patients 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.

Inclusion Criteria:

Patients MUST satisfy all of the following entry criteria before they will be allowed to participate in the study:

- Provision of written informed consent prior to any study related procedures.
- Patients (either sex) must be 18 years or older.
- Patients must be suffering from symptoms of diarrhoea and/or flushing at the time of study enrolment.
- Patients must have a documented diagnosis of a functioning midgut NET.
- In order to avoid patients with rapidly progressing tumours, only patients with well or moderately differentiated tumours and with a Ki67 proliferation index of <20% will be recruited.
- The clinically appropriate treatment for the patient must be therapy with a somatostatin analogue.
- Patients must have had either a positive somatostatin receptor scintigraphy result or a positive ^{68}Gallium-DOTATATE PET imaging result.

Exclusion Criteria:

If any of the following apply, the patient MUST not enter/continue in the study:

- If the patient is at risk of pregnancy or is breast feeding, unless treatment with Somatuline Autogel is clearly needed (as determined by the clinician).

	• The patient 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). • The patient 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. • The patient 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. • The patient has received interferon, chemotherapy, chemoembolisation or radionuclide therapy within 3 months prior to study entry. • The patient has a history of hypersensitivity to drugs with a similar chemical structure. • Females of childbearing potential must be using oral, double barrier or injectable contraception. Non childbearing potential is defined as being post-menopause for at least 1 year, surgical sterilisation or hysterectomy at least three months before the start of the study. • The patient has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.
Study Treatment:	**Investigational Medicinal Product (IMP):** Somatuline Autogel. Somatuline Autogel (lanreotide as acetate) is supplied as a white to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use. Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock. The injection should be given by a HCP. The skin should be stretched. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating the left and right side.

	Somatuline Autogel is available in three doses: 60, 90 or 120mg. Injections are generally administered every 28 days. Treatment will be for a period of one year. The starting dose in this study will be 120mg. Product will be ordered via Ipsen Customer Services as free of charge stock. The recruitment period will be 21 months although it could be extended if necessary to obtain the targeted number of patients. **Control Compound:** No comparative compound will be administered. There will not be a comparative group.
Study Evaluations:	**Primary Efficacy Endpoint and Evaluation:** Assessment of the clinical value of enumeration of circulating tumour cells (CTCs) to predict clinical symptomatic response in patients receiving Somatuline Autogel. The effect on both diarrhoea and flushing will be assessed in all patients, regardless of whether both symptoms are present at baseline. CTCs will be enumerated at weeks 1, 5, 17, 25 and 53. Patients will provide 24 hour symptom frequency and severity on a daily basis electronically for the first 16 weeks of the study. Subsequently, patients will provide 24 hour symptom frequency and severity 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, patients will provide 24 hour symptom frequency and severity on a daily basis on days 11 to 28. Symptom frequency and severity will be provided after enrolment for the 7 days preceding the first study treatment. Severity will be classed as mild, moderate and severe for flushing only. **Exploratory Primary Efficacy Endpoint and Evaluation:** To assess the clinical value of enumeration of CTCs to describe progression free survival in patients receiving Somatuline Autogel. **Secondary Efficacy Endpoints And Evaluations:** To assess the effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in patients with a functioning NET. To assess the effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-NET21 and the EORTC-QLQ-C30. The

questionnaires will be conducted at enrolment, and at weeks 13, 25 and 53.

Assessment of progression free survival at one year. Patients will undergo a CT or MRI scan at screening, week 25 and 53 within the local investigator site. Progression will be assessed using the RECIST criteria.

Exploratory Secondary Efficacy Endpoints and Evaluations:

To assess the effect of Somatuline Autogel on plasma chromogranin A, urinary and plasma 5-hydroxyindoleacetic acid (5-HIAA) and neurokinin A, and whether these biomarkers correlate with CTC numbers.

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

To investigate the genomic profile of CTCs at week 1 and at the time of any observed progression (RECIST evaluation at 25 and 53 weeks). To investigate the genomic profile of liver metastases at the time of any observed progression (RECIST evaluation at 25 and 53 weeks) in appropriate patients.

To evaluate the presence and density of somatostatin receptor (SSTR) subtypes 2 and 5 on CTCs at weeks 1, 5, 25 and 53 of the study.

To compare the SSTR2 and SSTR5 density on CTCs with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment.

To compare the density of SSTR2 and SSTR5 on CTCs with that on primary tumour and liver metastasis in the patients where the primary tumour or liver metastasis samples are available.

Safety Endpoints and Evaluations:

The following data will be evaluated in order to assess the long-term safety of Somatuline Autogel:

Incidence of adverse events (AEs).
Incidence of serious adverse events (SAEs)

Other assessment results to include:

Vital signs - heart rate (HR) and blood pressure (BP), weight, height.

Statistical Methods:	A sample size of 50 subjects has been chosen as an appropriate number 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 clear. 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). The relationship between CTC presence at baseline and clinical symptomatic response will be assessed using logistic regression. The odds ratio for the effect of CTC presence on response will be estimated from this model and the associated 95% confidence interval calculated. Additionally, the relationship between CTC presence and clinical symptomatic response will be assessed adjusted for the presence of other potentially influential patient characteristics (such as disease status (stage and grading of NET) and previous treatment) using multiple logistic regression. The potentially influential characteristics will be selected initially on the basis of simple logistic regressions (Wald test $p<0.2$) and included in a final multiple logistic regression model along with CTC presence. Using an appropriate stepwise procedure, a final multiple logistic regression model will be derived that includes CTC presence along with any still influential characteristics. From the final model the odds ratio for the effect of CTC presence on response will be estimated and the associated 95% confidence interval calculated The relationship between the absolute value of CTCs and clinical symptomatic response and the use of different CTC cut-off values for predicting clinical response will also be investigated, if possible. The relationship between CTC presence and progression free survival at 53 weeks will be investigated descriptively. The correlation between urinary and plasma 5-HIAA levels will be presented. Symptom frequency, quality of life and all other secondary endpoints will be investigated descriptively. Safety data will be summarised descriptively.

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APPENDICES

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Not applicable.

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event/Experience
CA	Competent Authorities
CDDS	Clinical Development Data Sciences (relates to Sponsor)
CgA	Chromogranin A
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
CRO	Contract Research Organisation
CTSU	Clinical Trial Supplies Unit (relates to Sponsor)
DMC	Data Monitoring Committee
E	Electronic
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GEP-NETs	Gastroenteropancreatic tumours
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HCP	Health Care Professional
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product synonymous with “study drug”
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NET	Neuroendocrine Tumour
NOS	Not Otherwise Specified
PI	Package Insert
PP	Per protocol
PD	Pharmacodynamics
PK	Pharmacokinetics
QoL	Quality of Life
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria Solid Tumours
SAE	Serious Adverse Event/Experience
SAS®	Statistical Analysis System®
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Somatostatin Analogues
SSRS	Somatostatin receptor scintigraphy
SSTR	Somatostatin Receptor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
5-HIAA	5-Hydroxyindoleacetic acid

2 INTRODUCTION

2.1 Disease Review

Neuroendocrine tumours (NETs) are a rare group of tumours with malignant potential, whose incidence is estimated to be about 3 cases/100,000/year with a slight predominance in females[2]. Their natural history is variable, with median survival ranging from approximately 6 months in aggressive high grade tumours to up to 20 years in more indolent disease. The aetiology of NET is currently not clear. Most of them are considered to be of sporadic origin, though a small familial risk has also been observed.

NET tumours originate from neuroendocrine cells; their location can be throughout the gastrointestinal tract (11-41%)[3] but also in the pancreas, pulmonary bronchi and the thyroid gland. NETs have been classified according to their embryological origin into tumours of foregut (bronchi, stomach, pancreas, gall bladder and duodenum) midgut (jejunum, ileum, appendix, right colon) and hindgut (left colon, rectum).

NETs are generally slow growing and if asymptomatic, may remain undiagnosed throughout life[4]. They are detected only once symptoms become apparent. The symptoms with which they present depend on the site of the primary tumour and the extent of the metastatic disease. NET metastases typically occur in the liver but may also involve the bones, lymph nodes, eyes and the skin.

The carcinoid syndrome is usually a result of metastasis to the liver, with the subsequent release of hormones (serotonin, tachykinins, and other vasoactive compounds) directly into the systemic circulation. This syndrome is characterised by flushing and diarrhoea. Some patients have lacrymation, rhinorrhoea, and episodic palpations when they flush.

Disease Monitoring and Progression

NETs are characterized by the overexpression of somatostatin receptors (SSTR), with five subtypes (SSTR1-SSTR5) having been identified, all of which are expressed with different frequencies in gastroenteropancreatic tumours (GEP-NETs [Table 1]).

Table 1: Expression of Somatostatin Receptors in Neuroendocrine Gastroenteropancreatic Tumours (%)[a]

Neuroendocrine tumours	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
All tumours	68	86	46	93	57
Non functioning	80	100	40	100	60
Mid gut neuroendocrine tumours	80	95	65	35	75

[a] Using receptor subtype antibodies (Oberg et al. Consensus report on the use of somatostatin analogues for the management of neuroendocrine tumours of the gastroenteropancreatic system. Annals of oncology 2004; 15:966-973[5].)

Over the past two decades there has been significant progress in our understanding of the molecular basis for the anti-proliferative effects of somatostatin and its analogues. Anti-tumoural activity appears to be mediated via direct and indirect mechanisms.

Direct mechanisms involve the activation of SSTR on tumour cells leading to modulation of intracellular signalling transduction pathways. Multiple in vitro studies using cell lines transfected with SSTR indicate that all receptor subtypes (SSTR1-5) may mediate inhibition of cell proliferation, whereas specific receptor subtypes (SSTR2, 3) may mediate apoptosis[6].

Indirect anti proliferative mechanisms include inhibition of mitogenic growth factors such as insulin-like growth factor (IGF), as well as inhibition of tumour angiogenesis through interaction with SSTR on endothelial cells and monocytes[6].

The recently completed CLARINET study (Ipsen sponsored study) is a phase III, randomized, double-blind, placebo-controlled, multicentre study to assess the effect of lanreotide Autogel 120 mg administered by deep subcutaneous injection every 28 days on progression free survival in patients with non-functioning enteropancreatic endocrine tumours, which are Neuroendocrine Tumours (NETs) (ClinicalTrials.gov identifier, NCT00353496, EudraCT No: 2005-004904-35).

Treatment with Somatuline® (lanreotide) Autogel® 120mg was found to be statistically significantly superior to placebo in extending time to either disease progression or death. The safety profile observed in the study is consistent with the known safety profile of Somatuline®. Comprehensive results from this study will be disclosed at the annual meeting of the European Society of Medical Oncology (ESMO) (Sept. 27 – Oct. 1, 2013)[7].

NET biomarkers may also be measured to assess disease progression such as plasma chromogranin A (CgA) and 5-hydroxyindole acetic acid (5-HIAA urine over 24 hours).

5-HIAA is a metabolite of serotonin, a chemical/neurotransmitter that is needed by the nervous system, mainly the brain, and is also needed by special cells in the lung and gastrointestinal tract. After the body uses serotonin (5-hydroxytryptophan), it is degraded in the liver and is broken down into metabolites, including 5-HIAA, which is excreted in the urine.

Serotonin and consequently 5-HIAA are produced in excess by most carcinoid tumours, especially those producing the carcinoid syndrome of flushing, hepatomegaly (enlarged liver), diarrhoea, bronchospasm, and heart disease. Quantification of urinary 5-HIAA is the best diagnostic test for functioning midgut NETs, but care must be taken to ensure specimen collection and patient preparation are correct. Midgut NETs may cause increased excretion of tryptophan, and histamine as well as serotonin. The collection of urine for 5-HIAA testing is done over 24 hours and must be strictly controlled. This study will look at 24 hour urine 5-HIAA sampling and 5-HIAA plasma sampling to examine if similar accuracy and

results can be obtained. Currently, testing of plasma 5-HIAA is not standard practice in all UK investigator sites.

CgA is used as a tumour marker. The test may be ordered in combination with 5-HIAA to help diagnose functioning midgut NETs. It is also used to help monitor the effectiveness of treatment to detect the recurrence of the tumour. It may also be used to detect the presence of other NETs, even those that do not secrete hormones.

Current methods of monitoring progression in NETs and response to treatment include serial imaging over many years with the addition of RECIST reviews.

Treatment

The initial treatment of functioning NETs consists of surgical removal of the tumour where possible, in patients with limited disease (primary tumour and metastasis in regional lymph nodes), and treatment of the hormonal syndrome. If the tumour enters into a more progressive phase, treatment may include hepatic artery embolization, chemotherapy, radio-labelled somatostatin analogues with or without interferon. These therapies however often do not stop the progression of the tumour.

Somatostatin analogues (SSAs) such as lanreotide and octreotide are the treatment of choice for hormone-related syndromes. SSAs work by inhibiting the secretion of serotonin and other hormones which cause the symptoms. They have been found to be effective in relieving the flushing and diarrhoea associated with the carcinoid syndrome[8,9]. The symptomatic treatment is usually long term[8]. More recently SSAs have also been found to have a growth inhibitory effect in patients with midgut tumours. In the PROMID study, patients with midgut tumours treated with the SSA octreotide had a median time to tumour progression of 14 months, as compared to only 6 months in patients treated with placebo[10].

Somatuline Autogel is registered for the treatment of symptoms associated with carcinoid tumours in over 50 countries worldwide.

Circulating Tumour Cells (CTCs)

In recent years, many new anti-cancer agents have been developed and introduced into clinical care. While these new agents have led to substantial gains in response rates and life expectancies, they have also increased the need for tools to select patients who would benefit from these therapies. Once patients develop metastatic disease, treatment is tailored to improving Quality of Life (QoL) and prolonging life expectancy, but it is always a trade-off against the side-effects that are inevitably associated with anti-tumour therapy underscoring the need to select only those patients who are likely to respond to a drug.

Circulating tumour cells (CTCs) have been shown to be detectable in around 50% of patients with midgut NET tumours using the CellSearch platform, and their presence confers an adverse prognosis[11]. CTCs have also been shown to be valuable as predictive markers following therapy and there is increasing interest in the

characterisation of CTCs as 'liquid biopsies' that can inform treatment decisions. CTC analysis has the benefit of being relatively non-invasive compared with conventional biopsy and is therefore an attractive method to monitor the tumour throughout the therapeutic sequence.

CTC Analysis

In this study CTC enumeration will be performed using the CellSearch (Veridex, Raritan, NJ) system. The CellSearch platform detects CTCs with high sensitivity, specificity, and reproducibility and is the only system approved by the US Food and Drug Administration. The CellSearch platform requires the cellular expression of the epithelial cell adhesion molecule (EpCAM). It has been reported that a majority of NETs have strong heterogeneous membranous expression of EpCAM and that CTCs can be detected in patients with NETs[12].

2.2 Compound Review

Somatuline (lanreotide) Autogel

Somatuline Autogel is a long-acting viscous aqueous formulation of lanreotide, which is supplied in a ready to use pre-filled syringes intended for deep subcutaneous injection. Somatuline Autogel provides consistent drug release and is effective in controlling the symptoms of NET when injected every 28 days[8,9].

Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock. The injection should be given by a Health Care Professional (HCP). The skin should be stretched. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating between the left and right side.

Somatuline Autogel is available in three doses: 60mg, 90mg or 120mg. Injections are generally administered every 28 days.

Product will be ordered via Ipsen Customer Services as free of charge stock.

2.3 Clinical Trial Rationale

Somatuline Autogel is licensed in the UK for the treatment of NET symptoms. The safety aspects of Somatuline Autogel have been investigated and observed in numerous phase IV post marketing studies, including recently the safety profile and efficacy of home administration.

CTCs are cells that have shed into the vasculature from a primary tumour or metastases and circulate in the bloodstream. CTCs thus constitute seeds for subsequent growth of additional tumours (metastasis) in distant organs, and it is metastatic disease that is responsible for the vast majority of cancer-related deaths. In patients with metastatic breast cancer, studies have shown that the number of CTCs present prior to commencing a new therapy are predictive of progression free and overall survival[13,14].

This study will assess the clinical value that enumeration will have in predicting the clinical symptomatic response and progression free survival in patients receiving Somatuline Autogel for functioning midgut NETs over a one year period.

3 STUDY OBJECTIVES

3.1 Primary Study Objective

To assess the clinical value of enumeration of circulating tumour cells (CTCs) to predict the clinical symptomatic response in patients receiving Somatuline Autogel. Patients 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, patients 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.

3.2 Exploratory Primary Study Objective:

To assess the clinical value of enumeration of CTCs to describe progression free survival in patients receiving Somatuline Autogel.

3.3 Secondary Study Objectives:

To assess the effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in patients with a functioning NET.

To assess the effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-NET21 and the EORTC-QLQ-C30. The questionnaires will be conducted at weeks 1, 13, 25 and 53.

Assessment of progression-free survival at one year. Patients will undergo a CT or MRI scan at screening, week 25 and week 53 within their local hospital Trust. Progression will be assessed using the RECIST criteria.

3.4 Exploratory Secondary Objectives:

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

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

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 patients.

To evaluate the presence and density of somatostatin receptor (SSTR) subtypes 2 and 5 on CTCs, and compare the density with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment.

To compare the density of SSTR2 and SSTR5 on CTCs with the density on primary tumour and liver metastasis in patients where the primary tumour or liver metastasis samples are available.

4 STUDY DESIGN

4.1 Overview

This is a prospective, pilot, phase IV, multicentre, open label, single group study to assess the clinical value of enumeration of CTCs to predict clinical symptomatic response in patients receiving deep subcutaneous administrations of Somatuline® Autogel® to treat the symptoms of functioning midgut NETs. The study will be conducted at 14 sites in the UK, with the Royal Free Hospital being the lead site and the Central and East London Comprehensive Local Research Network (CLRN) being the lead CLRN.

Patients who have given prior written informed consent and who are eligible for the study will receive Somatuline Autogel injections for a period of one year. Initially, one Somatuline Autogel 120mg injection will be administered every 28 days (± 3 days) for a period of 3 months. Patients' symptoms will be assessed after 3 injections and the dose will be titrated accordingly based on a clinical decision and a review of patient's symptoms. The decision will be recorded on the patient's eCRF.

During the course of the study, patients will have blood taken for CTC enumeration at weeks 1, 5, 17, 25 and 53. These samples will be used for SSTR2 profiling at weeks 1, 5, 25 and 53. Additional samples of blood will be collected at week 1, 5, 25 and 53 for SSTR5 profiling. If a patient misses a blood sampling visit the sampling may be performed at the next visit.

Symptoms will be monitored throughout the study by the patient. Reporting of 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, patients 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, patients will provide 24 hour symptom frequency (diarrhoea and flushing) and severity (flushing only) on a daily basis on days 11 to 28. Symptom frequency (diarrhoea and flushing) and severity (flushing only) will be provided after enrolment for the 7 days preceding the first study treatment. Severity will be classed as mild, moderate and severe for flushing only.

Symptoms summaries will be made available to treating clinicians via a study dashboard, which will be reviewed to make decisions on IMP dosage.

Patients will also have to complete QoL questionnaires via the EORTC QLQ-NET21 and the EORTC QLQ-C30 questionnaires to assess the effect of Somatuline Autogel treatment on QoL. The QoL questionnaires will be administered and completed by patients whilst they are awaiting their clinical appointments. QoL will be assessed at weeks 1 (baseline), 13, 25 and 53.

CT or MRI scans will be conducted at screening (scans which have been conducted within 6 weeks before screening can be used), week 25 and week 53 to assess progression free survival and disease progression using RECIST criteria (Version 1.1).

The genomic profile of CTCs will be examined at baseline and at the time of any observed progression (RECIST review at weeks 25 and 53). The genomic profile of liver metastases will be examined via analysis of liver biopsies in appropriate patients following observed progression (RECIST review at weeks 25 and 53).

Assessments of the effect of Somatuline Autogel on plasma chromogranin A, urinary and plasma 5-hydroxyindoleacetic acid (5-HIAA) and neurokinin A, will be made and a review of whether these biomarkers correlate with CTC numbers. The correlation between urine 5-HIAA and plasma 5-HIAA will be assessed.

Patients will have plasma samples taken for cell free DNA analyses at weeks 1, 25 and 53.

The presence and density of SSTR2 and SSTR5 on CTCs will be assessed and compared with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment. The density of SSTR2 and SSTR5 on CTCs will be compared with the density on primary tumour and liver metastasis in patients where the primary tumour or liver metastasis samples are available.

4.1.1 Population Characteristics

Approximately 50 patients (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 an SSA for tumour symptom control will be eligible for this study.

4.1.2 Design

This is a multicentre, open label, single group phase IV study which will be conducted across 14 sites in the UK. It is intended that the study will run for 33 months, which includes a 12 month treatment period and a 21 month recruitment period.

Eligible patients will be asked to provide written informed consent for their participation in this study. Patients who have provided written informed consent will initially receive Somatuline Autogel 120mg injections every 28 days for the first 3 injections. Patient'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.

4.1.3 Titration

Clinicians will review patient's symptoms via the study dashboard after 3 injections of Somatuline Autogel 120mg. According to clinical judgement patients may remain on the 120mg dose or be titrated to either 60mg or 90mg. At each study visit the response to treatment will be evaluated and the dosage titrated according to symptomatic response.

4.1.4 Administration of IMP

Somatuline Autogel will be injected via the deep subcutaneous route in the superior external quadrant of the buttock. The injection should be given by a HCP. The skin should be stretched. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating between the left and right sides.

4.1.5 CTC blood collection

During the course of the study, patients will have blood (10mls) taken for CTC enumeration at weeks 1 (baseline), 5, 17, 25, and 53. CTC enumeration will be conducted at the UCL Cancer Institute. Once taken, blood samples must be stored at room temperature and be shipped for analysis within 24 hours. CTC enumeration will be conducted within 96 hours as per manufacturer's instructions.

4.1.6 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 10mls 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 fluorescein isothiocyanate (FITC) or Phycoerythrin (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.

4.1.7 Urine 5-HIAA and Plasma 5-HIAA Samples

Patients 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-hydroxyindoleacetic acid (5-HIAA - a breakdown product of a hormone called serotonin) that is present in the urine. Before the collection of 5-HIAA urine sample, patients will be informed that the following items must be avoided for 12 hours prior to, and during, the 24 hour urine collection being performed:

- Foods including fruit, fruit juice, fruit jam, nuts and chocolate.
- Any processed food that may contain the above ingredients.
- Any health food supplements containing 5-Hydroxytryptophan (e.g. extract of Griffornia Simplicifolia seed).

Urine volume should be measured and a 10ml aliquot transferred to a sample tube and frozen at -20^{o}C. The remainder of the urine may be discarded.

A fasting blood sample of 7.5mls will be drawn to complete plasma 5-HIAA analysis and should be frozen at -20^{o}C. Patients should not eat anything for 12 hours prior to the blood test however they may drink a glass or two of clear water if required.

Urine and blood samples will be collected from patients at weeks 1 (baseline), 5, 17, 25 and 53 and shipped to the clinical biochemistry laboratory at the Leeds Teaching Hospital for analysis.

4.1.8 Chromogranin A (CgA) and Neurokinin A

A total blood sample of 7.5mls 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 and should be frozen at -20^{o}C and shipped to the pathology laboratory at the Royal Victoria Hospital, Belfast for analysis.

4.1.9 Cell free DNA analyses

Patients will require additional samples of blood (7.5mls) to be drawn at weeks 1 (baseline), 25 and 53 for cell free DNA analyses. Samples collected will be frozen at site to -20^{o}C and shipped to the UCL Cancer Institute for analyses of cell free DNA.

4.1.10 Symptoms

Patients will report both episodes of diarrhoea and flushing throughout the trial, regardless of whether both of these symptoms are present at baseline. Once the patient has provided informed consent and met the eligibility criteria for the study, a member of the study team will telephone an Interactive Voice Response System (IVRS) to register the patient into the study. The IVRS system will provide the patient's unique study identification number. In this trial patients will record their symptoms by telephoning the IVRS.

Symptom frequency and severity will be provided after enrolment (informed consent) for the 7 days preceding the first study treatment. Severity will be classed as mild, moderate and severe for flushing only. Patients 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.

Patients will record 24 hour symptom frequency and severity on a daily basis for the first 16 weeks, subsequently patients will provide 24 hour symptom frequency and severity on days 11 to 17 of each subsequent injection interval until week 49. After the final study drug injection at week 49, patients 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. Flushing symptom severity will be recorded using a 3 point scoring system. Symptom frequency and severity reports will be available to clinicians via a study dashboard.

4.1.11 Symptom Scoring System

Symptomatic efficacy will be assessed by the use of electronic symptom reporting throughout the study; the number of diarrhoea and flushing episodes patients experience will be recorded. Patients will also record the severity of any flushing episodes they have experienced, grading them as mild, moderate and severe.

4.1.12 QoL

Patients will also have to complete QoL questionnaires using the EORTC QLQ-NET21 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.

4.1.13 CT/MRI Scan

Patients 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 progression-free survival at one year, progression will be assessed using the RECIST criteria version 1.1.

4.1.14 Patient Disease Progression

When a patient's disease progresses, clinicians will decide if the patient should remain on the trial or withdraw from the trial. If a patient requires a further intervention, such as peptide receptor radionuclide therapy, the patient will be withdrawn from the study.

4.1.15 Stopping Rules and Discontinuation Criteria

Any decision taken as part of routine medical practice that affects whether or not the patient continues to receive Somatuline Autogel injections after enrolment into the trial will be recorded. The treating clinician will be asked to record the reason for the decision. If it is due to safety, tolerability or efficacy concerns, details should be supplied.

4.1.16 Early Study Termination

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

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

4.2 Endpoints

4.2.1 Safety Endpoints

The following data will be evaluated in order to assess the long-term safety of Somatuline Autogel:

- Incidence of adverse events and serious adverse events (AEs).

Other assessment results to include: vital signs (heart rate (HR) and blood pressure (BP), weight and height).

The incidence of safety issues (related AEs) during each 6 month reporting period, (as well as cumulative listings) will be described.

4.3 Justification of Design

This study is a phase IV study to assess the clinical value that CTC enumeration has on predicting the clinical symptomatic response and describing progression free survival in patients receiving deep subcutaneous administrations of Somatuline® Autogel® to treat the symptoms of functioning midgut NETs.

Patients will receive Somatuline Autogel 120 mg injections every 28 days for 3 injections, followed by titration depending on patients' symptomatic response. A starting dose of Somatuline Autogel 120mg is within the UK licence for the use of Somatuline Autogel to treat the symptoms associated with NETs. In February 2015 Ipsen Limited received a new licence extension or the use of Somatuline Autogel `10mg for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease. This licence extension was based upon the CLARINET study (see below), which utilised a dose of Somatuline Autogel of 120mg.

CLARINET (Ipsen sponsored study, EudraCT No: 2005-004904-35) is a phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the effect of lanreotide Autogel 120 mg administered by deep subcutaneous injection every 28 days on progression free survival in patients with non-functioning enteropancreatic endocrine tumours (a type of NET) (ClinicalTrials.gov identifier, NCT00353496).

All CT or MRI scans conducted to assess the extent of disease will include evaluation of RECIST criteria version 1.1.

The study is an open label study so patients' QoL, as well as number of symptoms (i.e. flushing and diarrhoea) and assessments of severity for flushing using a three level scoring system (mild, moderate and severe) can be identified and reported with minimum bias.

4.3.1 Study Population for Analysis

The primary population for analysis will be the Intention to Treat (ITT) population which will include all treated patients aged 18 years of age or older. This will allow inclusion of all patients including withdrawn patients, in the primary analysis.

4.3.2 Study Duration

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 patient has provided signed informed consent to participate in the study.

The study will be considered to have finished after the last patient has completed the last treatment period in the study. For notification to the competent authority, the study will be considered to have finished ("End of Study") when the last patient has completed the last study visit.

4.4 Banking of Residual Blood and Tissue Samples for Future Research

Patients will be invited to donate any residual blood, tumour and liver samples that have been sent to UCL Cancer Institute's laboratory for cell free DNA or genomic profiling during the CALM-NET study to the UCL Cancer Institute's Human Tissue Authority (HTA) approved Tissue Bank for future research. This will not involve taking any further samples and patients will be clearly informed that this is completely voluntary.

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

5.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) (Reference 16 (19)) Good Clinical Practice (GCP) Guidelines.

In addition, this study will adhere to all local regulatory requirements. Before initiating a trial, the Investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the trial protocol/amendment(s), written informed consent form, any consent form updates, patient emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

5.2 Informed Consent

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

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

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

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

6 STUDY POPULATION

6.1 Screening Log and Number of Patients

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

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

It is planned to recruit 50 patients at 14 centres in the UK. Section (11.3) provides a discussion of sample size.

6.2 Inclusion Criteria

All patients must fulfil the following:

1) Provision of written informed consent prior to any study related procedures.
2) Patients (either sex) must be 18 years or older.
3) Patients must be suffering from symptoms of diarrhoea and/or flushing at the time of study enrolment.
4) Patients must have a documented diagnosis of a functioning midgut NET.
5) In order to avoid patients with rapidly progressing tumours, only patients with well or moderately differentiated tumours and with a Ki67 proliferation index of <20% will be recruited.
6) The clinically appropriate treatment for the patient must be therapy with a somatostatin analogue

7) Patients must have had either a positive somatostatin receptor scintigraphy result or a positive ^{68}Gallium-DOTATATE PET imaging result.

6.3 Exclusion Criteria

Patients will not be included in the study if the patient:

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.
4) 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) Has received interferon, chemotherapy, chemoembolisation or radionuclide therapy within 3 months prior to study entry.
6) Has a history of hypersensitivity to drugs with a similar chemical structure.
7) 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.
8) Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.

6.3.1 Washout Criteria

Any patients 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 dose or a 6 week wash out period after a single long acting somatostatin analogue dose.

Patients 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 patients 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.

6.4 Patient Withdrawal Criteria

As this study is investigating the clinical value of CTC enumeration, no specific withdrawal criteria are specified for the trial. If a clinician decides to withdraw a patient from the trial or the patient wishes to withdraw consent this will be recorded into the eCRFs.

For patients who have disease progression whilst participating in this study, the treating physician will make a clinical decision to continue the patient on the trial or withdraw the patient from the clinical trial. Justification would be recorded on the eCRF and patient's notes. Patients who have disease progression and do continue in the clinical trial will continue with all study procedures, including administration of IMP.

6.5 Discontinuation/Withdrawal Procedures

If the patient is withdrawn from the study (i.e. ceases participation in the study prior to completion of the assessments planned in the protocol), the primary reason should be recorded in the case report form (CRF)/electronic case report form (eCRF). Withdrawal due to AEs should be distinguished from withdrawal due to insufficient response.

The Investigator will provide or arrange for appropriate follow-up (if required) for patients withdrawing from the study, and will document the course of the patient's condition. Where the patient has withdrawn due to an AE the Investigator should follow the procedures documented in Section 10 in order to assess the safety of the IMP.

7 METHODOLOGY

7.1 Study Schedule

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

Table 2 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

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**
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 patients' notes for NET symptoms at diagnosis and during prior somatostatin analogue treatment (d)	X															
Patient NET symptom reporting (7 days) (e)	X															
Patient NET symptom reporting			*Daily patient NET symptom reporting IVRS*				*Once monthly (days 11-17) patient NET symptom reporting IVRS*								*Days 11-28 patient 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
5HIAA 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

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**
Neurokinin A blood sample (h)			X	X			X		X							X
Liver genomic profiling (i)			X						X							X
Subject Questionnaires (QoL)			X			X			X							X
Clinician review of patient 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 patient reported NET symptoms									
Administration of IMP (120 mg) (j)			X(j)	X	X	X(k)	Administration of 60mg, 90mg or 120mg at each visit after clinician review of patient reported NET symptoms									
Administration of IMP (90mg) (j)						X(k)										
Administration of IMP (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
CRF 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 patients 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 patients

(e) Patient 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 patient misses a blood sampling visit the sampling may be performed at the next visit

7.2 Study Visits

7.2.1 Screening and washout (Visit 1)

All patients will attend a screening visit, during which written informed consent should be obtained prior to enrolment of patients onto the trial. A washout period can run alongside screening visits (only if required). During the screening visit the following assessments will be performed and recorded:

- Informed Consent
- Pregnancy testing (urine) will be required for female patients of child bearing potential.
- Eligibility check.
- Demographics.
- Medical history, including on-going medical management.
- Vital signs.
- Physical examination.
- CT/MRI Scan with RECIST 1.1 review (scan not required if patient has had a scan within the 6 weeks prior to the screening visit).
- Review patient notes for NET symptoms at diagnosis and during prior somatostatin analogue treatment (washout patients only).
- Patients will be asked to record NET symptoms for 7 days prior to administration of first IMP.
- Patients will be advised that NET symptom reporting will be on a daily basis for 16 weeks after the first injection.
- Concomitant medication check.

7.2.2 Study Visit 2 Administration of IMP

- Pregnancy testing (urine) will be required for female patients of child bearing potential who have undergone a washout period.
- If liver biopsy or surgical excision of tumour has been clinically indicated and performed previously, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision has been clinically indicated and performed previously, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Height and weight.
- Patients reminded that daily NET symptoms will be recorded for the next month.
- Clinician review of patient reported NET symptoms (following the last visit).
- 5-HIAA 24 hour urine sample collection.

- **Blood will be drawn for the following tests:**
  - 10 mls (2 teaspoons) for CTC enumeration, CTC genomic profiling and SSTR2 analysis.
  - 10mls (2 teaspoons) for SSTR5 analysis
  - 7.5mls (1.5 teaspoons) for cell free DNA analysis
  - 7.5mls (1.5 teaspoons) for 5-HIAA analysis
  - 7.5mls (1.5 teaspoons) for chromogranin A and neurokinin A analysis
- Liver genomic profiling - performed using liver samples available prior to study or if clinically required during study (same sample as used for SSTR profiling).
- Subject Questionnaires (QoL).
- Concomitant medication check.
- Adverse event reporting as required.
- Administration of IMP (120mg) following completion of all clinical procedures for visit.

7.2.3 Study Visit 3

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that daily NET symptoms will be recorded for the next month.
- Clinician review of patient reported NET symptoms (following the last visit).
- **Blood will be drawn for the following tests:**
  - 10mls (2 teaspoons) for CTC enumeration, CTC genomic profiling and SSTR2 analysis.
  - 10mls (2 teaspoons) for SSTR5 analysis
  - 7.5mls (1.5 teaspoons) for cell free DNA analysis
  - 7.5mls (1.5 teaspoons) for 5-HIAA analysis
  - 7.5mls (1.5 teaspoons) for chromogranin A and neurokinin A analysis
- 5-HIAA 24 hour urine sample collection.
- Administration of IMP (120mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.4 Study Visit 4

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that daily NET symptoms will be recorded for the next month.
- Clinician review of patient reported NET symptom (following the last visit).
- Administration of IMP (120mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.5 Study Visit 5

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that daily NET symptoms will be recorded for the next month.
- Subject Questionnaires (QoL).
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following titration review **and** completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.6 Study Visit 6

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.

- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- **Blood will be drawn for the following tests:**
  - 10mls (2 teaspoons) for CTC enumeration
  - 7.5mls (1.5 teaspoons) for 5-HIAA analysis
  - 7.5mls (1.5 teaspoons) for chromogranin A and neurokinin A analysis
- 5-HIAA 24 hour urine sample collection.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.7 Study Visit 7

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.8 Study Visit 8

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.

- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- CT/MRI scan with RECIST review.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- **Blood will be drawn for the following tests:**
  - 10mls (2 teaspoons) for CTC enumeration, CTC genomic profiling and SSTR2 analysis.
  - 10mls (2 teaspoons) for SSTR5 analysis
  - 7.5mls (1.5 teaspoons) for cell free DNA analysis
  - 7.5mls (1.5 teaspoons) for 5-HIAA analysis
  - 7.5mls (1.5 teaspoons) for chromogranin A and neurokinin A analysis
- 5-HIAA 24 hour urine sample collection.
- Liver genomic profiling - performed using liver samples available prior to study or if clinically required during study (same sample as used for SSTR profiling.
- Subject Questionnaires (QoL).
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.9 Study Visit 9

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.10 Study Visit 10

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.11 Study Visit 11

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.12 Study Visit 12

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.

- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.13 Study Visit 13

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (days 11-17) NET symptoms will be recorded for the next month.
- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medications check.
- Adverse event reporting as required.

7.2.14 Study Visit 14

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Patients reminded that once monthly (**days 11-28**) NET symptoms will be recorded for the next month.

- Dose titration decision based upon clinician review of patient reported NET symptoms.
- Administration of IMP (120mg, 90mg or 60mg) following completion of all clinical procedures for visit.
- Concomitant medication check.
- Adverse event reporting as required.

7.2.15 Study visit 15, study Completion or withdrawal

At the end of study visit 15 the following procedures should be completed:

- If liver biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- If primary tumour biopsy or surgical excision of tumour is clinically indicated during study duration, request sample for storage and report at the UCL Cancer Institute.
- Vital signs.
- Physical examination.
- Height and weight.
- **Blood will be drawn for the following tests:**
  - 10mls (2 teaspoons) for CTC enumeration, CTC genomic profiling and SSTR2 analysis.
  - 10mls (2 teaspoons) for SSTR5 analysis
  - 7.5mls (1.5 teaspoons) for cell free DNA analysis
  - 7.5mls (1.5 teaspoons) for 5-HIAA analysis
  - 7.5mls (1.5 teaspoons) for chromogranin A and neurokinin A analysis
- CT/MRI scan with RECIST.
- 5-HIAA 24 hour urine sample collection.
- Liver genomic profiling - performed using liver samples available prior to study or if clinically required during study (same sample as used for SSTR profiling.
- Subject Questionnaires (QoL).

If a patient discontinues from the study prematurely, every effort should be made to perform an early withdrawal visit.

8 STUDY EVALUATIONS

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

8.1 Primary Endpoints and Evaluations

8.1.1 Primary Efficacy Endpoint and Evaluation:

Assessment of the clinical value of enumeration of circulating tumour cells (CTCs) to predict clinical symptomatic response in patients receiving Somatuline Autogel.

8.1.2 Exploratory Primary Efficacy Endpoint and Evaluation:

To assess the clinical value of enumeration of CTCs to describe progression free survival in patients receiving Somatuline Autogel.

8.2 Secondary Endpoints and Evaluations

8.2.1 Secondary Efficacy Endpoints and Evaluations:

To assess the effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in patients with a functioning NET.

8.2.2 Quality of Life End Points:

To assess the effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-NET21 and the EORTC-QLC-C30.

8.2.3 Progression Free Survival at One year end point:

Assessment of progression free survival at one year.

8.2.4 Exploratory Secondary Efficacy Endpoints and Evaluations:

To assess the effect of Somatuline Autogel on plasma CgA, urinary and plasma 5-HIAA and neurokinin A, and whether these biomarkers correlate with CTC numbers.

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

To investigate the genomic profile of CTCs at baseline and at the time of any observed progression.

To investigate the genomic profile of liver metastases at the time of any observed progression in appropriate patients. To evaluate the presence and density of SSTR subtypes 2 and 5 on CTCs.

To compare the SSTR2 and SSTR5 density with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment.

To compare the density of SSTR2 and SSTR5 on CTCs with that on primary tumour and liver metastasis in the patients where the primary tumour or liver metastasis samples are available.

8.3 Safety Endpoints and Evaluations

8.3.1 Adverse Events

AEs will be monitored from the time that the patient gives informed consent to the time when the patient's participation in the study is considered to have ended (as defined in Section 4.3.2). AEs will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 10.

8.3.2 Physical Examination

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

8.3.3 Vital Signs

Blood pressure and heart rate (supine after resting for 3 minutes or standing after 1 minute), will be recorded at each study visit. Height and weight should be measured at weeks 1 and 53.

8.3.4 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be taken at screening, week 1, 5, 17, 25 and 53 and will consist of the following:

CTC enumeration: bloods will be drawn in special tubes which will be provided by Ipsen Ltd. 10 ml of blood will be drawn and shipped to UCL within 24 hours of samples being taken.

SSTR5 profiling of CTCs blood sample: bloods will be drawn in special tubes which will be provided by Ipsen Ltd. 10 ml of blood will be drawn and shipped to UCL within 24 hours of samples being taken.

5-HIAA urine (24 hours) and blood samples will be collected. Urine volume will be measured and a 10ml aliquot transferred to a separate tube and frozen at -20^{o}C for shipment. Plasma samples will be frozen at -20^{o}C at site. Plasma and urine samples will be sent to the pathology laboratory at Leeds Teaching Hospital for analyses. 7.5 ml of blood will be collected from patients according to section 7 (Methodology) of the protocol.

CgA and neurokinin A blood samples will be collected. Plasma samples will be frozen at site at -20^{o}C and sent to the clinical biochemistry laboratory at the Royal Victoria Hospital, Belfast for analyses. 7.5 ml of blood will be collected from patients according to section 7 (Methodology) of the protocol.

Patients will have an additional 7.5 ml of blood drawn at weeks 1, 25 and 53 for cell free DNA analysis. This blood sample will be frozen at -20^{o}C and shipped to the University College London (UCL) Institute of Cancer Research.

Pregnancy A urine sample will be collected for a pregnancy dipstick test in the clinic at study entry for female patients of childbearing potential to test for pregnancy. If this is found to be positive, the investigator will decide whether the patient should be included in the study.

If pregnancy occurs during treatment on urine testing it will be confirmed by plasma testing and the investigator will decide whether treatment with Somatuline Autogel should be continued.

Clinical laboratory tests will be performed by the laboratories specified above. Details of the methodology and reference ranges will be provided in the Trial Master File (TMF).

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

8.4 Total Blood Volume

The total blood during the whole course of the study will be approximately 187.5mls per patient.

9 STUDY TREATMENTS

9.1 Study Treatments Administered

Patients included in the programme will be receiving Somatuline Autogel injections for the treatment of their NET symptoms. The decision to prescribe Somatuline Autogel will be made prior to, and independently from the decision to enrol the patient in the CALM-NET study.

Somatuline Autogel (lanreotide as acetate) is supplied as a white to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use.

Somatuline Autogel is available in three dosages; 60mg, 90mg or 120mg and administered every 28 days. The dose of administration will be determined on an individual patient basis by the treating clinician in accordance with usual medical practice and may be titrated during the period of this study.

Regardless of the site of injection, the skin should be stretched. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating the left and right sides.

9.2 Subject Identification and Allocation to Study Treatment

All patients will be automatically allocated a unique patient number when an enrolment visit is created in the IVRS. In order to maintain confidentiality, this number in conjunction with the patient's initials will be used to identify the patients study data.

All patients enrolled must be identifiable throughout the study. The Investigator will maintain a list of patient numbers and names to enable records to be found at a later date if required.

9.2.1 Randomisation

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

9.3 Study treatment supply, packaging and labelling

Somatuline Autogel will be ordered free of charge from Ipsen Limited Customer Services and administered with usual medical practice. Somatuline Autogel packs will be labelled in accordance with the approved UK labelling for the product.

9.4 Study Treatment Storage and Accountability

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

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

9.5 Concomitant Medication/Therapy

The following medications should be used cautiously whilst receiving Somatuline Autogel:

- Cyclosporin: Concomitant administration of lanreotide injections with cyclosporin may decrease blood levels of cyclosporin.

10 ADVERSE EVENT REPORTING

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

10.1 Disease Progression

The study is an oncology based trial; disease progression will not be recorded as an AE, but will be reported on the eCRF.

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

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

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

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

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

10.2.2 Causality Classification

The relationship of an AE to the Study Treatment (Somatuline Autogel) will be classified according to the following:

Related: reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the IMP in the sense that it is plausible, conceivable or likely.

Not related: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the IMP.

10.2.3 Assessment of expectedness

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

The reference document for assessing expectedness of AEs/reactions in this study will be: The currently registered UK Summary of Product Characteristics for Somatuline Autogel 60mg, Somatuline Autogel 90mg, and Somatuline Autogel 120mg.

10.2.4 Laboratory Test Abnormalities

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

- They result in a change in IMP schedule of administration (change in dosage [not including titration based dosage changes], delay in administration, IMP discontinuation).
- They require intervention or a diagnosis evaluation to assess the risk to the patient.
- They are considered as clinically significant by the Investigator.

10.2.5 Abnormal Physical Examination Findings

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

10.2.6 Other Investigation Abnormal Findings

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

10.3 Recording and Follow-up of Adverse Events

At each visit the patient should be asked a non-leading question such as: "Do you feel different in any way since starting the new treatment/the last assessment?"

Follow-up of all AEs will be conducted in accordance with the usual clinical practice.

AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

10.4 Serious Adverse Events

10.4.1 Definitions

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

A SAE is any AE occurring at any dose that:

1) results in death;
2) Is life threatening, that is any event that places the patient at immediate risk of death from the reaction as it occurred? It does not include a reaction that, had it occurred in a more severe form, might have caused death;
3) results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further);
4) results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
5) results in congenital anomaly/birth defect in the offspring of a patient who received the IMP;
6) Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

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

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.

- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the Investigator or treating physician**. For protocol-specified hospitalisation in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.

- Pre-planned or elective treatments/surgical procedures should be noted in the patient's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequels which meet the criteria for seriousness described above.

10.4.2 Reporting Requirements

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

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

10.4.3 Mandatory Information for Reporting an SAE

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

- Trial number
- Centre number
- Patient number
- AE
- Investigator's name and contact details

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

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

10.5 Pregnancy

Pregnancy itself is not a criterion for seriousness. However, any pregnancy occurring during treatment with Somatuline Autogel should be reported to the pharmacovigilance contact specified at the beginning of this protocol in the same timelines as an SAE (within 24 hours of becoming aware of it), using the Standard Pregnancy Outcome form and entered on the AE form in the eCRF. The investigator/ monitoring physician will be instructed by the sponsor in the tracking of the pregnancy outcome (a specific form to obtain the information required will be sent to the monitoring physician).

Investigators must instruct all female patients to inform them immediately should they become pregnant during the study. In the event of a pregnancy the investigator will decide whether treatment with Somatuline Autogel should be continued.

10.6 Deaths

All AEs related to Somatuline Autogel and resulting in death must be reported as an SAE within 24 hours of the Investigator's knowledge of the event.

The convention for recording death is as follows:

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

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

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to Somatuline Autogel.

If Somatuline Autogel is discontinued due to an SAE it must be reported immediately to the Sponsor's designated representative.

In all cases the Investigator must ensure the patient receives appropriate medical follow-up.

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

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CA), IECs, IRBs and other Investigators

involved in this study. Reporting will be done in accordance with the applicable regulatory requirements.

11 STATISTICAL CONSIDERATIONS

11.1 Subject Classification and Definitions

- **Enrolled subject:** Patient fully informed about the study who has given written informed consent to participate (before any occurrence of trial related procedure)
- **Screened failure subject:** Enrolled patient who fails to fulfil one or more entry criteria and thus does not proceed to the treatment phase of the study. Although not exposed to study medication, they may have been exposed to some study related procedures. Records up to the time of premature termination should be completed including the reason for termination.
- **Treated subject :** Enrolled patient who is treated with at least one dose of study medication
- **Study Completed subject:** Treated patient who has completed all specified phases/assessments/IMP of the study.
- **Drop-out subjects** Treated patient who did not complete the study and/or treatment.

11.2 Analyses Populations Definitions

- **Screened population**: All subjects enrolled
- **Safety population** All subjects who received at least one dose of study medication and have at least one post-baseline safety assessment
- **Intention to Treat (ITT)/Treated population** All subjects who received at least one dose of study medication
- **Per Protocol Population** All subjects in the ITT population for whom no major protocol deviations occurred during the trial.

11.3 Populations Analysed

The primary analysis based on the primary efficacy endpoint(s) will be performed on the ITT population. In addition a supportive analysis will be performed on the PP population (if sample size allows). The analyses of safety data will be performed based on the safety population.

11.4 Sample Size Determination

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)

11.5 Significance Testing and Estimations

As this is an exploratory study, statistical testing will only be carried out for exploratory purposes. Unless otherwise stated, testing will be performed at the 5% level of significance. Where appropriate, 95% confidences intervals for estimates will be presented. No adjustment for multiplicity will be performed.

11.6 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO) managed by the sponsor. A Reporting and Analysis plan (RAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9 or higher).

11.7 Demographic and Other Baseline Characteristics

In order to characterise the study population, descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data will be presented for the ITT, PP and Safety populations.

11.8 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled, treated, withdrawn and included in each population will be tabulated. In addition, primary reasons for discontinuation of study treatment will be tabulated. The number of doses and dosage of study drug received will also be tabulated.

11.9 Efficacy Evaluation

11.9.1 Primary Efficacy Analysis

As indicated in section *8.1,* the primary efficacy endpoint is an assessment of the clinical value of enumeration of circulating tumour cells (CTCs) to predict clinical symptomatic response in patients receiving Somatuline Autogel. Thus the endpoint is assessed using two efficacy variables; CTCs which will be enumerated at baseline and weeks 1, 5, 17, 25 and 53 and clinical symptomatic response. Clinical symptomatic response will be based on 24 hour symptom frequency and severity which will be measured on a daily basis for the 7 days preceding the first study treatment, for the first 16 weeks of the study and 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, patients will provide 24 hour symptom frequency and severity on a daily basis on days 11 to 28.

The relationship between CTC presence at baseline and clinical symptomatic response will be assessed using logistic regression. The odds ratio for the effect of CTC presence on response will be estimated from this model and the associated 95% confidence interval calculated.

The relationship between CTC presence and clinical symptomatic response will also be assessed adjusted for the presence of other potentially influential patient characteristics (such as disease status (stage and grading of NET) and previous treatment) using multiple logistic regression. The potentially influential characteristics will be selected initially on the basis of simple logistic regressions. Those characteristics with a Wald test $p<0.2$ will be retained for inclusion in a multiple logistic regression model that will also include CTC presence. Using an appropriate stepwise procedure, a final multiple logistic regression model will be derived that includes CTC presence along with any still influential characteristics. From the final model the odds ratio for the effect of CTC presence on response, adjusted for any will be estimated and the associated 95% confidence interval calculated.

The relationship between the absolute value of CTCs and clinical symptomatic response and the use of different CTC cut-off values other than 0 for predicting clinical response will also be investigated using logistic regression if there is a sufficient range of CTC values observed in the study.

11.9.2 Exploratory Primary Efficacy Analysis

There is an additional exploratory primary efficacy endpoint of progression free survival and its relationship with CTC enumeration. The exploratory primary efficacy variable of progression free survival at 53 weeks will be assessed using RECIST 1.1.

The relationship between CTC presence and progression free survival at 53 weeks will be investigated descriptively by summarizing the percentage of patients progression free at 53 weeks by CTC presence and overall.

11.9.3 Secondary Efficacy Analyses

11.9.3.1 Effect of Somatuline Autogel on the symptoms of diarrhoea and flushing in patients with a functioning NET

Symptom frequency and severity will be summarised descriptively over time. Clinical response will be summarised descriptively by CTC presence (CTCs>0) and overall.

11.9.3.2 Effect of Somatuline Autogel treatment on quality of life via the EORTC QLQ-NET21 and EORTC-QLC-C30

Quality of life domain scores will be summarised descriptively over time.

11.9.3.3 Progression Free Survival at one year

Progression free survival at 53 weeks will be summarised descriptively.

11.9.4 Exploratory Secondary Analyses

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

Plasma CgA, urinary and plasma 5-HIAA and plasma neurokinin A levels will be summarised descriptively and plotted against CTC numbers.

11.9.4.2 Correlation between urinary 5-HIAA and plasma 5-HIAA.

The correlation between urinary and plasma 5-HIAA levels will be presented.

11.9.4.3 Genomic profile of CTCs at baseline and at the time of any observed progression

The genomic profile of CTCs will be summarised descriptively.

11.9.4.4 Genomic profile of liver metastases at the time of any observed progression

The genomic profile of liver metastases will be summarised descriptively.

11.9.4.5 Presence and density of SSTR subtypes 2 and 5 on CTCs

The presence and density of SSTR2 and SSTR5 on CTCs will be summarised descriptively over time.

11.9.4.6 Comparison of the SSTR2 and SSTR5 density with patients' clinical symptomatic response and progression free survival during Somatuline Autogel treatment.

Furthermore the density of SSTR2 and SSTR5 on CTCs will be summarised descriptively by clinical symptomatic response and by progression free survival.

11.9.4.7 Comparison of the density of SSTR2 and SSTR5 on CTCs with that on primary tumour and liver metastases in the patients where the primary tumour or liver metastases samples are available.

The density of SSTR2 and SSTR5 on CTCs will also be compared with that on primary tumour and liver metastases by summarising the data descriptively in patients with primary tumour and liver metastasis samples available.

11.10 Safety Evaluation

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

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

Incidence of all reported AEs, Treatment Emergent AEs (TEAEs), SAEs and non-serious AEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs associated with premature withdrawal of study medication.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and by overall will be presented for vital signs (blood pressure and heart rate) at each assessment with change from baseline.

11.11 Analyses and Data Monitoring

No interim analysis will be performed.

12 MONITORING PROCEDURES

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and wellbeing of patients are protected, that trial data are accurate (complete and verifiable to source data) and that the trial is conducted in compliance with the protocol, GCP and regulatory requirements.

12.1 Routine Monitoring

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

The site must complete the eCRFs within 5 days of the patient's visit and on an on-going basis to allow regular review by the study monitor, both remotely via the internet and during site visits. The central study monitor at IPSEN will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

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

13 STUDY MANAGEMENT

13.1 Inspections and Auditing Procedures

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

Auditors and inspectors must have direct access to study documents and site facilities as specified in section 12.1, and to any other locations used for the purpose of the study in question (e.g., laboratories).
In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

13.2 Data Recording of Study Data

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

The Investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The Investigator, by completing the signature log, may formally designate authority to complete /eCRFs to appropriately qualified staff having certified user access to the eCRF.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each "visit status" eCRF page to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the Investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF. All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

13.3 Source Data Verification

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

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

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

The following information is expected to be seen in the investigators patient's notes for this trial.

- demographics
- date of informed consent, identity of the study, patient number
- visit dates with patients status
- results of physical examinations
- diagnosis and medical history
- eligibility criteria
- concomitant medication
- study treatment administration
- results of laboratory tests
- CTC enumeration
- CT/MRI scan results and RECIST reports/measurements.
- vital signs
- evolution of the clinical picture
- all AEs/SAEs with start/end dates
- the date the patient completed or withdrew from the study and the reason for withdrawal, if applicable

Furthermore, completed questionnaires by patient (QoL) will be considered as source data. Electronic copies will be transmitted and sent to data management.

Definition for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH GCL Section 1.51].

- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate, copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). [ICH GCP Section 1.52].

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

13.4 Data Quality

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. The electronic signatures consist of an individual and confidential username and password combination. It is declared to be legally binding equivalent of the hand written signature. Only sponsors' authorised users will get access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Paper CRFs will be available to ensure business continuity in case the eCRF are unavailable at the site for a prolonged period; they will be used after prior permission is gained from the sponsor.

Data management will be conducted by a CRO. All data management procedures will be completed in accordance with Ipsen and contracted CRO SOPs. Data will be monitored at the investigator site (see section 12). CRF (i.e. patient questionnaires)

and other data documentation removed from the investigator sites will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical trial, in an electronic format (PDF) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will be raised within the EDC system. It is the central study monitors responsibility to ensure that all queries are resolved by the relevant parties.
The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

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

13.5 Record Archiving and Retention

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

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

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

14 ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

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

14.2 Publication Policy

Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians, subject to the consent of each individual and entity concerned, including acknowledgement of Sponsor. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee.

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

The Sponsor will publish results of the Clinical Trial, whether positive or negative, on a free publicly accessible clinical trial results database within one year of the Clinical Study Report completion.

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

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

14.3 Clinical Study Report

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

14.4 Contractual and Financial Details

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

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

14.5 Insurance, Indemnity and Compensation

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

15 PROTOCOL AMENDMENTS

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

- ***Non-Substantial Amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs/IRBs or Competent Authorities (CA) for information purposes.

- ***Substantial Amendments*** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the patients;
  - the scientific value of the trial;
  - the conduct or management of the trial; or
  - the quality or safety of the IMP used in the trial.

Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the EU member states, approval or 'favourable opinion' can be assumed if

the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.

- ***Urgent Amendments*** are those that require urgent safety measures to protect the trial patients from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

16 REFERENCES

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

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[3] Kloppel, G et al. Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. Endocrine Tumours of the Gastrointestinal Tract: Part I Volume 19, Issue 4, August 2005, Pages 507–517.

[4] Weil C. Gastroenteropancreatic endocrine tumours. Klin Wochenschr. 1985; 63: 433-59.

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[6] Strosberg J and Kvols L. Antiproliferative effects of somatostatin analogs in gastroenteropancreatic neuroendocrine tumors. World J Gastroenterol 2010; 16: 2963-70.

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[8] Khan MS et al. Long-term results of treatment of malignant carcinoid syndrome with prolonged release lanreotide (Somatuline Autogel). Aliment Pharmacology Ther 2011; 34:235-242.

[9] Ruszniewski P et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. Neuroendocrinology 2004; 80: 244-251.

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[11] Khan M et al. Circulating Tumour Cells As Prognostic markers in Neuroendocrine Tumours. J of Clin Oncology 2013; 31: 365-72.

[12] Khan M et al. Circulating Tumour Cells and EpCAM Expression in Neuroendocrine Tumours. Clin Canc Res 2011; 17: 337-45.

[13] Cristofanilli M et al. Circulating tumor cells: A novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol 2005; 23: 1420-1430.

[14] Cristofanilli M et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004; 351: 781-791.

APPENDIX 1

Protocol Amendment SA02

PROTOCOL AMENDMENT FORM

STUDY NUMBER:	A-97-52030-270
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).
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol version 5.0 dated 19 December 2014

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**11 DECEMBER 2013**	**19 DECEMBER 2014**
Page	**Section**	**WAS**	**IS**
4	Synopsis Study Population	Patients may have undergone recent surgery with curative intent but have residual NET tumour and symptoms.	Patients may have undergone ~~recent~~ surgery with curative or debulking intent but have residual NET tumour and symptoms.
23	Study Design – 4.1.2	**4.1.2. Design** This is a multicentre, open label, single group phase IV study which will be conducted across 12 sites in the UK. It is intended that the study will run for 2 years, which includes a 1 year treatment period.	**4.1.2. Design** This is a multicentre, open label, single group phase IV study which will be conducted across 14 sites in the UK. It is intended that the study will run for 2.5 years, which includes a 1 year treatment period and an 18 month recruitment period.

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28	Study Duration	***4.3.2 Study Duration*** The overall duration of the study will be approximately 24 months, which is inclusive of an approximate recruitment period of 12 months and a 12 month follow up period. The study will be considered to have started when the first patient has provided signed informed consent to participate in the study. The study will be considered to have finished after the last patient has completed the last follow-up period in the study. For notification to the competent authority, the study will be considered to have finished ("End of Study") when the last patient has completed the last study visit.	***4.3.2 Study Duration*** The overall duration of the study will be approximately ~~24~~ 30 months, which is inclusive of an approximate recruitment period of ~~12~~ 18 months and a 12 month ~~follow-up~~ treatment period. The study will be considered to have started when the first patient has provided signed informed consent to participate in the study. The study will be considered to have finished after the last patient has completed the last ~~follow-up~~ treatment period in the study. For notification to the competent authority, the study will be considered to have finished ("End of Study") when the last patient has completed the last study visit.
29	Study Population	**6.1 Screening Log and Number of Patients** It is planned to recruit approximately 50 patients at approximately 12 centres. Section (11.3) provides a discussion of sample size.	**6.1 Screening Log and Number of Patients** It is planned to recruit ~~approximately~~ 50 patients at ~~approximately~~ ~~12~~ 14 centres in the UK. Section (11.3) provides a discussion of sample size.

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29/30	Study Population	**6.2 Inclusion Criteria** All patients must fulfil the following: 1) Provision of written informed consent prior to any study related procedures. 2) Patients (either sex) must be 18 years or older. 3) Patients must have a documented diagnosis of a functioning midgut NET. 4) In order to avoid patients with rapidly progressing tumours, only patients with well or moderately differentiated tumours and with a Ki67 proliferation index of <20% will be recruited. 5) The clinically appropriate treatment for the patient must primarily be monotherapy with a somatostatin analogue 6) Patients must have had either a positive somatostatin receptor scintigraphy result or a positive ^{68}Gallium-DOTATATE PET imaging result. 7) Patients must have a documented urinary or plasma 5-HIAA result within the year prior to study entry which is above the laboratory reference range.	**6.2 Inclusion Criteria** All patients must fulfil the following: 1) Provision of written informed consent prior to any study related procedures. 2) Patients (either sex) must be 18 years or older. 3) Patients must be suffering from symptoms of diarrhoea and/or flushing at the time of study enrolment. 4) Patients must have a documented diagnosis of a functioning midgut NET. 5) In order to avoid patients with rapidly progressing tumours, only patients with well or moderately differentiated tumours and with a Ki67 proliferation index of <20% will be recruited. 6) The clinically appropriate treatment for the patient must ~~primarily~~ be ~~mono~~therapy with a somatostatin analogue 7) Patients must have had either a positive somatostatin receptor scintigraphy result or a positive ^{68}Gallium-DOTATATE PET imaging result. 8) ~~Patients must have a documented urinary or plasma 5-HIAA result within the year prior to study entry which is above the laboratory reference range.~~
30	Study Population	**6.3 Exclusion Criteria** 5) Requires medical treatment for the symptoms of the NET other than primarily monotherapy with a somatostatin analogue	**6.3 Exclusion Criteria** ~~5) Requires medical treatment for the symptoms of the NET other than primarily monotherapy with a somatostatin analogue.~~

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31	Study Population	**6.3.1 Washout Criteria** Any patients 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 dose or a 6 week wash out period after a single long acting somatostatin analogue dose.	**6.3.1 Washout Criteria** Any patients 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 dose or a 6 week wash out period after a single long acting somatostatin analogue dose. Patients 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 patients 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.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	A-97-52030-270	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Protocol version 5.0 dated 19 December 2014**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	1. Clarification of the wording regarding surgical history (synopsis page 4). 2. Addition to the inclusion criteria stating that patients must be symptomatic at the time or enrolment into the study. Although this is implicit in the primary study outcome some investigators suggested greater clarification was required. 3. To include patients who have had more than one injection of long acting somatostatin analogue prior to surgery with curative intent. Once patients have had surgery it is felt that prior treatment is no longer relevant. 4. To clarify the use of concomitant medications for acute symptomatic episodes during the study. 5. To extend the recruitment period from 12 to 18 months as	

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	recruitment has been slower than expected. 6. Change of the wording "follow-up period" to "treatment period" in section 4.3.2 as there is no follow up period in this study. **ADDITIONAL ITEMS – (NOT IN PROTOCOL):** 7. Removal of Oxford site. The PI at Oxford felt that he had insufficient time to conduct the study and a replacement could not be found therefore the site was never initiated. 8. Addition of three new sites: In order to facilitate recruitment three new sites have been identified to replace Oxford and to further boost recruitment: o University Hospital Southampton o Maidstone Hospital o Basingstoke and North Hampshire Hospital 9. To provide a flowchart of the patient schedule (version 1.0 dated 19 December 2014) to simplify informed consent discussions. It was felt that this would assist in informing patients in initial study discussions prior to them reading the full patient information leaflet. 10. To provide a referral flyer (version 1.0 dated 19 December 2014) for use in doctor's offices and a referral letter (version 1.0 dated 19 December 2014) offering a small fee to cover the cost of identifying and approaching patients and providing copies of relevant hospital notes. This is also to boost patient recruitment, particularly for tertiary sites where patients are often already on established treatment regimens. It is hoped that this will facilitate the referral of patients who are more treatment naïve at these sites. 11. A 'Retained Laboratory Sample Instruction Form' has been included for patients to indicate how they would like the frozen DNA blood samples and any tumour/liver tissue samples to be treated at the end of the study. If patients do not wish to donate samples to the UCL Cancer Institute Tissue Bank they may opt to have the samples destroyed in the laboratory or returned to their referring hospital site (version 1.0 dated 19 December 2014). 12. The GP letter has been updated with the amended inclusion and exclusion criteria (version 4.0 dated 19 December 2014). 13. The Patient Information Sheet has been updated with the revised protocol number (version 3.0 dated 19 December 2014).	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒

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		(tick one)
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

APPENDIX 2

Protocol Amendment A03

PROTOCOL AMENDMENT FORM

STUDY NUMBER:	A-97-52030-270
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).
AMENDED PROTOCOL VERSION NUMBER & DATE	Protocol version 6.0 dated 27 October 2015

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**19 DECEMBER 2014**	**27 OCTOBER 2015**
Page	**Section**	**WAS**	**IS**
1 2	Title Page Protocol Signatures	PPD	PPD
3	Summary of Changes	Not present	Section added
5	Synopsis – Study Design	Recruitment will be approximately 18 months; therefore study duration is expected to be 30 months.	Recruitment will be approximately ~~18~~ 21 months; therefore study duration is expected to be ~~30~~ 33 months.
8	Synopsis – Study Treatment	The recruitment period will be 18 months although it could be extended if necessary to obtain the targeted number of patients.	The recruitment period will be ~~18~~ 21 months although it could be extended if necessary to obtain the targeted number of patients.
23	Study Design – 4.1.2	**4.1.2. Design** This is a multicentre, open label, single group phase IV study which will be conducted across 14 sites in the UK. It is intended that the study will run for 2.5 years, which includes a 1 year treatment period and an 18 month recruitment period.	**4.1.2. Design** This is a multicentre, open label, single group phase IV study which will be conducted across 14 sites in the UK. It is intended that the study will run for 33 months ~~2.5 years~~, which includes a ~~1 year~~ 12 month treatment period and a~~n~~ ~~18~~ 21 month recruitment period.

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27 / 28	Justification of Design – 4.3	**Paragraph 2** Patients will receive Somatuline Autogel 120 mg injections every 28 days for 3 injections, followed by titration depending on patients' symptomatic response. A starting dose of Somatuline Autogel 120mg is within the UK licence for the use of Somatuline Autogel to treat the symptoms associated with NETs and is supported by data from recent Ipsen clinical trials (CLARINET and PRIMARYS) which have utilised a starting dose of Somatuline Autogel 120mg. **Paragraph 4** PRIMARYS (Ipsen sponsored study) is a phase IIIb, single arm, open-label, multicentre study to assess the tumour volume reduction and growth hormone/insulin-like growth factor 1 control with lanreotide Autogel 120mg every 28 days in patients with GH-secreting macroadenoma associated with acromegaly (ClinicalTrials.gov identifier, NCT00690898, EudraCT No: 2007-000155-34)). Somatuline Autogel 120mg was well tolerated in the PRIMARYS study. No patients withdrew from the study due to gastrointestinal effects[15].	**Paragraph 2** Patients will receive Somatuline Autogel 120 mg injections every 28 days for 3 injections, followed by titration depending on patients' symptomatic response. A starting dose of Somatuline Autogel 120mg is within the UK licence for the use of Somatuline Autogel to treat the symptoms associated with NETs. ~~and is supported by data from recent Ipsen clinical trials (CLARINET and PRIMARYS) which have utilised a starting dose of Somatuline Autogel 120mg.~~ In February 2015 Ipsen Limited received a new licence extension for the use of Somatuline Autogel 120mg for the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded. The licence is in adult patients with unresectable locally advanced or metastatic disease. This licence extension was based upon the CLARINET study (see below), which utilised a dose of Somatuline Autogel of 120mg. **Paragraph 4 (deleted)** ~~PRIMARYS (Ipsen sponsored study) is a phase IIIb, single arm, open-label, multicentre study to assess the tumour volume reduction and growth hormone/insulin-like growth factor 1 control with lanreotide Autogel 120mg every 28 days in patients with GH-secreting macroadenoma associated with acromegaly (ClinicalTrials.gov identifier, NCT00690898, EudraCT No: 2007-000155-34)). Somatuline Autogel 120mg was well tolerated in the PRIMARYS study. No patients withdrew from the study due to gastrointestinal effects[15].~~

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28	Study Duration	***4.3.2 Study Duration*** The overall duration of the study will be approximately 30 months, which is inclusive of an approximate recruitment period of 18 months and a 12 month treatment period. The study will be considered to have started when the first patient has provided signed informed consent to participate in the study.	***4.3.2 Study Duration*** 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 patient has provided signed informed consent to participate in the study.
	Appendices	**Appendix I and Appendix 2 added**	Protocol amendment forms for SA02 and A03 inserted.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	A-97-52030-270		
AMENDED PROTOCOL VERSION NUMBER & DATE	**Protocol version 6.0 dated 27 October 2015**		
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒		
REASON(S) FOR CHANGES	1. New medical director from Sept 2015 – PPD 2. Summary of changes (page 3) not present in original document 3. Recruitment has been slower than expected with this patient population and although 72% of patients (36) have been recruited and there are still 2 months recruitment period left we are not confident that we can recruit 50 patients in that time. We have also had 3 screen failures that should be replaced. 4. Update to the Somatuline Autogel licensing information (4.3) and deletion of reference relating to acromegaly (PRIMARYS). 5. Appendices 1 and 2 (protocol amendment forms for Substantial Amendment SA02 and Non-Substantial Amendment A03).		
	CRF UPDATE	Yes ☐ No ☒	
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒	
	DATABASE UPDATE	Yes ☒ No ☐	
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐	