PROTOCOL TITLE: PHASE IIA, OPEN LABEL, DOSE ASCENDING STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, SAFETY AND TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A SINGLE DOSE OF LANREOTIDE PRF IN SUBJECTS WITH ACROMEGALY PREVIOUSLY TREATED AND CONTROLLED WITH EITHER OCTREOTIDE LAR OR LANREOTIDE AUTOGEL

STUDY PROTOCOL
STUDY NUMBER: 8-55-52030-309

LANREOTIDE PRF SOLUTION FOR INJECTION
EudraCT Number: 2014-002389-62

Final Version (with Amendment 7): 16 December 2016

Sponsor's Medically Responsible Person:
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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol 8-55-52030-309 entitled "phase IIA, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with either octreotide LAR or lanreotide Autogel". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), 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: _____

TITLE: _____ SIGNATURE: _____

DATE: _____

OFFICE: _____

Sponsor's Representative Signature:

NAME: David Rich, MPhil

TITLE: Medical Development Director - Endocrinology SIGNATURE: _____

DATE: _____

OFFICE: _____

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol 8-55-52030-309 entitled "phase IIA, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with either octreotide LAR or lanreotide Autogel". I am aware of my responsibilities as a coordinating investigator under the guidelines of GCP, 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: Sebastian J.C.M.M. Neggers, MD, PhD

TITLE: Principal Investigator SIGNATURE: _____

DATE: _____
OFFICE: _____

SUMMARY OF CHANGES

The initial version of the protocol dated 01 September 2014 was amended six times. The current version of the protocol was released on 16 December 2016 and includes Amendments 1 to 7. The protocol amendment forms were prepared and are provided in Appendices 3 to 8 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	19 November 2014	Appendix 3
2	18 February 2015	Appendix 4
3	12 June 2015	Appendix 5
4	27 July 2015	Appendix 6
5	22 March 2016	Appendix 7
6	20 May 2016	Appendix 8
7	16 December 2016	Appendix 9

SYNOPSIS

Name of sponsor/company: Ipsen Pharma SAS

Name of finished product: Lanreotide prolonged release formulation (PRF), solution for injection
Name of active ingredient(s): Lanreotide acetate

Title of study: Phase IIa, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with either octreotide LAR or lanreotide Autogel
Study number: 8-55-52030-309

Number of planned centres: up to 40

Planned study period: 02/2015 to 06/2018 | **Phase of development:** Phase IIa

Objectives:
Primary:
- To identify the maximum tolerated dose (MTD) and to investigate the pharmacokinetics (PK) of a single dose of lanreotide PRF in subjects with acromegaly

Secondary:
- To investigate the safety and tolerability of a single dose of lanreotide PRF
- To investigate the pharmacodynamics (PD) of a single dose of lanreotide PRF
- To investigate the PK of the excipient

Exploratory:
Biobanking of blood samples for further biomarkers analysis in subjects who consent to the exploratory part of the study

Methodology:
Subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR) or lanreotide Autogel will be recruited to this open label study. Eligible subjects will enter a 4 week run in period (or up to 6 weeks under certain circumstances), during which they will receive the same single dose of either octreotide LAR or lanreotide Autogel as their previous treatment. A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks or up to 6 weeks under certain circumstances after the last octreotide LAR or lanreotide Autogel administration). Subjects will remain at the study centre for 24 hours after the dose. A follow up period of 12 additional weeks after the 12 week treatment period, will also be included. During the follow up period, subjects will not receive any treatment for acromegaly. Study visits will be performed on Days 1, 2, 3, and 5, and Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at Weeks 15, 17, 19, 21, 23 and 25 during follow up. All study visits can be performed at the study site. However, study visits on Weeks 4, 7, 11, 15, 19 and 23 can be performed at the study site and/or at the subjects home as per investigator's and subject's decision.
It is planned to include three cohorts of subjects; Cohort 1 will receive lanreotide PRF 180 mg, Cohort 2 will receive 270 mg and Cohort 3 will receive 360 mg. Nine subjects will be allocated to each lanreotide PRF treatment cohort. Each cohort must enrol at least six subjects previously treated with octreotide LAR. Each cohort can enrol up to three subjects previously treated with lanreotide Autogel.
Progression to each ascending dose cohort (or groups of subjects) will be dependent upon a review of data from the preceding cohort (or groups of subjects) during meetings of the data review committee (DRC). The DRC will review the safety data from each cohort after all subjects in the cohort completed Visit 5 (Week 2 postdose). At this time, if no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next treatment cohort (or groups of subjects). The dose escalation will proceed with a 3+3+3 scheme in order to enrol nine subjects within each dose cohort. In Cohort 2 subjects will be reviewed on a 1+2+2+2+2 scheme and in Cohort 3 on a 2+2+2+3 scheme.
If any serious adverse events (SAEs) occur, a relationship with the exposure to lanreotide PRF will be assessed. The pre-established stopping rules for the DRC decision for study discontinuation

and/or inclusion of the subsequent treatment cohort include the occurrence of dose limiting toxicities (DLTs). A DLT is defined as an adverse event (AE; excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Visit 5 (Week 2)) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre-established criteria (more often grade 3 or 4 toxicity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria). The occurrence of 2 DLTs would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects (2 more subjects for Cohort 2 and Cohort 3) at the same dose level.

The identification of the MTD will be left to the discretion of the DRC.

Assessments throughout the follow up period will evaluate the safety, tolerability and PK of lanreotide PRF. Levels of insulin like growth factor-1 (IGF-1) and growth hormone (GH) will also be evaluated. The proportion of subjects with age adjusted IGF-1 levels <1.3 x upper limit of normal (ULN), with GH ≤2.5 ng/mL and with GH ≤1.0 ng/mL will be recorded. During the follow up period, if the investigator judges that the subject requires any treatment for acromegaly (reappearance of clinical or biochemical symptoms of acromegaly), the subject will be withdrawn from the study and will receive treatment according to routine clinical practice.

The overall duration of the study will be approximately 32 months. Each subject will participate in the study for up to 7.5 months.

Number of subjects planned:

A maximum of 27 subjects will be treated with lanreotide PRF (nine subjects per cohort).

Diagnosis and criteria for inclusion:

Subjects with acromegaly, well controlled by a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

Inclusion criteria:

All subjects must fulfil all of the following criteria to be included in the study:

(1) Documented diagnosis of acromegaly.
(2) Provided written informed consent prior to any study related procedures.
(3) Between 18 and 75 years of age inclusive.
(4) Female of nonchildbearing potential or male. Nonchildbearing potential is defined as being postmenopausal for at least 1 year, or women with documented infertility (natural or acquired).
(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (up to 7.5 months).
(6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on local laboratory results, during the Screening period).
(7) If the subject is receiving treatment for hypertension, the dose has been stable for at least 1 month prior to study entry.
(8) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow up evaluation as specified in the protocol.

Exclusion criteria:

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

(1) Has undergone radiotherapy within 2 years prior to study entry.
(2) Has been treated with a dopamine agonist and/or GH receptor antagonist or has undergone pituitary surgery within 3 months prior to study entry.
(3) Is anticipated to require pituitary surgery or radiotherapy during the study.

(4) Has clinically significant hepatic abnormalities and/or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 x ULN and/or alkaline phosphatase (ALP) ≥2.5 x ULN and/or total bilirubin ≥1.5 x ULN and/or gamma-glutamyl transpeptidase (GGT) ≥2.5 x ULN during the Screening period (central laboratory results) or a history of these findings when on somatostatin analogue (SSTa) treatment.
(5) Has clinically significant pancreatic abnormalities and/or amylase and/or lipase ≥1.5 x ULN during the Screening period (central laboratory results).
(6) Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN during the Screening period (central laboratory results).
(7) Has uncontrolled diabetes (glycosylated haemoglobin (HbA1c) ≥9%, centrally assessed during the Screening period), or has diabetes treated with insulin for less than 6 months prior to study entry.
(8) Has any known uncontrolled cardiovascular disease or had any of the following within 6 months of Screening: ventricular or atrial dysrhythmia ≥grade 2, bradycardia ≥grade 2, electrocardiogram (ECG) QT interval corrected (QTc) prolonged ≥grade 2, myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, hypertension not adequately controlled by current medications.
(9) Use of any hormone replacement therapy (HRT) with oestrogens.
(10) Has symptomatic gallstones/sludge at the Screening Visit echography (local assessment) OR is asymptomatic but has echography showing clear evidence of impending inflammation such as localised mucosal thickening suggesting the subject is at high risk of developing acute disease. Subjects with asymptomatic gallstones/sludge and otherwise normal echography may be entered at the discretion of the investigator.
(11) Has abnormal findings during the Screening period, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.
(12) Has been treated with any other investigational medicinal product (IMP) prior to the first study visit without undergoing a washout period of seven times the elimination half life of the investigational compound.
(13) Has a known hypersensitivity to any of the test materials or related compounds.
(14) Is likely to require treatment during the study with drugs that are not permitted by the study protocol.
(15) Has a history of, or known current, problems with alcohol or drug abuse.
(16) Has any mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

Test product, dose, mode of administration:

Lanreotide PRF will be supplied in a 1.2 mL prefilled syringe fitted with a 1.2/1.4 mm (inner diameter/outer diameter) needle packed in a laminated pouch.

The product is intended to deliver 180, 270 or 360 mg lanreotide (potency is expressed as lanreotide base) for the phase 2a clinical study. The different strengths are dose proportional as syringes are filled with increasing quantities of the same lanreotide supersaturated bulk solution.

All strengths will be provided in the same presentation.

Lanreotide PRF will be administered by deep subcutaneous injection in the superior, external quadrant of the buttock at the doses indicated in the table below. Nine subjects will be allocated to each dose cohort.

Cohort [a]	Lanreotide PRF dose
1	180 mg
2	270 mg
3	360 mg

a each subsequent dose cohort will be initiated following recommendations from the DRC.

Duration of treatment:
Overall study duration: Approximately 32 months for three dose levels.
Subject study participation: Up to 7.5 months (4 week run in period or up to 6 weeks under certain circumstances, a 12 week treatment period and a 12 week follow up period without treatment).

Reference therapy, dose and mode of administration: Not applicable.

Criteria for evaluation (treatment period):

Safety variables:

- AEs, throughout the study.
- Vital signs (supine and standing blood pressure and heart rate, and body temperature) at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.
- Physical examination at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.
- 12-lead ECG, QTc interval will be calculated using Fridericia methodology in all subjects at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, 24 hours postdose, and at Weeks 2, 5 and 13.
- Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, 24 hours postdose on Day 2, Day 3, and Weeks 2, 3, 4, 5, 9 and 13 of the treatment period.
- HbA1c at Screening and Week 13.
- Estimated glomerular filtration rate (eGFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula [1], at Screening, Baseline (predose on Day 1), and Weeks 2, 5, 9 and 13 of the treatment period.
- Gallbladder echography at Screening, Week 5 and Week 13 of the treatment period.
- Putative antibodies to lanreotide at Baseline (predose on Day 1) and Week 13.
- Evaluation of injection site reactions (appearance, local symptoms). These will be evaluated on a specific form in the electronic case report form (eCRF) at 1 and 6 hours postdose on Day 1, 24 hours postdose and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.

Pharmacokinetic variables:

Lanreotide serum concentration at the following timepoints after administration of lanreotide PRF:

- Baseline (predose on Day 1 of lanreotide PRF administration).
- At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1).
- At 24 hours postdose (Day 2).
- On Days 3 and 5, and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration (the Week 13 sample will be on Day 85 and will correspond to the concentration at the end of the dosing interval (C_{trough})).
- Noncompartmental analysis will be performed and the following PK parameters will be computed: C_{trough}, maximum serum concentration (C_{max}), time to maximum serum concentration (T_{max}), area under the serum concentration time curve from time 0 to 85 days (AUC_{0-85}), area under the concentration time curve extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal half life ($t_{1/2}$), mean residence time (MRT), apparent clearance (CL/F) and apparent volume of distribution (V/F).

Excipient serum concentration at the following timepoints:

- Baseline (predose on Day 1 of lanreotide PRF administration).
- At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration.
- Noncompartmental analysis of the excipient time concentration data will be performed and the following PK parameters will be computed: C_{max}, T_{max}, area under the serum concentration time curve from time 0 to last quantifiable timepoint (AUC_t), $AUC_{0-\infty}$, $t_{1/2}$, MRT, CL/F and V/F.

Pharmacodynamic variables:
The following PD variables will be assessed in all subjects:

- IGF-1 at Screening, Baseline (predose on Day 1), at 6 hours postdose on the day of dosing (Day 1) and at Weeks 5, 9 and 13.
- GH cycle (five sampling times with a sample every 30 minutes for 2 hours in the morning) at Screening, Baseline (predose on Day 1) and at Weeks 5 and 13.
- Random GH sample at 6 hours postdose on the day of dosing (Day 1) and at Week 9.
- Free triiodothyronine (FT_3), free thyroxine (FT_4), thyroid stimulating hormone (TSH) and prolactin (PRL) at Screening, Baseline (predose on Day 1), and at Weeks 2, 5 and 13 of the treatment period.

Biobanking:
Blood samples will be collected at Baseline (predose on Day 1), Weeks 5 and 13 and stored for further biomarkers analysis after the end of the study in subjects who consent to the exploratory part of the study.

Criteria for evaluation (follow up period):
During the follow up period, study visits will be conducted every 2 weeks (±3 days).
Assessments for all subjects will include the following safety and PK variables:

- AEs throughout the study
- Concomitant medications, throughout the study
- Vital signs (supine and standing blood pressure and heart rate, and body temperature) at each follow up visit
- Physical examination at each follow up visit
- Gallbladder echography (only at Week 25 or at early withdrawal (EW))
- Clinical laboratory assessments at each follow up visit
- HbA1c (only at Week 25 or at EW)
- eGFR at Weeks 17, 21 and 25 (or at EW)
- Evaluation of injection site reactions at each follow up visit
- Putative antibodies to lanreotide (only at Week 25 or at EW)
- PK blood sample for lanreotide at Weeks 17, 21 and 25 (or at EW)

The following PD variables will also be assessed for all subjects at Weeks 17, 21 and 25 (or at EW):

- IGF-1
- Random GH sample
- FT_3, FT_4, TSH, PRL (only at Week 25 or at EW)

Statistical methods:
Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule (in Cohort 2 on a 1+2+2+2+2 and in Cohort 3 on a 2+2+2+3 decision rule) focussing a priori on the subject safety. This means that the addition of up to nine subjects would be based on the MTD profile and decisions made at that dose level. In addition, the sample size is based on prior clinical experience with this type of study and subject population and should be sufficient to meet the study objectives. As this is a descriptive safety, tolerability and PK/PD study, no formal statistical testing will be performed.
Each subject who receives the single dose of lanreotide PRF and who has at least one postbaseline safety assessment will be analysed for safety (Safety population). Safety data (TEAEs, SAEs, vital signs, ECG and clinical laboratory tests) will be presented by dose cohort and overall.
The analysis of PK data for lanreotide and the excipient will be performed by a contract research organisation (CRO) under Ipsen's Pharmacokinetics and Drug Metabolism (PDM) Department supervision using a noncompartmental approach. Descriptive summary statistics (number of observations (n), mean, median, standard deviation (SD), range, geometric mean and geometric coefficient of variation for continuous variables, and n and percentage for categorical/nominal variables) will be presented for the serum concentration data of lanreotide and the excipient and PK parameters per dose cohort.

Additional exploratory model-based analysis (population PK analysis) might also be conducted to characterise lanreotide PK parameters such as clearance and volume of distribution, as well as their interindividual variability.
The magnitude of the effect on PD parameters (change from Baseline) will be summarised by using 95% confidence intervals (CIs) for the intent to treat (ITT) and per protocol (PP) populations. To investigate the relationship between PD variables (GH and IGF-1) and lanreotide exposure, exploratory PK/PD modelling may be performed if a relationship can be defined. Details regarding PK and PK/PD modelling will be described in a separate Data Analysis Plan and the results will be reported as a standalone report.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC_{0-85}	Area under the serum concentration time curve from time 0 to 85 days
$AUC_{0-\infty}$	Area under the concentration time curve extrapolated to infinity
AUC_t	Area under the serum concentration time curve from time 0 to last quantifiable timepoint
CA	Competent Authorities
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent clearance
C_{max}	Maximum serum concentration
C_{trough}	Concentration at the end of the dosing interval
CRO	Contract research organisation
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT(s)	Dose limiting toxicity(ies)
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EU	European Union
EW	Early withdrawal
FDA	Food and Drug Administration
FT_3	Free triiodothyronine
FT_4	Free thyroxine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GH	Growth hormone
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HRT	Hormone replacement therapy
IB	Investigator’s brochure

ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IGF-1	Insulin like growth factor-1
IMP	Investigational Medicinal Product
INR	International normalised ratio
IRB	Institutional review board
ITT	Intent to treat
LAR	Long acting release
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLN	Lower limit of normal
LSLV	Last subject, last visit
MDD	Medical Development Director
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Pharmacodynamics
PDM	Pharmacokinetics and Drug Metabolism
PK	Pharmacokinetics
PP	Per protocol
PR	Prolonged release
PRF	Prolonged release formulation
PRL	Prolactin
QTc	QT interval corrected
RIA	Radioimmunoassay
RIPA	Radioimmunoprecipitation assay
SAE	Serious adverse event
SAS®	Statistical Analysis System®
SD	Standard deviation
SOP	Standard Operating Procedure
SST	Somatostatin
SSTa	Somatostatin analogue(s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Apparent terminal half life
TEAE	Treatment emergent adverse event

T_{max}	Time to maximum serum concentration
TMF	Trial Master File
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
V/F	Apparent volume of distribution
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

Acromegaly is a rare (incidence approximately 3 cases per million persons per year; prevalence approximately 60 per million), chronic disease caused by excessive secretion of growth hormone (GH) from a pituitary tumour [2]. Increased plasma levels of GH cause the symptoms and pathology of the disease, either directly through actions on target tissues, or indirectly by stimulating excessive secretion of insulin like growth factor-1 (IGF-1).

Disease control of acromegaly consists of different components: biochemical control, tumour volume reduction and improvement of clinical symptoms [3]. GH and IGF-1 concentrations are the main biochemical markers used to measure the response to treatment and represent the most frequent primary endpoints in clinical trials that evaluate efficacy. Both GH and IGF-1 responses have been associated with improved prognosis and mortality decrease.

The treatment of choice is trans-sphenoidal surgery, sometimes in association with radiotherapy [4, 5]. However, despite these measures acromegaly remains active in many patients, as defined by increased systemic levels of GH and IGF-1, the persistence of clinical symptoms, and increased morbidity and mortality [4, 5]. For example, between 40% and 60% of macroadenomas are unlikely to be controlled with surgery alone. Primary medical therapy or surgical debulking followed by medical therapy and/or radiation therapy are options for treatment of such tumours [4].

Somatostatin analogues (SSTa) successfully reduce GH and IGF-1 secretion in approximately 70% of patients [4]. They alleviate many symptoms of acromegaly, improve related comorbid complications, and may reduce or stabilise tumour size in a subset of patients.

Compared to short acting SSTa, long acting formulations have been shown to provide equivalent or better control of acromegaly [6]. The main adverse events (AEs) associated with SSTa are gastrointestinal disorders, including abdominal cramps and an increased incidence of gallbladder sludge and/or stones [4].

1.2 Name and Description of Investigational Medicinal Product(s)

Lanreotide is a well established, synthetic octapeptide analogue of the naturally occurring hormone somatostatin (SST). Compared to SST, the biochemical stability, and thereby the half life of this synthetic molecule has been increased by the incorporation of modified amino acids. In the same way as the native hormone, lanreotide inhibits the secretion of a variety of hormones, including GH, and has antiproliferative activity [7, 8, 9]. Lanreotide has a high affinity for human SST receptors 2 and 5, and activity at these receptors is the primary mechanism considered responsible for GH inhibition.

Laboratory code: BIM23014

INN: Lanreotide

Chemical formula: D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

Empirical formula: $C_{54}H_{69}N_{11}O_{10}S_2$

Molecular weight: 1096.34

Lanreotide is marketed for several indications, including for the long term treatment of acromegaly in patients with an inadequate response to surgery and/or radiotherapy, or for whom pituitary surgery is not an option.

Numerous studies have shown that various formulations of lanreotide are effective in the treatment of acromegaly, with no safety concerns identified [10, 11]. The recommended dosing intervals for current lanreotide formulations are every 7, 10 or 14 days for lanreotide prolonged release (PR) and every 28 days for lanreotide Autogel. However, the need for frequent repeated

treatment for life can be inconvenient. The development of a more extended prolonged release formulation (PRF) of lanreotide will facilitate ease of use and treatment compliance for patients with acromegaly.

A new formulation of lanreotide (lanreotide PRF) has been developed with a view to increasing the dosing interval compared to the currently marketed lanreotide formulations (lanreotide PR and lanreotide Autogel).

The development of lanreotide PRF, with a targeted dosing interval of 12 weeks, will therefore aid in reducing the burden of repeat administration for patients with acromegaly. The new lanreotide PRF formulation is a solution for deep subcutaneous injection and includes the addition of glycofurol as an excipient. Lanreotide PRF is supplied in three dose strengths (180, 270 and 360 mg) as ready to use prefilled syringes. The syringes contain the same bulk product, with the quantity provided in each syringe adjusted to deliver the targeted dose. A more detailed description of the product is given in Section 3.4.

1.3 Findings from Nonclinical and Clinical Studies

Lanreotide has been extensively studied and has proved to be an effective treatment for acromegaly. Further details may be found in the investigator's brochure (IB). This study represents the first in man study of glycofurol formulated lanreotide (lanreotide PRF).

In the frame of the development of the new lanreotide PRF formulation, nonclinical pharmacokinetic (PK)/local tolerance studies performed in dogs with lanreotide PRF (270 and 450 mg) showed a PK profile consistent with 3 month coverage, with lanreotide serum concentrations maintained above a target therapeutic level over 3 months. Assessment of the local tolerance of lanreotide PRF showed a subcutaneous granulomatous inflammation at the injection site at the end of 3 and 6 month periods. These histological findings have already been described for lanreotide Autogel in dogs.

Glycofurol is identified as an excipient in at least two other marketed pharmaceutical products administered by intramuscular (Mobic® (meloxicam), a nonsteroidal anti-inflammatory drug supplied by Boehringer Ingelheim) or intravenous (Phenhydan® (phenytoin), an anticonvulsant supplied by Desitin Pharma) route. To complement the use of glycofurol in the present PRF for subcutaneous injection, toxicology studies were conducted in rats and dogs by daily subcutaneous administration of glycofurol alone at doses of 30, 90 or 180 mg/kg/day for 4 weeks. They showed no systemic effects and glycofurol alone was rapidly absorbed (T_{max} from 0.5 to 2 h in dogs and 0.25 to 0.5 h in rats) and eliminated ($t_{½}$ from 0.37 to 1.3 h in dogs and 1 to 2.8 h in rats). There was no accumulation of glycofurol after daily s.c. administration for 4 weeks in both species. At the injection sites, a spectrum of inflammatory changes comprising subcutaneous necrosis, fibrosis/fibroplasia, subcutaneous subacute inflammation, and haemorrhage in rat and dog, as well as granulomatous panniculitis in dog were induced. Most of these local signs were reversible at the end of the treatment free period. In fact, in humans, the maximum dose of lanreotide PRF planned to be administered by single injection every 3 months is 360 mg, constituting approximately 2 mg/kg of glycofurol for a person of 70 kg. Therefore, the doses of glycofurol tested in the toxicology studies (30 mg/kg to 180 mg/kg) were not only administered with a higher frequency (daily for 4 weeks versus once every 3 months) but were way above the intended clinical dose (15 to 90 times, respectively). Consequently, the local effects that were recorded in the toxicology studies were considered without clinical relevance.

Lanreotide PRF has been tested in a parallel phase I study where the participants were healthy volunteers with cholecystectomy (study DFR-52030-345 and EUDRACT number: 2015-004338-85). Four healthy volunteers received a single injection of lanreotide PRF 180 mg in February 2016. Two of the volunteers had no side effects but two experienced abdominal

pain on the day of the injection and their blood biochemistry revealed elevated hepatic and pancreatic enzymes. These levels returned to within normal ranges by Day 5. These elevations met the protocol-defined criteria for DLT. As a result, no further healthy volunteers were entered into that study. A full safety analysis for the subjects in this study (309) was performed and no similar trends were seen in Cohort 1 or the first subject dosed in Cohort 2. The study DRC on 29th February 2016 recommended to continue study 309 as planned with some precautionary changes that were included in amendment 5.

1.4 Known and Potential Risks and Benefits to Human Patients

1.4.1 Individual Benefits

Lanreotide is an effective treatment of acromegaly. It relieves clinical symptoms and reduces or normalises GH and IGF-1 levels. A complete overview of the efficacy of lanreotide is available in the IB.

The main potential benefit of lanreotide PRF for participating subjects is a reduced number of SSTa injections (from 3 to 1 injection) to maintain optimal disease control.

1.4.2 Collective Benefits

Eligible subjects are expected to participate for a duration of up to 7.5 months. Due to the shortness of this period, even with a reduced number of injections, a collective impact could not be expected.

1.4.3 Known and Potential Risks

The most commonly expected adverse drug reactions following lanreotide treatment are gastrointestinal disorders (most commonly reported are diarrhoea and abdominal pain, usually mild or moderate and transient), cholelithiasis (often asymptomatic), and injection site reactions (pain, nodules and indurations). It should be emphasised that patients with acromegaly have an increased incidence of gallstones compared to the general population, irrespective of SSTa treatment.

No specific risks are identified for the glycofurol excipient, so far. Glycofurol is nontoxic when administered by deep subcutaneous injection at the doses selected for clinical purposes (see details in the IB).

The medical procedures during the study are considered to be safe (venous puncture and gallbladder echography) and do not put participating subjects at any procedure related increased risk.

The half-life of lanreotide PRF in human is not yet known. However, based on dog data, 5 times the mean terminal half-life (t½ ~35 days) of lanreotide PRF corresponds to 175 days (i.e. ~6 months). Therefore a 6-month follow up should be sufficient to cover more than 95% of the profile if the half-life in dogs is similar in human.

The rationale for a follow up of 3 months after the potential 3 months treatment period is based on the need for the study subjects to resume treatment with their approved somatostatin analogue to control acromegaly and GH / IGF-1 levels. Given the similar class of active ingredient, the sponsor believes it is reasonable to let the participants go back to their regular treatment after three months follow up as longer periods off therapy may be associated with unnecessarily higher rates of symptoms. Furthermore after a single dose of lanreotide PRF, anticipated to provide 3 months treatment and after 3 months additional follow-up, it is reasonable to consider that the residual lanreotide concentrations are low enough not to trigger any new safety concern when standard treatment is resumed. Should any concern about this residual concentration arise during the study the sponsor will notify the investigators about the

level of residual concentration which would allow adjusting the restart of either octreotide or lanreotide Autogel treatment.

The risk of reactivation of the disease with clinical symptoms within the 3 month follow up period is taken into consideration. IGF-1 and GH concentrations will be monitored monthly during this period. If the investigator judges that the subject requires any treatment for acromegaly (reappearance of clinical or biochemical symptoms of acromegaly) during the follow-up period, the subject will be withdrawn from the study and will receive treatment according to routine practice.

Additional information regarding risks and benefits to human subjects may be found in the IB.

1.5 Selection of Investigational Medicinal Products and Doses

The new formulation of lanreotide will present as a solution for injection in a prefilled syringe. Lanreotide PRF is expected to ensure a 3 month period of coverage of active serum levels of lanreotide compared to the currently marketed lanreotide Autogel formulation. The three levels of dose correspond to three times the common doses of lanreotide used for the treatment of acromegaly (Table 2).

Table 2 Lanreotide Doses

Lanreotide dose	Lanreotide PRF dose
60 mg	180 mg
90 mg	270 mg
120 mg	360 mg

PRF=prolonged release formulation.

Lanreotide PRF is provided in three strengths as sterile, ready to use, prefilled syringes containing the same lanreotide supersaturated bulk solution at 44% w/w lanreotide base. The product is intended to deliver 180, 270 or 360 mg lanreotide (potency is expressed as lanreotide base). The different strengths are dose proportional as syringes are filled with increasing quantities of the same lanreotide supersaturated bulk solution.

Lanreotide PRF will be injected via the deep subcutaneous route in the superior, external quadrant of the buttock according to the recommendations detailed in Section 6.1.

The three dose levels proposed for lanreotide PRF (180 mg, 270 mg and 360 mg) are targeted as three times the common doses of lanreotide Autogel used for the treatment of acromegaly (60, 90 and 120 mg).

A robust PK/PD model developed with lanreotide Autogel in acromegalic patients which relates lanreotide trough concentrations (at 1 month for Autogel) to GH and IGF-1 concentrations, has proven that if the lanreotide concentration remains above a target therapeutic level over the whole dosing interval, acromegalic patients remain controlled in terms of GH and IGF-1. Therefore, the trough concentrations (C_{trough}) observed at 3 months with lanreotide PRF were compared to the target therapeutic levels reached at 1 month with lanreotide Autogel (using a 'translation' from human data to dogs). In dogs, the C_{trough} achieved with lanreotide PRF 240, 270 and 450 mg were comparable to those achieved with the corresponding dose of lanreotide Autogel (i.e., lanreotide PRF dose divided by 3), which justifies the selected doses of lanreotide PRF.

From a safety point of view, the C_{max} and AUC of lanreotide PRF in dogs were carefully reviewed and compared to the commercial formulation lanreotide Autogel 120 mg and a previous development formulation of lanreotide Autogel$^{23\%}$ 240 mg. The mean C_{max} of 58 ng/mL observed with the highest dose tested in dogs (PRF 450 mg) is increased by 60-70% compared to the mean C_{max} of 36 ng/mL observed with lanreotide Autogel 120 mg (highest dose commercially available of the 1-month formulation) and in dogs the mean exposure over

3 months after a single injection of lanreotide PRF 450 mg (706 ng.day/mL) is similar to the exposure over 3 months after three injections of lanreotide Autogel 120 mg every 4 weeks (737 ng.day/mL). Therefore, if the PK profile of lanreotide PRF in human is consistent with dog data, comparable safety ratios to those observed with lanreotide Autogel 120 mg (200- to 400-fold in rats and 16- to 23-fold in dogs) could be anticipated with lanreotide PRF.

Moreover the mean C_{max} of lanreotide PRF tested in dogs is 2-fold lower than that observed with a dose of 240 mg of lanreotide Autogel$^{23\%}$ (a previous development formulation tested in a Phase 1 study in healthy volunteers) which was not well tolerated in healthy subjects.

Furthermore, in the dog PK study performed with lanreotide PRF, assessment of the local tolerance of lanreotide PRF containing glycofurol showed a s.c. granulomatous inflammation at the injection site at the end of the 3-month and 6-month periods. These histological findings have already been described for lanreotide Autogel in dogs thus the excipient glycofurol does not aggravate the local tolerance of the therapeutic compound.

In conclusion, the choice of the lanreotide PRF doses as 3 times the doses of Autogel is confirmed, from an efficacy perspective, by the C_{trough} reached at 3 months. In terms of safety, the selected doses of lanreotide PRF are expected to show similar or lower exposure than with the highest dose of the commercially available 1-month formulation (lanreotide Autogel 120 mg). Consequently, no change in the safety ratios is expected. Moreover, the local tolerance of the lanreotide PRF in dog was not different from that observed with lanreotide Autogel.

1.6 Compliance Statement

The study will 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) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. The Electronic Data Capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject 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.

1.7 Population to Be Studied

The study will enrol adult subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of either octreotide long acting release (LAR) or lanreotide Autogel. A minimum of six octreotide LAR subjects must be recruited in each cohort and up to three lanreotide Autogel subjects can be enrolled in each cohort.

The choice of subjects stable on octreotide LAR as the main study population, instead of subjects stable on lanreotide Autogel, was guided by the need to avoid crossinterference between the different formulations of lanreotide in the primary PK analysis. The required PK analysis can be done on a minimum of six octreotide LAR subjects per cohort. The inclusion of up to three lanreotide Autogel subjects per cohort will provide preliminary PK data from this population.

Possible subject combinations per cohort are shown in Table 3.

Table 3 Possible Subject Combinations Per Cohort

	Octreotide LAR	Lanreotide Autogel
Cohort 1, 2 and 3	6	3
Cohort 1, 2 and 3	7	2
Cohort 1, 2 and 3	8	1
Cohort 1, 2 and 3	9	0

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The role of SSTa is to provide a primary medical therapy in patients with acromegaly for whom a surgical cure is unlikely. These hormone analogues successfully alleviate many symptoms of acromegaly, improve related comorbid complications and may reduce or stabilise tumour size [4]. Long acting formulations have been shown to provide equivalent or better control of acromegaly compared to short acting SSTa [6]. As discussed in Section 1.2, the recommended dosing intervals for current lanreotide formulations are every 7, 10 or 14 days (lanreotide PR) and every 28 days (lanreotide Autogel). Lanreotide PRF has been developed with a view to increasing the dosing interval (up to 3 months) compared to the currently marketed lanreotide formulations in order to provide equivalent disease control and to decrease patient burden with regard to injection frequency.

This clinical study aims to identify the maximum tolerated dose (MTD) and to investigate the PK, pharmacodynamics (PD), safety and tolerability of a single dose of the new lanreotide formulation (lanreotide PRF) in subjects with acromegaly.

A modified lanreotide autogel formulation has been studied in a single Phase 1 study in healthy volunteers, however its profile was not compatible with adequate exposure for a 3 month dosing interval and exaggerated adverse effects were observed in the study subjects (Study 2-55-52030-724). As mentioned in the IB, biliary toxicity (3 subjects experienced cholelithiasis which was symptomatic and severe in 2 of them) was described in the 16 healthy volunteers treated with lanreotide Autogel 240 mg (Study 2-55-52030-724).

2.2 Study Objectives

The primary objective of the study is to identify the MTD and to investigate the PK of a single dose of lanreotide PRF in subjects with acromegaly.

The secondary objectives of the study are as follows:

- To investigate the safety and tolerability of a single dose of lanreotide PRF.
- To investigate the PD of a single dose of lanreotide PRF.
- To investigate the PK of the excipient.

The exploratory objective of the study is to evaluate the impact of lanreotide PRF on gene expression of proteins of relevance for the mechanism of action of lanreotide and those of relevance for safety, tolerability and potential clinical benefit.

Blood samples will be collected for all subjects who will sign a separate informed consent to participate in the optional biobanking research study. These samples will be stored in a Biobank for further biomarkers analysis after the end of the study. Please refer to Appendix 1 for further information.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is an open label, dose ascending study to assess the PK, PD, safety and tolerability of a single dose of lanreotide PRF, a new sustained release formulation of lanreotide. Doses of 180 mg, 270 mg and 360 mg will be investigated in adults with acromegaly previously treated and controlled with a stable dose of either octreotide LAR or lanreotide Autogel. The study consists of a 4 week (or up to 6 weeks under certain circumstances) run in period, followed by a 12 week treatment period, and then a 12 week follow up period.

A maximum of 27 adult subjects, aged 18 to 75 years will be treated in the study.

Three cohorts of subjects will be included, with nine subjects allocated to each lanreotide PRF treatment cohort (180 mg, 270 mg and 360 mg). Subjects in each cohort will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks (or up to 6 weeks if extended) after the last octreotide LAR or lanreotide Autogel administration). Specific details of the dose cohorts are given in Section 6.1.

Each cohort of nine subjects must be made up of at least six previously controlled on octreotide LAR. The remaining subjects can be up to three subjects previously controlled on lanreotide Autogel (see Table 3).

Progression to each ascending dose cohort (or groups of subjects) will be dependent upon a review of data from the preceding cohort (or groups of subjects) by a data review committee (DRC; see Section 10.6). The DRC will review the safety data for each dose cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). If no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort (or groups of subjects). The occurrence of 2 dose limiting toxicities (DLTs) would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects (2 more subjects for Cohort 2 and Cohort 3) at the same dose level (see Section 6.1.1).

Screening of subjects will take place 28 to 42 days before administration of study treatment (Day −42 to Day −28). Eligible subjects will receive the same single dose of octreotide LAR or lanreotide Autogel as their previous treatment and will enter a 4 week run in period. The 4 week run in period (28 days) can be extended to up to 6 weeks (42 days) under the following circumstances and only in specific cases:

(1) When there is a delay in receiving blood results or having to re-collect a blood sample e.g. due to a clotted sample being received by the central laboratory.

(2) The data review of the group of 2 prior subjects is ongoing and not completed by the end of a 4 week run in. In this circumstance, the run in period can be extended by a further 2 weeks. This would make the run in a maximum of 6 weeks in total.

(3) At the investigator's discretion after discussion with the sponsor.

Any extension to the run in period will be done in close consultation with the investigator to ensure that there is no safety risk to the subject.

On Day 1, subjects will receive lanreotide PRF by deep subcutaneous injection in the superior, external quadrant of the buttock and a 12 week treatment period will then commence. Treatment will be administered at the study centre and subjects will remain at the study centre for 24 hours postdose. Throughout the treatment period, study assessments will be performed to evaluate PK, PD, safety and tolerability of lanreotide PRF.

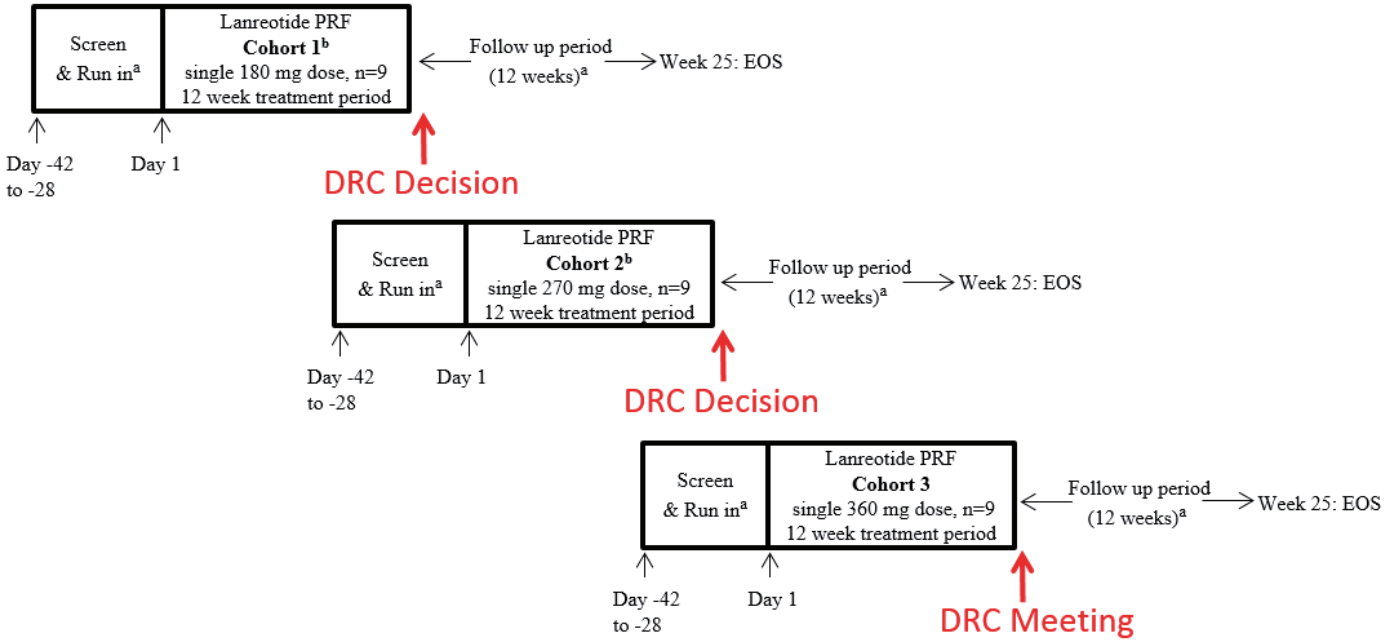
At the end of the 12 week treatment period, a 12 week follow up period will ensue, with further assessments to evaluate the PK, PD, safety and tolerability of lanreotide PRF performed

periodically throughout. During the follow up period, subjects will not receive any treatment for acromegaly. However, if the investigator judges that the subject requires treatment for acromegaly (reappearance of clinical or biochemical symptoms of acromegaly), the subject will be withdrawn from the study and receive treatment according to routine clinical practice.

The overall study design is presented in Figure 1.

Subjects who complete the study will have final procedures and assessments performed at the end of study (EOS) visit (Week 25; Visit 18). Subjects who withdraw from the study before the completion of the 24 week evaluation period will have Week 25 (Visit 18) procedures and assessments performed at their final visit (early withdrawal (EW) visit).

Figure 1 Study Design



For each patient:
- Day -42 to -28: Octreotide LAR as per subjects previous treatment and start of 4 week (or up to 6 weeks if extended) run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

DRC=Data Review Committee; EOS=end of study; LAR=long acting release; PD=pharmacodynamic; PK=pharmacokinetic; PRF=prolonged release formulation.

a each cohort will undergo a 4 week run in period (or, if extended, the run in can be up to a maximum of 6 weeks) and two subsequent 12 week periods for treatment and follow up unless the subject withdraws from the study prematurely.

b each successive dose increase will proceed only on the recommendation of the DRC after review of the safety data for the preceding dose cohort after all subjects in the cohort have reached Visit 5 (Week 2 postdose). The DRC will meet after every 2 subjects starting from Cohort 2 onwards instead of the 3 subject blocks and prior to the final 3 subjects in Cohort 3.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Safety Variables

The safety and tolerability of lanreotide PRF will be assessed throughout the study by evaluation of the following parameters:

- Adverse events, throughout the study.
- Vital signs (supine and standing blood pressure, heart rate, body temperature) at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at each follow up visit.
- Physical examination at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at each follow up visit.
- 12-lead electrocardiogram (ECG), QT interval corrected (QTc) will be calculated using Fridericia methodology in all subjects at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, 24 hours postdose, and at Weeks 2, 5 and 13.
- Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, 24 hours postdose (Day 2), 48 hours postdose (Day 3), at Weeks 2, 3, 4, 5, 9 and 13 of the treatment period, and at each follow up visit.
- Glycosylated haemoglobin (HbA1c) at Screening, Week 13 and Week 25 (or EW).
- Estimated glomerular filtration rate (eGFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula [1], at Screening, Baseline (predose on Day 1), and Weeks 2, 5, 9 and 13 of the treatment period, and at Weeks 17, 21 and 25 (or EW) during follow up in all subjects.
- Gallbladder echography at Screening, Week 5 and Week 13 of the treatment period and at Week 25 (or EW) in all subjects.
- Putative antibodies to lanreotide at Baseline (predose on Day 1), Week 13 and Week 25 (or EW) in all subjects.
- Evaluation of injection site reactions (appearance, local symptoms). These will be evaluated on a specific form in the electronic case report form (eCRF) at 1 and 6 hours postdose on Day 1, 24 hours postdose, at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at each follow up visit.

3.2.2 Pharmacokinetic Variables

- Lanreotide serum concentration at the following timepoints after administration of lanreotide PRF:
  - Baseline (predose on Day 1 of lanreotide PRF administration)
  - At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1)
  - At 24 hours postdose (Day 2)
  - On Days 3 and 5, and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration (the Week 13 sample will be on Day 85 and will correspond to the concentration at the end of the dosing interval (C_{trough}))
  - At Weeks 17, 21 and 25 (or EW) during follow up
- Lanreotide PK parameters:
  - C_{trough}
  - maximum serum concentration (C_{max})

- T_{max}
- area under the serum concentration time curve from time 0 to 85 days (AUC_{0-85})
- area under the concentration time curve extrapolated to infinity ($AUC_{0-\infty}$)
- $t_{½}$
- mean residence time (MRT)
- apparent clearance (CL/F)
- apparent volume of distribution (V/F)

• Excipient serum concentration at the following timepoints after administration of lanreotide PRF:
  - Baseline (predose on Day 1 of lanreotide PRF administration)
  - At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration
• Excipient PK parameters:
  - C_{max}
  - T_{max}
  - area under the serum concentration time curve from time 0 to last quantifiable timepoint (AUC_t)
  - $AUC_{0-\infty}$
  - $t_{½}$
  - MRT
  - CL/F
  - V/F

3.2.3 Pharmacodynamic Variables

• IGF-1 at Screening, Baseline (predose on Day 1), at 6 hours postdose on the day of dosing (Day 1), and at Weeks 5, 9 and 13 of the treatment period and Weeks 17, 21 and 25 (or EW) during follow up.
• GH cycle (five sampling times with a sample every 30 minutes for 2 hours in the morning) at Screening, Baseline (predose on Day 1) and at Weeks 5 and 13.
• Random GH sample at 6 hours postdose on the day of dosing (Day 1), at Week 9 and Weeks 17, 21 and 25 (or EW) during follow up.
• Free triiodothyronine (FT_3), free thyroxine (FT_4), thyroid stimulating hormone (TSH) and prolactin (PRL) at Screening, Baseline (predose on Day 1), Weeks 2, 5 and 13 of the treatment period, and at Week 25 (or EW).

3.2.4 Biobanking

Blood samples will be collected at Baseline (predose on Day 1), Weeks 5 and 13 and stored for further biomarkers analysis after the end of the study in subjects who consent to the exploratory part of the study.

3.3 Randomisation and Blinding

This is a nonrandomised, open label study.

3.4 Study Treatments and Dosage

The test product, lanreotide PRF, will be administered as a single deep subcutaneous injection at Visit 2 (Day 1). Depending on the dose cohort, doses of 180 mg, 270 mg or 360 mg will be administered. A more detailed description of administration procedures is given in Section 6.1.

Lanreotide PRF will be packaged and released by Beaufour Ipsen Industrie (France) and delivered to the investigational centre or interim storage depending on the country. A sufficient quantity of lanreotide PRF will be supplied, as well as an acknowledgement of receipt form.

Lanreotide PRF will be released from Beaufour Ipsen Industrie to the sponsor (Ipsen Pharma). A Certificate of Analysis reflecting the product release statement will be issued for each batch of lanreotide PRF used in this study, together with a Certificate of Compliance.

The core label texts for all packaging units will be in compliance with Annex 13 of the European Union (EU) Guide to Good Manufacturing Practice (GMP) and should be translated or adjusted to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the lanreotide PRF labels is displayed below:

- Sponsor name,
- Study Number,
- Pharmaceutical dosage form,
- Route of administration,
- Quantity of dose units,
- Batch number,
- A treatment box number or a specific blank space to enter the subject identifier,
- “Keep out of reach of children”,
- “For clinical study use only”
- Name, address and telephone number of the sponsor, contract research organisation (CRO) or investigator (the main contact for information on the product and the clinical study)
- Storage conditions
- Expiry date

The investigator, or designee, will only administer lanreotide PRF to subjects included in this study. Each subject will only be given the lanreotide PRF carrying his/her number. The dispensing for each subject will be documented in the eCRF.

3.5 Study Duration

This study will consist of a Screening visit, followed by a 4 week run in period (or up to 6 weeks under certain circumstances), a 12 week open label treatment period and a 12 week follow up period. Subjects are expected to participate in this study for up to 7.5 months.

The subject’s participation in the study will be considered to have ended at the time of the last follow up visit (EOS visit) or the EW visit in the case of early withdrawals.

The overall duration of the study will be approximately 32 months. The study will be considered to have started when the first subject has been screened and signed the informed consent form.

The study will be considered to have ended after the last subject has completed the EOS or EW visit.

3.6 Stopping Rules and Discontinuation Criteria

3.6.1 Discontinuation

A subject may discontinue participation in the study at any time for any reason (e.g. lost to follow up, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 12.1.2, noncompliance with the protocol conditions or AE).

Withdrawn subjects will not be replaced.

During the follow up period, if the investigator judges that the subject requires treatment for acromegaly, the subject will be withdrawn from the study and will receive treatment according to routine clinical practice. Individual subject withdrawal criteria are specified in Section 4.3. An EW visit must be conducted for any subject who does not complete the study (see Section 5.2.4.2). Subject status in the study will be recorded on the visit status page in the eCRF.

3.6.2 Stopping Rules

The DRC will review the safety data from each treatment cohort to determine whether the next treatment cohort should ensue (Section 10.6). The pre-established stopping rules for the DRC decision for study discontinuation and/or inclusion of the subsequent treatment cohort include the occurrence of DLTs occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration (see Section 3.6.3). If any serious adverse event (SAE) occurs (see Section 8.1.4), a relationship with the exposure to lanreotide PRF will be assessed.

All toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June, 2010; see Section 8.1.2.1).

The study may be terminated by the sponsor at any time.

3.6.3 Definition of Dose Limiting Toxicity

Taking into account the safety profile of lanreotide (detailed in the IB), a DLT is defined as an AE (excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre-established criteria listed in Table 4.

In the event of hepatic enzyme (aminotransferases and/or bilirubin) increases, refer to Appendix 2 for an algorithm for safety management.

Table 4 Criteria for Defining Dose Limiting Toxicities

Toxicity	Any of the following criteria
Hepatic	NCI CTCAE grade ≥3 ALT, AST Total bilirubin ≥2.0 to <3.0 x ULN for >7 consecutive days NCI CTCAE grade ≥2 bilirubin and NCI CTCAE grade ≥2 ALT or AST
Renal	NCI CTCAE grade ≥3 serum creatinine Serum creatinine ≥2.0 to ≤3.0 x ULN for >7 consecutive days
Pancreatic	NCI CTCAE grade ≥3 amylase or lipase with abdominal pain NCI CTCAE grade ≥3 amylase or lipase for >7 consecutive days without abdominal pain If necrotising pancreatitis is suspected, the subject should be hospitalised
Endocrine/Metabolic	NCI CTCAE grade ≥4 hyperglycaemia (confirmed by a repeat FPG within 24 hours) that does not resolve to CTCAE grade ≤2 within 14 consecutive days despite optimal antidiabetic treatment (14 consecutive days counts from the day of initiation of antidiabetic treatment)
Cardiac	NCI CTCAE grade ≥3
Other AEs	Any event CTCAE ≥3 except for ALP grade ≥4 NCI CTCAE grade ≥3 diarrhoea despite optimal antidiarrheal treatment NCI CTCAE grade ≥3 vomiting despite optimal antiemetic therapy In the view of the investigators and Ipsen, any other unacceptable toxicity encountered

AE=adverse event; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; FPG=fasting plasma glucose; NCI=National Cancer Institute; ULN=upper limit of normal.

The occurrence of the following toxicities will be assessed throughout the study period and at the EOS or EW visit:

- Grade ≥3 cholelithiasis-related gallbladder obstruction or cholecystitis,
- Grade ≥3 injection site reaction,
- Prolonged grade 2 toxicities or investigation abnormalities.

3.7 Investigational Medicinal Product Preparation Storage and Accountability

3.7.1 Investigational Medicinal Product Storage and Security

The investigator, or an approved representative (e.g. pharmacist), will ensure that all lanreotide PRF and any other study related material is stored in a secured area, under monitored conditions and at the recommended temperature (between +2°C and +8°C), in accordance with applicable regulatory requirements.

3.7.2 Investigational Medicinal Product Preparation

Lanreotide PRF is supplied as a ready to use syringe, therefore no preparation is required. The investigator, or an approved representative (e.g. pharmacist), will ensure that all lanreotide PRF is administered by qualified staff members.

3.7.3 Investigational Medicinal Product Accountability

All lanreotide PRF and any other study related material is to be accounted for on the 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 who will ensure that lanreotide PRF administration in the eCRF, the accountability log and the number of used/unused treatments are consistent. The investigator or approved representative (e.g. pharmacist) should ensure adequate records are maintained in the accountability log. Lanreotide PRF will be destroyed at the investigational site. The destruction of used and unused lanreotide PRF should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted by the sponsor or its representative.

3.8 Maintenance of Randomisation and Blinding

Not applicable as this is a nonrandomised, open label study.

3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP, the sponsor assigned monitor will 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 a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), lanreotide PRF administration, and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

The definitions of 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 study. Source data are contained in source documents (original records or certified copies).
- **Source documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local, and possibly foreign Competent Authorities (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

All laboratory parameters will be analysed centrally to confirm subject eligibility against the inclusion and exclusion criteria, with the exception of IGF-1. Age adjusted IGF-1 will be based on local laboratory results at Screening. Samples for analysis of IGF-1 by central laboratory will also be collected during Screening. Unscheduled tests may be performed during the study. The results will be recorded in the eCRF. All toxicities will be graded according to NCI CTCAE, Version 4.03.

4.1 Inclusion Criteria

All subjects must fulfil all of the following criteria to be included in the study:

(1) Documented diagnosis of acromegaly.

(2) Provided written informed consent prior to any study related procedures.

(3) Between 18 and 75 years of age inclusive.

(4) Female of nonchildbearing potential or male. Nonchildbearing potential is defined as being postmenopausal for at least 1 year, or women with documented infertility (natural or acquired).

(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (up to 7.5 months).

(6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x upper limit of normal (ULN), based on local laboratory results, during the Screening period).

(7) If the subject is receiving treatment for hypertension, the dose has been stable for at least 1 month prior to study entry.

(8) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow up evaluation as specified in the protocol.

4.2 Exclusion Criteria

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

(1) Has undergone radiotherapy within 2 years prior to study entry.

(2) Has been treated with a dopamine agonist and/or GH receptor antagonist or has undergone pituitary surgery within 3 months prior to study entry.

(3) Is anticipated to require pituitary surgery or radiotherapy during the study.

(4) Has clinically significant hepatic abnormalities and/or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 x ULN and/or alkaline phosphatase (ALP) ≥2.5 x ULN and/or total bilirubin ≥1.5 x ULN and/or gamma-glutamyl transpeptidase (GGT) ≥2.5 x ULN during the Screening period (central laboratory results) or a history of these findings when on SSTa treatment.

(5) Has clinically significant pancreatic abnormalities and/or amylase and/or lipase ≥1.5 x ULN during the Screening period (central laboratory results).

(6) Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN during the Screening period (central laboratory results).

(7) Has uncontrolled diabetes (HbA1c) ≥9%, centrally assessed during the Screening period) or has diabetes treated with insulin for <6 months prior to study entry.

(8) Has any known uncontrolled cardiovascular disease or had any of the following within 6 months of Screening: ventricular or atrial dysrhythmia ≥grade 2, bradycardia ≥grade 2, ECG QTc prolonged ≥grade 2, myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischaemic attack, pulmonary embolism, hypertension not adequately controlled by current medications.

(9) Use of any hormone replacement therapy (HRT) with oestrogens.

(10) Has symptomatic gallstones/sludge at the Screening Visit echography (local assessment) OR is asymptomatic but has echography showing clear evidence of impending inflammation such as localised mucosal thickening suggesting the subject is at high risk of developing acute disease. Subjects with asymptomatic gallstones/sludge and otherwise normal echography may be entered at the discretion of the investigator.

(11) Has abnormal findings during the Screening period, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.

(12) Has been treated with any other investigational medicinal product (IMP) prior to the first study visit without undergoing a washout period of seven times the elimination half life of the investigational compound.

(13) Has a known hypersensitivity to any of the test materials or related compounds.

(14) Is likely to require treatment during the study with drugs that are not permitted by the study protocol.

(15) Has a history of, or known current, problems with alcohol or drug abuse.

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

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.6 and 8.1.7.

Should a subject decide to withdraw from the study after administration of lanreotide PRF, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.4.2) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, and/or until the subject is referred to the care of a local health care professional. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol.

Subjects participating in the optional biobanking have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which the sample is kept). If a subject wishes to withdraw his consent for biobanking and the samples are still at the investigator site or at the central laboratory at this

time, the investigator must first inform the study monitor in writing of the subject's decision and destroy the samples, respectively after informing the monitor the investigator will need to contact the central laboratory to destroy the samples. If the samples are already at Fisher BioServices (biobanking vendor), i.e. post-study, the investigator must inform Ipsen directly using the following e-mail address:PPD , mentioning only the ID of the subject in this e-mail. Ipsen will ensure destruction of the samples and all corresponding aliquots, issue confirmation of the withdrawal, and forward corresponding destruction certificate to the investigator.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 5 (Screening to Week 13, including treatment period) and Table 6 (Follow up period; Weeks 15 to 25).

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3	4	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28 (up to −42)	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide or lanreotide Autogel administration [d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide PRF		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X	X	X								
PD assessments																				
IGF-1 [e]	X	X					X									X		X		X
GH cycle [f]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) *(Cont.)*

Visit	1 [a]	2									3	4	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [g]	X	X					X [h]			X [i]	X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [j]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [k]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit. Screening of subjects will take place 28 to 42 days before administration of study treatment (Day −42 to Day −28). The 4 week run in period (28 days) can be extended to up to 6 weeks (42 days) under certain circumstances.

b Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. A reduced physical examination will be performed at home visits and weight will not be measured. More information on how those home visits are performed are described in the study manual.

c Baseline.

d after Screening, subjects will enter a 4 week run in period (or up to 6 weeks under certain circumstances) and will receive a single dose of either octreotide LAR or lanreotide Autogel at the same dose as they received previously.

e IGF-1 testing will be conducted by a central laboratory using a validated method. During the Screening period, IGF-1 will be analysed locally.

f five sampling times in the morning, with a sample every 30 minutes for 2 hours.

g blood and urine samples taken for clinical laboratory tests.

h evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.

i at 24 hours postdose before hospital discharge (Day 2) only blood chemistry will be analysed. A urine sample will not be collected.

j measured by MDRD formula [1].

k Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

Table 6 Study Procedures and Assessments (Follow Up; Weeks 15 to 25)

Visit	13 [a]	14	15 [a]	16	17 [a]	18 (EOS or EW)[b]
Week [c]	**15**	**17**	**19**	**21**	**23**	**25/EW**
Acromegaly symptoms						X
Concomitant medications	x----------x					
PK blood samples						
Lanreotide PRF		X		X		X
PD assessments						
IGF-1 [d]		X		X		X
Random GH sample		X		X		X
FT_3, FT_4, TSH , PRL						X
Safety assessments						
AEs	x----------x					
Physical examination	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X	X	X	X
HbA1c						X
eGFR [e]		X		X		X
Vital signs	X	X	X	X	X	X
Gallbladder echography						X
Evaluation of injection site reactions	X	X	X	X	X	X
Putative antibodies to lanreotide						X

AE=adverse event; eGFR=estimated glomerular filtration rate; EOS=end of study; EW=early withdrawal; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Study visits on Weeks 15, 19 and 23 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. A reduced physical examination will be performed at home visits and weight will not be measured. More information on how those home visits are performed are described in the study manual.

b EOS for subjects completing the follow up period or EW visit for subjects who withdraw from the study during the follow up period.

c follow up visits will be conducted every 2 weeks (±3 days).

d during follow up visits, IGF-1 testing will be conducted by a central laboratory using a validated method.

e measured by MDRD formula [1].

The total volume of blood drawn for all evaluations throughout this study is approximately 579 mL for each subject. The total amount of blood to be collected from all subjects is presented in Table 7 and Table 8.

Table 7 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	10	20.5 mL for 10 visits	205
PD	7 IGF-1 20 GH Cycle 2 random GH	2 2 2	58
PK	15 for lanreotide; 10 for excipient	4 4	100
HbA1c	2	2	4
FT_3, FT_4, TSH and PRL	5	3.5	17.5
Antibody testing	2	4	8
Biobanking [b]	3	10	30
Total	75	Up to 132.5 mL per visit (Visit 2)	422.5

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis. Creatine kinase will only be measured at Baseline (predose) and 6 and 24 hours postdose.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

Table 8 Blood Volume Calculation for Follow Up Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	6	20.5 mL	123
PD	3 IGF-1 3 random GH	2 2	12
PK	3 for lanreotide	4	12
HbA1c	1	2	2
FT_3, FT_4, TSH and PRL	1	3.5	3.5
Antibody testing	1	4	4
Total	18	Up to 38 per visit (Visit 18)	156.5

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

A volume of approximately 14 mL of urine will be collected at each of the visits that includes a clinical laboratory assessment.

5.2 Study Visits

5.2.1 Procedures for Screening and Enrolment (Visit 1)

A signed and dated informed consent form will be obtained before any Screening procedures are started.

After informed consent is obtained, subjects who are screened will be allocated a subject number which will be used in place of subject names on study records to maintain confidentiality. All screened subjects must be identifiable throughout the study. The

investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

The Screening visit (Visit 1) will take place 28 to 42 days prior to the start of treatment with lanreotide PRF (Day −42 to −28).

The following assessments will be performed:

- Demographic data (date of birth/age, sex will be collected according to individual country requirements)
- Medical history, including ongoing medical history
- Acromegaly symptoms
- Eligibility check (inclusion/exclusion criteria)
- PD assessments (IGF-1 and GH cycle)
- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- HbA1c
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure and heart rate, and body temperature)
- 12-lead ECG
- Gallbladder echography
- Prior and concomitant medications/therapies, nondrug therapies and surgical procedures in the last month prior to study entry. Prior medication for acromegaly will be recorded for the last 3 months prior to study entry.
- Review of AEs. Any AEs or SAEs occurring during the run in period will be reported but will not be included in the analysis of treatment emergent AEs (TEAEs; see Section 10.4.7).

Under normal circumstances subjects will not be screened more than once. There are three exceptions:

(1) IGF-1 may be re-tested once if the screening value is just above 1.3 x ULN (analysis by local laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN.

(2) If the time elapsed between the original Screening visit (Visit 1) and Visit 2 is >28 days (±2 days) then re-screening of the subject for inclusion is permitted.

(3) If deemed acceptable by the investigator, the subject may be re-screened once for inclusion if they previously failed screening due to the presence of asymptomatic gallstones/sludge. This follows the change to exclusion criterion #10 in protocol amendment 7.

Following confirmation of eligibility for the study, subjects will be enrolled into the study and allocated to one of the dose cohorts specified in Section 6.1. At the Screening visit, enrolled subjects will then receive their usual dose of either octreotide LAR or lanreotide Autogel according to standard clinical practice.

Each investigator will also maintain a record of all subjects screened into the study (i.e. who signed the informed consent form). In the event that the subject was not receiving lanreotide PRF, the primary reason will be recorded.

5.2.2 Procedures Before Study Treatment (Baseline, Visit 2 Predose)

On Day 1±2 days (Visit 2), subjects will be admitted to the study centre where they will undergo Baseline assessments prior to the administration of study treatment.

The following procedures will be performed at Baseline on Day 1±2 days of the study, prior to the administration of study treatment:

- Eligibility check
- PK blood samples for lanreotide and excipient
- Baseline PD assessments (IGF-1 and GH cycle)
- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, creatine kinase (CK), serum electrolytes and urinalysis)
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- 12-lead ECG
- Putative antibodies to lanreotide
- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Biobanking samples for further biomarkers analysis will only be collected for those individuals who have signed a specific consent to participate in the optional biobanking research study

5.2.3 Procedures During Study Treatment (Visit 2 Postdose to Visit 12)

Following Baseline assessments on Day 1±2 days, study treatment will be administered. Subjects will remain at the study centre for 24 hours postdose, during which time further assessments will be performed.

The following procedures will be performed at the indicated timepoints relative to administration of study treatment at Visit 2 (Day 1±2 days):

- PK blood samples for lanreotide and excipient at 1 (±5 min), 2 (±5 min), 4 (±10 min), 6 (±10 min), 8 (±10 min) and 12 (±30 min) hours postdose
- Evaluation of injection site reactions at 1 hour postdose
- Review of AEs
- Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, international normalised ratio (INR), postprandial glycaemia, and postprandial insulinaemia, CK) at 6 hours postdose
- Evaluation of injection site reactions at 6 hours postdose
- Physical examination at 6 hours postdose
- Vital signs (supine and standing blood pressure, heart rate and body temperature) at 6 hours postdose
- 12-lead ECG (for QTc interval) at 6 hours postdose
- PD assessments (IGF-1 and random GH sample) at 6 hours postdose
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries

The following procedures will be performed 24 hours after administration of study treatment at Visit 2 (Day 2±2 days), before hospital discharge:

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide and excipient (24 (±2) hours)
- Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, CK and GGT)
- Evaluation of injection site reactions
- Physical examination
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- 12-lead ECG

Following the assessments on Visit 2; Day 2±2 days (24 hours postdose), subjects will be discharged from the study centre, returning at the following timepoints for further assessments.

The following procedures will be performed at Visit 3 (Day 3±1 day):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- PK blood samples for lanreotide and excipient

The following procedures will be performed at Visit 4 (Day 5±1 day):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide and excipient

The following procedures will be performed at Visit 5 (Week 2±1 day):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide
- Evaluation of injection site reactions
- Physical examination
- Central clinical laboratory assessments
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- 12-lead ECG

The following procedures will be performed at Visit 6 (Week 3±2 days) and Visit 7 (Week 4±2 days). Visit 7 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide (not Week 4; Visit 7)
- Evaluation of injection site reactions

- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- Vital signs (supine and standing blood pressure, heart rate and body temperature)

The following procedures will be performed at Visit 8 (Week 5±2 days):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide
- PD assessments (IGF-1 and GH cycle)
- Evaluation of injection site reactions
- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- 12-lead ECG
- Gallbladder echography
- Biobanking samples for further biomarkers analysis will only be collected for those individuals who have signed a specific consent to participate in the optional biobanking research study

The following procedures will be performed at Visit 9 (Week 7±2 days) and Visit 11 (Week 11±2 days). Visits 9 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Evaluation of injection site reactions
- Physical examination
- Vital signs (supine and standing blood pressure, heart rate and body temperature)

The following procedures will be performed at Visit 10 (Week 9±2 days):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide
- PD assessments (IGF-1 and random GH sample)
- Evaluation of injection site reactions
- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)

The following procedures will be performed at Visit 12 (Week 13±1 day):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Acromegaly symptoms
- PK blood samples for lanreotide. Importantly, this sample will be on Day 85 and will correspond to the concentration at the end of the dosing interval (C_{trough}). Therefore, the visit window for this visit (±1 day) must be strictly adhered to.
- PD assessments (IGF-1 and GH cycle)
- Evaluation of injection site reactions
- Physical examination
- Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)
- HbA1c
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- 12-lead ECG
- Gallbladder echography
- Putative antibodies to lanreotide
- Blood samples for further biomarkers analysis will only be collected from those individuals who have signed a specific consent to participate in the optional biobanking research study

5.2.4 Procedures After Study Treatment

During the 12 week follow up period, study visits will be conducted every 2 weeks (±3 days).

5.2.4.1 Follow Up Visits

The following procedures will be performed at Visit 13 (Week 15±3 days), Visit 15 (Week 19±3 days) and Visit 17 (Week 23±3 days). Visits 13 and 15 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Physical examination
- Central clinical laboratory assessments
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- Evaluation of injection site reactions

The following procedures will be performed at Visit 14 (Week 17±3 days) and Visit 16 (Week 21±3 days):

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- PK blood samples for lanreotide
- PD assessments (IGF-1 and random GH sample)
- Physical examination
- Central clinical laboratory assessments

- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- Evaluation of injection site reactions
- eGFR measured by MDRD formula [1]

5.2.4.2 End of Study Visit (Week 25, Visit 18) or Early Withdrawal Visit

Subjects who participate in the study in compliance with the protocol until the last follow up visit (Visit 18) will be considered to have completed the study.

EW should not take place before Week 13 after the injection of lanreotide PRF due to the expected 12 week duration of action. However, in the case of withdrawal within the 12 week treatment period or within the follow up period (Section 4.3), final evaluations will be performed as soon as possible after the decision to withdraw. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.

The following procedures will be performed at the EOS (Week 25±3 days; Visit 18), or EW visit:

- Review of AEs
- New or changed concomitant medications/therapies/nondrug therapies/ surgeries
- Acromegaly symptoms
- PK blood samples for lanreotide
- PD assessments (IGF-1 and random GH sample)
- Physical examination
- Central clinical laboratory assessments
- HbA1c
- FT_3, FT_4, TSH, PRL
- eGFR measured by MDRD formula [1]
- Vital signs (supine and standing blood pressure, heart rate and body temperature)
- Gallbladder echography
- Evaluation of injection site reactions
- Putative antibodies to lanreotide

6 TREATMENT OF SUBJECTS

6.1 Investigational Medicinal Product Administered

At Screening, subjects will be allocated a subject number. Following informed consent and confirmation of eligibility for the study, subjects will be allocated to one of the following treatment cohorts:

Table 9 Treatment Cohorts

Cohort [a]	Lanreotide PRF dose
1	180 mg
2	270 mg
3	360 mg

PRF=prolonged release formulation.
a each subsequent dose cohort will be initiated following recommendations from the DRC.

6.1.1 Dose Escalation Schema

Subjects will be assigned to a treatment cohort and will receive lanreotide PRF at a single dose level.

The dose escalation will proceed with a 3+3+3 scheme. At each dose level, a total of nine subjects will be enrolled if ≤3 DLTs are reported. See Section 3.6.3 for the definition of DLT.

Subject enrolment into the study will begin at Dose Level 1 (180 mg).

Dose level: 180 mg. The study will start dosing three subjects. If none or one out of the three dosed subjects experiences a DLT, three more subjects will be dosed at the same dose. If two out of the three dosed subjects experiences a DLT, the DRC will decide whether three more subjects may be dosed. If all three subjects have experienced a DLT, dosing will be stopped and the dose will be declared the maximum administered dose.

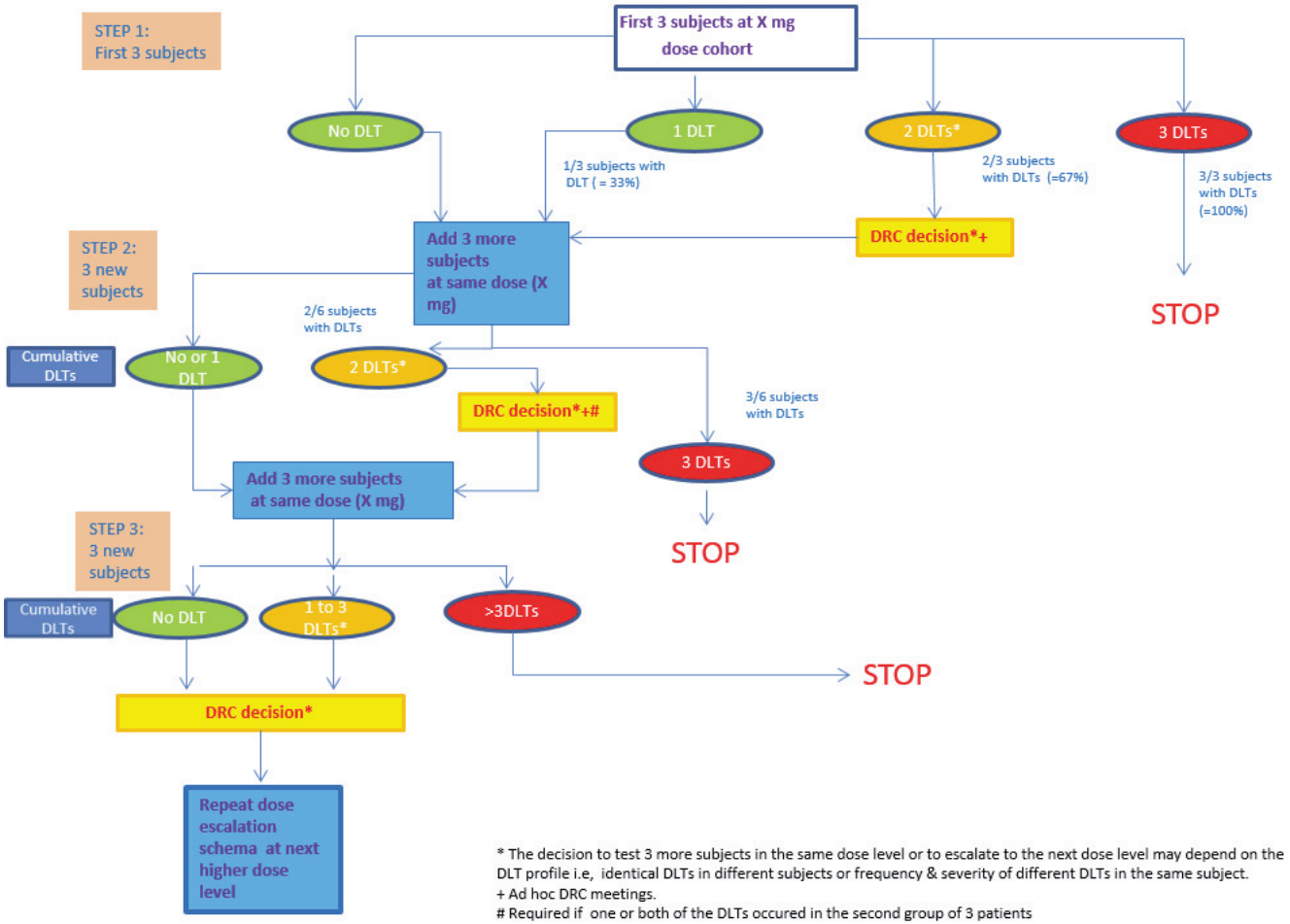
If none or one of the six dosed subjects experience a DLT, three more subjects can be dosed at the same dose. If two of the six dosed subjects experience a DLT, and one or both of the DLTs occurred in the second group of three subjects, the DRC will decide whether three more subjects may be dosed. If a total of three or more out of six subjects experience a DLT, dosing will be stopped and the dose will be declared the maximum administered dose.

Dose escalation: If more than three out of nine subjects experience a DLT, dose escalation will be stopped and the dose will be declared the maximum administered dose. If ≤3 DLTs have been observed in the nine treated subjects, then the dose may be escalated to 270 mg. The DRC will determine if progression to the next dose cohort should occur after reviewing data from the preceding cohort. The same rules will be applied to the next dose level and the decision to escalate to 360 mg will be done in the same way.

At any time the DRC can ask for an ad hoc review of the data prior to any dosing if it is judged necessary.

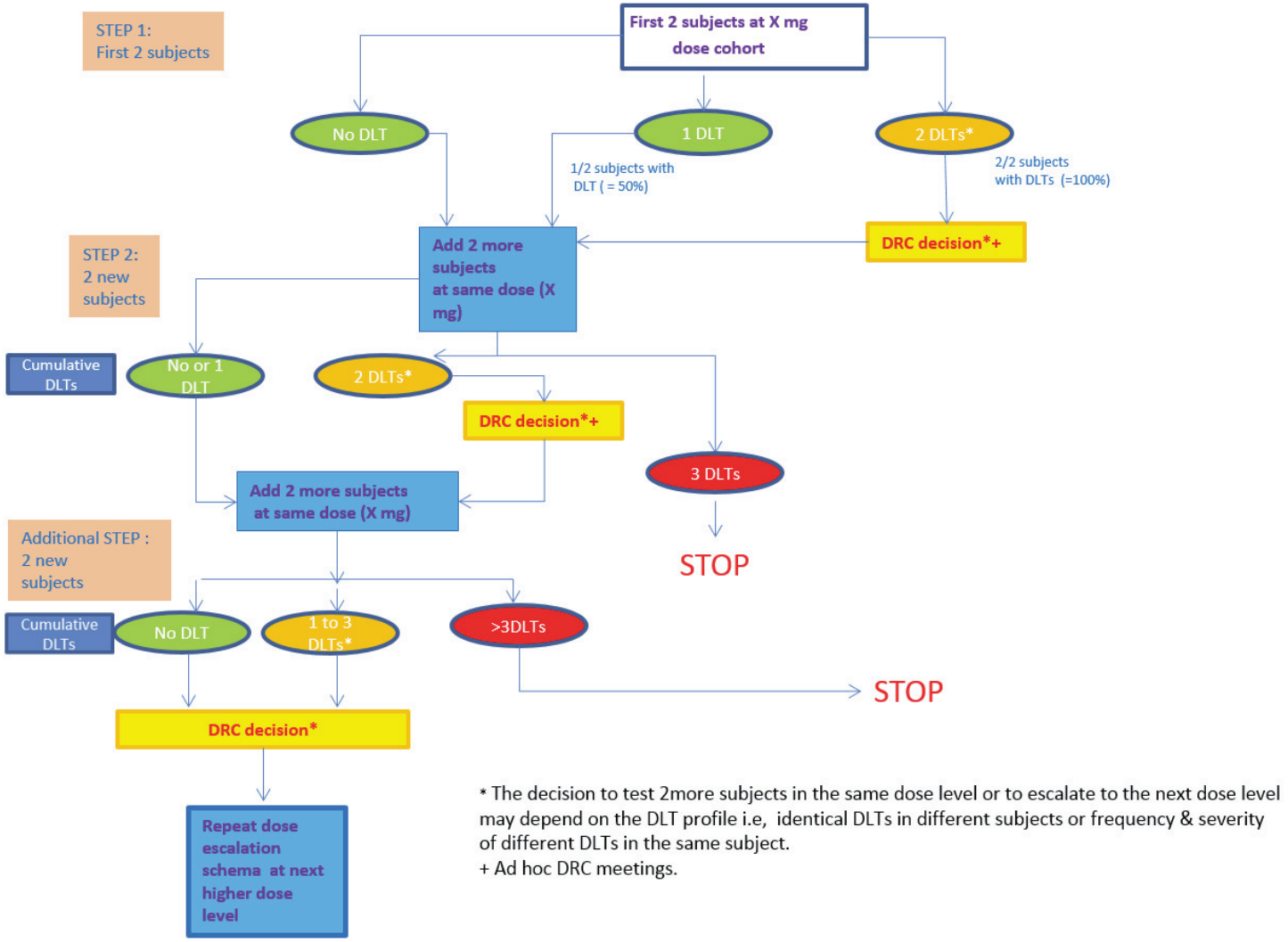
Details of the adaptive 3+3+3 or 1+2+2+2+2 (Cohort 2) or 2+2+2+3 (Cohort 3) dose escalation scheme with the most likely outcome are provided in Figure 2 and Figure 3.

Figure 2 Adaptive 3+3+3 Dose Escalation Scheme with the Most Likely Outcome



DLT=dose limiting toxicity; DRC=Data Review Committee.

Figure 3 Adaptive 2 per 2 Dose Escalation Scheme with the Most Likely Outcome



* The decision to test 2more subjects in the same dose level or to escalate to the next dose level may depend on the DLT profile i.e, identical DLTs in different subjects or frequency & severity of different DLTs in the same subject.
+ Ad hoc DRC meetings.

DLT=dose limiting toxicity; DRC=Data Review Committee.

6.1.2 Definition of Maximum Tolerated Dose

The identification of the MTD will be left to the discretion of the DRC.

The DRC may agree to define a MTD in the absence of a DLT at Week 2 (Visit 5) if the overall toxicity profile of lanreotide PRF suggests that further escalation is not possible (delayed toxicity, i.e. symptomatic cholelithiasis, or grade ≥3 injection site reaction or prolonged grade ≥2 toxicity).

6.1.3 Investigational Medicinal Product

Lanreotide PRF formulation will be supplied in a 1.2 mL prefilled syringe fitted with a 1.2/1.4 mm (inner diameter/outer diameter) needle packed in a laminated pouch.

The product is intended to deliver 180, 270 or 360 mg lanreotide (potency is expressed as lanreotide base) for this phase 2a clinical study. The different strengths are dose proportional as syringes are filled with increasing quantities of the same lanreotide supersaturated bulk solution.

All strengths will be evaluated (180, 270 and 360 mg) and they will be provided in the same presentation.

Lanreotide PRF will be administered by deep subcutaneous injection in the superior, external quadrant of the buttock at the doses indicated in Table 9. Nine subjects will be allocated to each dose cohort.

6.2 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a subject in the last month before study entry and throughout the study will be indicated on the eCRF. Prior medications for acromegaly for the 3 months prior to study entry will also be recorded on the eCRF. Dose and generic name or trade name will be indicated.

The following concomitant medications/therapies are not permitted during this study:

- Hormone replacement therapy (HRT) with oestrogens,
- Dopamine agonist and GH receptor antagonist, or pituitary surgery,
- Radiotherapy.

The following concomitant medications are permitted during this study, but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study.

- Bradycardia inducing drugs (e.g. beta blockers),
- Substrate of CYP3A4 (e.g. quinidine, erythromycin, simvastatin).

For information regarding the effects on blood glucose and the need for monitoring and adjustment of anti-diabetic agents, as well as information about the possible effects on cyclosporine bioavailability, please refer to the IB (Summary of Data and

Guidance for the Investigator, Section 6.4.4 Glycoregulation and Section 6.4.7 Drug Interactions).

6.3 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

Lanreotide PRF will be administered to subjects by study staff at each study site.

Deviation from the scheduled amount of lanreotide PRF intake will be regarded as a major protocol violation.

7 ASSESSMENT OF EFFICACY

Efficacy is not assessed in this study. However, clinical and biochemical symptoms of acromegaly will be closely monitored.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, non leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no lanreotide PRF has been administered.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

All toxicities will be graded according to the NCI CTCAE Version 4.03 (June, 2010).

8.1.2.2 Causality Classification

The relationship of an AE to lanreotide PRF administration 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 dechallenge and/or rechallenge) to assume a causal relationship with lanreotide PRF administration 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 lanreotide PRF administration.

8.1.2.3 Assessment of Expectedness

The reference document for assessing expectedness of AEs/events in this study will be the IB for lanreotide.

8.1.2.4 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 lanreotide PRF schedule of administration (i.e. delay in administration),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

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

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g. ECG changes) that result in a change in administration schedule, or in discontinuation of the study,

or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Recording and Follow Up of Adverse Events

During the informed consent process and on an ongoing basis subjects should be reminded to report any AEs as soon as possible to their study site and not to wait until their next visit if they experience any unexpected medical symptoms.

At each visit, the subject should be asked a non leading question such as: "How have you felt since starting the new treatment/last dose/the last assessment?" All observed or volunteered AEs, regardless of suspected causal relationship to lanreotide PRF, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation's of pre-existing illnesses should be recorded.

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. lanreotide PRF or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow up of the AE is required if the AE or its sequelae persist. Follow up is required until the AE or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

For information on actions to be taken, monitoring and/or follow-up procedures in case of cardiac disorders, pancreatic and renal abnormalities, hyperglycaemia, and gallstones please refer to the IB (Summary of Data and Guidance for the Investigator, Section 6.4.1 Cardiac Safety, Section 6.4.3 Effects on Gallbladder and Pancreas, Section 6.4.4 Glycoregulation, and Section 6.4.6 Special Patient Populations).

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment cohort or suspected relationship to lanreotide PRF 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 either by faxing a detailed written report using the SAE report form or by telephone. If the report is first reported by telephone, this must be followed by a faxed SAE report form. The process for notifying the Medical Development Director (MDD) will be specified in the SAE reporting plan.

An SAE is any AE that:

(1) Results in death,

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event 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 a congenital anomaly/birth defect in the offspring of a subject who received lanreotide PRF,

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or the investigator considers serious should be reported immediately 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 studies, 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 the criteria for "seriousness" but is not an adverse experience and thus is not pertinent to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the subject's Screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae that meet the criteria for seriousness described above.

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 AE/SAE with a suspected causal relationship to lanreotide PRF administration occurring at any other time after completion of the study must be promptly reported.

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

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. 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 that occurred as complications.

8.1.5 Pregnancy

Only females of nonchildbearing potential are eligible to participate in the study (Section 4.1). If the investigator becomes aware of a pregnancy occurring in the partner of a male subject participating in the study, this should be reported to the sponsor. After the partner has given written consent, she should be counselled and followed up. Monitoring of the partner should continue until conclusion of the pregnancy.

8.1.6 Deaths

All AEs resulting in death during the study, or within 12 weeks after lanreotide PRF administration, must be reported as an SAE within 24 hours of the investigator's knowledge of the event.

The convention for recording death is as follows:

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

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

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

If a subject is discontinued due to an SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4). In all cases, the investigator must ensure that the subject receives appropriate medical follow up (see Section 8.1.3).

8.1.8 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 CA, IECs and other investigators concerned with the administration of lanreotide PRF. Reporting will be done in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected according to the study schedule in Table 5 and Table 6 for the evaluation of haematology, serum chemistry and urinalysis. Clinical laboratory tests will be conducted at a central laboratory. Details of the sample handling methodology and reference ranges will be provided in the study manual and archived in the Trial Master File (TMF).

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

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.

Any unscheduled test (indication and results) will be recorded on the dedicated page in the eCRF.

8.2.1 Haematology

Blood samples (3 mL) will be collected in a potassium ethylenediaminetetraacetic acid (EDTA) tube to assess the following parameters: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin

concentration, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count.

8.2.2 Coagulation

Blood samples (4.5 mL) will be collected to assess the following coagulation parameters: activated partial thromboplastin time, prothrombin time and its derived measures of prothrombin ratio and INR.

8.2.3 Blood Biochemistry

Blood samples (6 mL) will be collected to assess the following parameters:

- urea, creatinine, CK, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- ALP, AST, ALT, GGT
- albumin, total protein, total cholesterol, triglycerides, postprandial glucose, and postprandial insulin
- pancreatic enzymes, glucagon

Blood samples (2 mL) will also be collected to assess HbA1c.

8.2.4 Urinalysis

Fresh urine samples (approximately 14 mL) will be collected to assess the following parameters: chloride, bicarbonates, sodium, potassium, calcium, pH, proteins, ketones, glucose, blood, bilirubin and urobilinogen.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as AEs in the eCRF.

8.2.5 Putative Antibody Testing

Blood samples (4 mL) will be collected for the assay of putative antibodies to lanreotide. The tubes should be left to stand for 30 minutes and then centrifuged at 1000 g to 1300 g for 10 minutes at 4°C. The resulting serum will be stored as two 1 mL aliquots at -20°C in polypropylene tubes prior to shipment to the analysis laboratory PPD Each tube should be labelled with the sample identification, study number, site number, subject number and initials, visit number (when applicable) and the planned time of collection.

Full details regarding the requirements for processing, labelling and shipment of these samples will be provided in the central laboratory manual and archived in the TMF.

The determination of putative antibodies to lanreotide will be evaluated using a validated radioimmunoprecipitation assay (RIPA) method PPD . Moreover, a few of the samples (backup samples not used for determination of putative antibodies by the RIPA method) will be shipped to another CRO and used to cross validate a new method for determination of putative antibodies (electrochemiluminescence assay method). The results of the cross validation will not be part of this study and will be reported in a separate report.

8.3 Estimated Glomerular Filtration Rate

Glomerular filtration rate will be estimated from serum creatinine, age, gender and race, according to the MDRD formula [1].

Details of the sample handling methodology and reference ranges will be provided in the central laboratory manual and archived in the TMF.

Any clinically significant abnormalities will be recorded as AEs.

8.4 Physical Examination

Physical examinations, including body weight, will be conducted according to the study schedule in Table 5 and Table 6. Height will be measured at Screening. A reduced physical examination will be performed at home visits and weight will not be measured.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed up by the investigator until resolution or until reaching a clinically stable endpoint.

8.5 Vital Signs

Blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes rest in a supine position and after 1 minute standing. Body temperature will also be recorded.

All vital signs assessments will be conducted at the timepoints specified in the study schedule (Table 5 and Table 6).

Any clinically significant abnormalities will be recorded as AEs.

8.6 Electrocardiography

ECG analysis will be included as a safety evaluation/endpoint in this study.

Computerised standard 12-lead ECGs will be used so that the different ECG parameters (sinus rhythm, heart rate, RR interval, PR interval, QRS interval, QT and QTc) can be measured automatically. QTc will be calculated using Fridericia methodology. The ECG will be recorded with the subject in a supine position after five minutes of rest until four regular consecutive complexes are available. Automated ECG interval estimates taken from the ECG recorder will be used in this study.

Any clinically significant abnormalities will be recorded as AEs. A copy of the ECG trace and report will be retained.

8.7 Gallbladder Echography

Gallbladder echography will be conducted according to study site procedures. The results will be recorded in the eCRF. Any clinically significant abnormalities will be recorded as AEs. In particular, sites should be aware of any subject who has gallstones or sludge present at baseline.

In the case that a subject develops gallstone(s) during the study but they are asymptomatic, they can remain in the study and complete the protocol as planned. If a subject develops symptoms of either a pre-existing gallstone(s) or a newly developed gallstone, they may remain in the study at the discretion of the investigator. As this is a single-dose protocol, the subject will not be exposed to any additional IMP.

In case of the development of (symptomatic) gallstones/sludge this will be treated according to the study sites' routine practice.

8.8 Evaluation of Injection Site Reactions

Injection sites will be evaluated by the investigator (or appropriately trained healthcare professional) for appearance and local symptoms according to NCI CTCAE criteria at the timepoints specified in the study schedule (Table 5 and Table 6). Results will be recorded on a dedicated form in the eCRF.

Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Sample Collection

Blood samples (4 mL each) for determination of lanreotide and excipient serum concentrations will be collected at the timepoints indicated in Table 5 and Table 6. Although the sample collection procedures for lanreotide and the excipient are the same, separate blood samples will be collected for each analyte.

During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, and lanreotide PRF administration must be recorded in the eCRF.

The tubes will be left to stand for 30 minutes and will then be centrifuged at 1000 g to 1300 g for 10 minutes at 4ºC. For each analyte, the resulting serum will be stored as two 1 mL aliquots at –20°C in polypropylene tubes prior to shipment to the analysis laboratory. Each tube should be labelled in accordance with the sponsor's requirements. Aliquots will be shipped on dry ice.

Details of the sample handling methodology and reference ranges will be provided in the central laboratory manual and archived in the TMF.

9.1.2 Analytical Procedures

Serum will be analysed to determine concentrations of lanreotide using a validated, specific and sensitive radioimmunoassay (RIA) method PPD Concentrations of excipient will be analysed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method PPD under the supervision of Ipsen's Pharmacokinetics and Drug Metabolism (PDM) Department. Moreover, a few of the PK samples (backup samples not used for determination of lanreotide concentrations by RIA) will be shipped to another CRO and used to cross validate a new method for determination of serum lanreotide concentrations (mass spectrometry method). The results of the cross validation will not be part of this study and will be reported in a separate report.

9.1.3 Data Analysis

Individual serum concentrations for lanreotide and excipient will be listed and summarised by timepoint and dose level using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation (SD), minimum, maximum, geometric mean, and geometric coefficient of variation assuming log-normally distributed data). Linear and semilogarithmic plots of individual and mean serum concentration-time profiles, as well as spaghetti plots will be reported.

The analysis of PK data will be performed by a CRO under the supervision of Ipsen's PDM Department using a noncompartmental approach and Phoenix WinNonLin Version 6.3 or higher.

The following parameters will be computed from lanreotide serum concentration data: C_{trough}, C_{max}, T_{max}, AUC_{0-85}, $AUC_{0-\infty}$, $t_{½}$, MRT, CL/F and V/F.

For the excipient, the following PK parameters will be computed: C_{max}, T_{max}, AUC_t, $AUC_{0-\infty}$, $t_{½}$, MRT, CL/F and V/F.

Descriptive summary statistics (the number of observations (n), mean, median, SD and range for continuous variables, and n and percentage (%) for categorical/nominal variables) will be presented.

In order to assess dose proportionality, a power model will be used for AUC_{0-85}, $AUC_{0-\infty}$ and C_{max}. Dose independence for $t_{1/2}$, V/F and CL/F will also be investigated using the same model.

Additional exploratory model-based analysis (population PK analysis) might also be conducted to characterise lanreotide PK parameters, such as clearance and volume of distribution, as well as their interindividual variability.

The percentage of subjects developing putative anti-lanreotide antibodies will be calculated at Baseline (predose on Day 1) and at Weeks 13 and 25 (or EW).

9.2 Pharmacodynamics

9.2.1 Sample Collection

Blood samples (2 mL) for assessment of PD parameters will be taken at the timepoints indicated below, as presented in Table 5 and Table 6.

- IGF-1 will be assessed at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1 and at Weeks 5, 9, 13, 17, 21 and 25 (or EW).
- A 2 hour GH cycle (5 sampling times every 30 minutes) will be performed in the morning at Screening, Baseline (predose on Day 1) and at Weeks 5 and 13.
- Subjects will also have random GH samples taken at 6 hours postdose on Day 1 and Weeks 9, 17, 21 and 25 (or EW).

Blood samples (2 mL) will also be collected to assess endocrinology parameters (FT_3, FT_4, TSH and PRL) according to the study schedule (Table 5 and Table 6).

- FT_3, FT_4, TSH and PRL at Screening, Baseline (predose on Day 1), and at Weeks 2, 5, 13 and 25 (or EW).

Details of the sample handling methodology and reference ranges will be provided in the central laboratory manual and archived in the TMF.

9.2.2 Analytical Procedures

Measurement of IGF-1 and GH concentrations will be performed by a central laboratory using a validated method (see the central laboratory manual for further details).

Measurement of IGF-1 concentrations at the screening visit will be performed locally.

9.2.3 Data Analysis

All summaries for the PD endpoints will be based on the intent to treat (ITT) and per protocol (PP) populations. To investigate the relationship between PD variables (GH and IGF-1) and lanreotide exposure, exploratory PK/PD modelling may be performed if a relationship can be defined. Details regarding PK and PK/PD modelling will be described in a separate Data Analysis Plan and the results will be reported as a standalone report.

9.2.3.1 IGF-1 (Age Adjusted)

Summary statistics by dose cohort and overall will be tabulated for each assessment, at each timepoint, as well as for the changes from Baseline (predose on Day 1), with 95% confidence interval (CI). If needed, IGF-1 values will be log transformed. Also, at each assessment timepoint, the percentage of subjects with normalised IGF-1 during predose and postdose will be tabulated by dose cohort and overall. IGF-1 levels at each assessment for individual subjects will be graphically presented by dose cohort as a percentage of the ULN (i.e. % ULN). Time to escape (defined as time from lanreotide PRF administration to the time when the IGF-1 $\geq$1.3 x ULN) will be summarised by dose cohort.

9.2.3.2 Growth Hormone

Summary statistics by dose cohort and overall will be tabulated for each assessment, at each timepoint, as well as for the changes from Baseline (predose on Day 1) with 95% CI. If needed, GH values will be log transformed. $AUC_{0\text{-}2h}$ will be graphically presented by dose cohort at

Baseline and at Day 85. The GH levels at each assessment will also be presented as % ULN. Also, at each assessment timepoint, the percentage of subjects with normalised GH (GH ≤1 ng/mL or ≤2.5 ng/mL) during predose and postdose will be tabulated by dose cohort and overall. For those subjects who had a normalised GH value at Baseline, their time to escape (defined as time from lanreotide PRF administration to the time when GH >1 ng/mL or >2.5 ng/mL) will be summarised.

9.2.3.3 Other Endocrine Parameters

For PRL, TSH, FT_3 and FT_4, the change from Baseline (predose on Day 1) assessment will be listed for each postbaseline assessment, together with the raw values, the lower limit of normal (LLN) and the ULN. Summary statistics by dose cohort and overall will be tabulated for each assessment, at each timepoint, as well as for the changes from Baseline (predose on Day 1).

The PRL, TSH, FT_3 and FT_4 levels at each assessment will be graphically presented by dose cohort. The PRL, TSH, FT_3 and FT_4 levels at each assessment will also be presented as % ULN.

10 STATISTICS

10.1 Analysis Populations

The following populations will be used during statistical analyses:

- **Screened population:** All subjects screened (i.e. who signed the informed consent form).
- **Randomised population:** Not applicable.
- **Safety population:** All subjects who receive the single dose of lanreotide PRF and have at least one postbaseline safety assessment.
- **ITT population:** All treated subjects.
- **PP population:** All subjects in the ITT population for whom no major protocol violations/deviations occur.
- **PK valid population:** All subjects who receive at least one dose and have no major protocol deviations affecting the PK variables and who have a sufficient number of serum lanreotide concentrations to estimate the main PK parameters (C_{max}, T_{max}, and AUC).

10.1.1 Populations Analysed

The primary analysis based on the primary safety and PK will be performed on the safety and PK valid populations, respectively. In addition, analyses based on ITT and PP populations may be performed as secondary on the PD data.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol Deviation Document and its impact on inclusion in each analysis population (ITT, PP, safety and PK valid populations) for any subject will be specified. The final list of protocol deviations impacting the PP population will be reviewed during the data review meeting held prior to database lock. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population.

10.2 Sample Size Determination

Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule focussing a priori on the subject safety. This means that the addition of up to nine subjects would be based on the MTD profile and decisions made at that dose level. In addition, the sample size is based on prior clinical experience with this type of study and subject population and should be sufficient to meet the study objectives.

10.3 Significance Testing and Estimations

As this is a descriptive safety, tolerability and PK/PD study, no formal statistical testing will be carried out.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A Reporting and Analysis plan describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

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

10.4.1 Demographic and Other Baseline Characteristics

In order to ensure balance among dose cohorts, descriptive summary statistics (n, mean, SD, median, minimum, maximum) or frequency counts of demographic and Baseline data (medical history, concomitant medications, etc.) will be presented by dose cohort and overall for the safety population(s).

10.4.2 Homogeneity of Treatment Cohorts

Not applicable.

10.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in the safety population will be tabulated by dose cohort. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were treated, discontinued and completed at each dose level will be tabulated. Primary reasons for discontinuation of study treatment will be tabulated per dose level.

10.4.4 Pharmacokinetic Data

The PK data analysis will be performed independently by a CRO under the supervision of Ipsen's PDM Department as described in Section 9.1.3.

Individual listings and summary tables of lanreotide and excipient concentrations will be provided.

10.4.5 Efficacy Evaluation

Not applicable. For the analysis of PD data, see Section 9.2.

10.4.6 Adjustment for Country/Centre Effect

Not applicable.

10.4.7 Safety Evaluation

Safety analyses and summary tables will be based on the safety population. Adverse events reported by investigators using the NCI CTCAE classification (Version 4.03) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 16.1 or higher).

All safety data will be included in the subject data listings. Listings of AEs will be presented by subject, system organ class and preferred term.

Based upon the definitions of DLTs provided in Section 3.6.3, subject profiles will be prepared for individual subjects to facilitate the review of the DRC. Summaries of DLTs by dose cohorts will also be provided.

All AEs and SAEs occurring during the Screening period will be reported; however, these will not be considered in the analysis of TEAEs. The incidence of all reported TEAEs and SAEs will be tabulated by dose cohort and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

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

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

All TEAEs will be flagged in the AEs listings.

Summary incidence tables will be provided, classified by body system, preferred term and associated NCI CTCAE worst grade. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (grade 5 >grade 4 >grade 3 >grade 2 >grade 1 >missing >not applicable) will be chosen.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI CTCAE criteria. The NCI CTCAE grade 3 and 4 haematology and biochemistry parameters by subject and by cycle will be listed. For white blood cells, neutrophils, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir will be calculated.

Concomitant medication will be coded by using the World Health Organisation (WHO) Drug Dictionary (Version June 2014 or higher) and will be summarised by dose cohort with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) by treatment cohort and overall will be presented for vital signs (blood pressure and heart rate) and clinical laboratory tests at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. For the ECG parameters, clinically significant findings will be listed by dose cohort and overall.

10.5 Subgroup Analyses

If sufficient numbers of subjects are available to permit these analyses, descriptive statistics will be provided within each category of the following variables: Previous treatment and dose (octreotide LAR, lanreotide Autogel), sex, age (≤65, >65 years).

10.6 Interim Analyses/Data Review Committee

Before each decision of the dose escalation, safety data will be summarised and presented to the DRC. This DRC will be composed of an expert in Endocrinology and an ad hoc expert in Hepatogastroenterology. A specific charter will be developed to define roles and responsibilities.

The DRC will review safety data from each cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). At this time, if no DLT or unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort.

The DRC will also advise on any restriction on subject enrolment with regard to dose of pre-study octreotide or lanreotide Autogel for cohorts 2 and 3, based on considerations of safety and PK assessment of preceding cohort(s).

The DRC will meet after the last subject, last visit (LSLV) has been completed to review the overall safety and to identify any delayed grade ≥3 adverse reactions (cholelithiasis-related gallbladder obstruction or cholecystitis ≥grade 3, or ≥grade 3 injection site reaction) or prolonged grade ≥2 toxicity.

However, ad hoc DRC meetings would take place if 2 DLTs occur during cohort accrual.

Details of the DRC set up, membership, management and responsibilities will be provided in the DRC charter and archived in the TMF.

Details regarding stopping boundaries and early stopping rules will be described in the charter.

Interim analyses may be performed by the Sponsor to facilitate the planning of future clinical studies of lanreotide PRF.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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 12.4, 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's representative as soon as possible, to assist with preparations for the inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations, Violations, and Exceptions

A protocol deviation is nonadherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e. nonadherence on the part of the subjects, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the eCRF.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study 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 according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor 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 subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

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

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.6]). The EDC system will comply with FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject 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.

13.2 Informed Consent

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

The sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

For the storage and sampling of blood for circulating markers, including pharmacogenetic and pharmacogenomic biomarkers, the blood sampling procedure will be explained after the subject has given written informed consent for the main study. A separate consent form will then be requested from subjects agreeing to participate in this additional blood sampling requirement.

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

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

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.

13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In the eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 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 subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, lanreotide PRF 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. Subject completed diaries and questionnaires will be printed or electronic.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book 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.

14.2 Data Management

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

Data management will be conducted by a CRO (directed by the sponsor's data management department). All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Study Monitoring). The CRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

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

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be managed by the sponsor's Biometry Group. Concomitant medications will be coded using WHO Drug Dictionary and AEs/medical history terms will be coded using MedDRA.

14.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study 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 25 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.

15 FINANCING AND INSURANCE

15.1 Contractual and Financial Details

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

15.2 Insurance, Indemnity and Compensation

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

16 REPORTING AND PUBLICATIONS OF RESULTS

16.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

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

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

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

16.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study 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.

17 REFERENCES

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12 CCI [redacted].

13 CCI [redacted]

18 LIST OF APPENDICES

Appendix 1 Biobanking

Biobanking:

One of the exploratory evaluations involves the collection of blood samples for the biobanking project. Blood samples will be collected only in patients who have signed a separate consent for the exploratory part, particularly for the biobank samples, during specific timepoints described in Table 5 of the protocol. One of the 3 blood samples will be centrifuged (serum sample); the two other samples will not be centrifuged (blood samples in RNA Paxgen tubes). The samples should be clearly and appropriate labelled with the following minimum information: study code, patient number, and visit name. The samples will be shipped to the central laboratory and stored at -80°C. At the end of the study one shipment will be made by the central laboratory with all samples to the biobanking central laboratory, FISHER, in dry ice. Upon receipt of each shipment of samples, an acknowledgment of receipt made out by the contact person will be sent to the site. The samples will then be stored at the biobanking central laboratory, FISHER, for future exploratory biomarker analysis, including pharmacogenetic and pharmacogenomic biomarker research required to further the understanding of (i) treatment response and the the safety profile, (ii) drug treatment mode of actions, and (iii) disease understanding. Samples will be stored for up to 15 years at the biobanking central laboratory, FISHER. After 15 years of storage any remaining samples will be destroyed. Samples may be destroyed earlier if subjects withdraw consent from the biobanking project.

Ribonucleic Acid (RNA) Biobank

Where not prohibited by local regulations, blood will be collected from all subjects for analysis of gene expression of relevance for the mechanism of lanreotide and those of relevance for safety, tolerability, and potential clinical benefit

Serum Biobank

Where not prohibited by local regulations, blood will be collected from all subjects for analysis of protein of relevance for the mechanism of Lanreotide and those of relevance for safety, tolerability, and potential clinical benefit

All the detailed procedures will be described in a separate laboratory manual.

Shipment contact and addresses

FISHER (biobanking central laboratory)

Address: Fisher BioServices, 1 Woodside, Bishops Stortford, Herts, CM23 5RG, England

Phone: PPD

Fax: +PPD

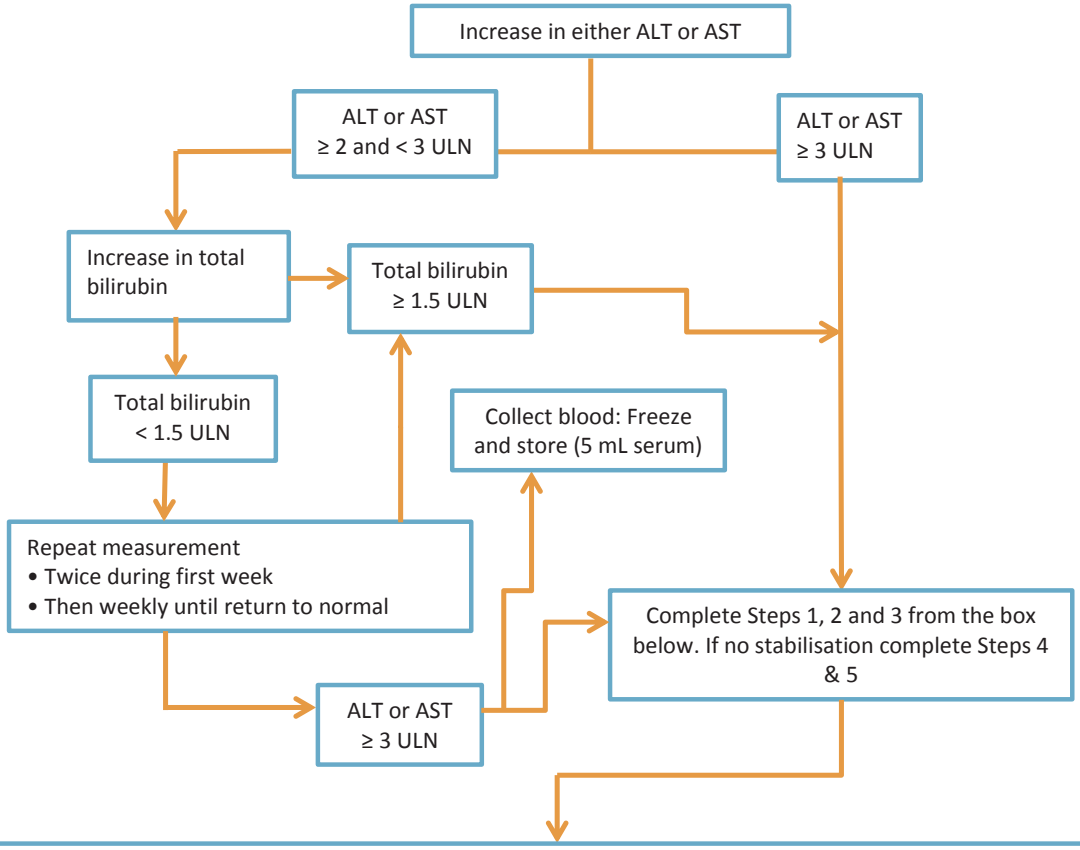
E-mail:PPD

Appendix 2 Liver Safety Algorithm

Liver Safety Algorithm - Increase in Aminotransferases & Bilirubin

(Expressed as a multiple of the ULN of the Study Central Laboratory)

As this is a single-dose study, where possible, all patients should remain in the trial during management and follow-up of elevations in liver enzymes and/or bilirubin



1. Perform the following tests immediately –
- AST, ALT, ALP (alkaline phosphatase), total and conjugated Bilirubin, Prothrombin Time/INR (as mentioned above)
- CPK (creatine phosphokinase), serum creatinine, complete blood count
- Anti-HIV IgM, anti-HBc IgM, anti-HCV IgM, anti-CMV IgM
- Specific serologic markers of recent infection with EBV, Herpes viruses and toxoplasma (depending on the clinical context)
- Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
- Collect blood, freeze and store (5 mL serum)

2. Monitor aminotransferases (AST/ALT) and/or bilirubin–
-Twice during the first week, then weekly until return to normal

3. Interview the subject again –
- Consumption of alcohol, concomitant medication, drugs and herbals before and during the study
- Recent history of febrile illness or jaundice
- History of blood or blood product transfusion, travel to Africa, Asia, intravenous drug addiction

If values are not stabilising or reducing;
4. Consider subject hospitalization –
- If INR>2 (or PT<50%), or obvious bleeding or jaundice
- And/or signs of central nervous system disturbances suggesting hepatic encephalopathy

5. Consider consultation with hepatologist

Appendix 3 Protocol Amendment 1 (19 November 2014)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Octreotide LAR
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 1.0 Version 2.0: 19 November 2014

The following amendment(s) is/are proposed:

Version Date		**01 September 2014**	**19 November 2014**
Page	**Section**	**WAS**	**IS**
5	Synopsis	If any serious adverse events (SAEs) occur, a relationship with the exposure to lanreotide PRF will be assessed. The pre established stopping rules for the DRC decision for study discontinuation and/or inclusion of the subsequent treatment cohort include the occurrence of any dose limiting toxicity (DLT). A DLT is defined as an adverse event (AE; excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Visit 5 (Week 2)) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre established criteria (more often grade 3 or 4 toxicity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria). The occurrence of ≥2 DLTs would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level.	If any serious adverse events (SAEs) occur, a relationship with the exposure to lanreotide PRF will be assessed. The pre established stopping rules for the DRC decision for study discontinuation and/or inclusion of the subsequent treatment cohort include the occurrence of ~~any~~ dose limiting ~~toxicity~~ **toxicities** (DLT**s**). A DLT is defined as an adverse event (AE; excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Visit 5 (Week 2)) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre established criteria (more often grade 3 or 4 toxicity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria). The occurrence of ~~≥~~2 DLTs would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level.
2	Investigator's Agreement	NAME:Sebastian J.C.M.M. Neggers, MD, PhD TITLE: Principal Investigator	The Principal Investigator's name and title was moved from the Investigator's Agreement signature page to the Coordinating Investigator's Agreement signature page (page 3).
20	1.3	They showed no systemic effects, rapid absorption (time to maximum	They showed no systemic effects~~,~~ ~~rapid absorption (time to maximum~~

		serum concentration (T_{max}) 0.5 hours) and elimination (apparent terminal half life (t½) 2.8 hours) phases, as well as no accumulation between Day 0 and Week 4. At the injection sites, a spectrum of inflammatory changes comprising subcutaneous necrosis, fibrosis/fibroplasia, subcutaneous subacute inflammation, and haemorrhage in rat and dog, as well as granulomatous panniculitis in dog were induced. Most of these local signs were reversible at the end of the treatment free period. Infact, in humans, the maximum dose of lanreotide PRF planned to be administered by single injection every 3 months is 360 mg, constituting approximately 2 mg/kg of glycofurol. Therefore, the doses of glycofurol tested in the toxicology studies (30 mg/kg to 180 mg/kg) were not only administered with a higher frequency (daily for 4 weeks versus once every 3 months) but were way above the intended clinical dose (15 to 90 times, respectively). Consequently, the local effects that were recorded in the toxicology studies were considered without clinical relevance.	~~serum concentration (Tmax) 0.5 hours) and elimination (apparent terminal half life (t½) 2.8 hours) phases, as well as no accumulation between Day 0 and Week 4.~~ **and glycofurol alone was rapidly absorbed (T_{max} from 0.5 to 2 h in dogs and 0.25 to 0.5 h in rats) and eliminated (t½ from 0.37 to 1.3 h in dogs and 1 to 2.8 h in rats). There was no accumulation of glycofurol after daily s.c. administration for 4 weeks in both species.** At the injection sites, a spectrum of inflammatory changes comprising subcutaneous necrosis, fibrosis/fibroplasia, subcutaneous subacute inflammation, and haemorrhage in rat and dog, as well as granulomatous panniculitis in dog were induced. Most of these local signs were reversible at the end of the treatment free period. ~~Infact~~ **In fact**, in humans, the maximum dose of lanreotide PRF planned to be administered by single injection every 3 months is 360 mg, constituting approximately 2 mg/kg of glycofurol **for a person of 70 kg.** Therefore, the doses of glycofurol tested in the toxicology studies (30 mg/kg to 180 mg/kg) were not only administered with a higher frequency (daily for 4 weeks versus once every 3 months) but were way above the intended clinical dose (15 to 90 times, respectively). Consequently, the local effects that were recorded in the toxicology studies were considered without clinical relevance.
21	1.4.3	The medical procedures during the study are considered to be safe (venous puncture and gallbladder echography) and do not put participating subjects at any procedure related increased risk. The risk of reactivation of the disease with clinical symptoms within the 3 month follow up period is taken into consideration.	The medical procedures during the study are considered to be safe (venous puncture and gallbladder echography) and do not put participating subjects at any procedure related increased risk. **The half-life of lanreotide PRF in human is not yet known. However, based on dog data, 5 times the mean terminal**

		IGF-1 and GH concentrations will be monitored monthly during this period. If the investigator judges that the subject requires any treatment for acromegaly (reappearance of clinical or biochemical symptoms of acromegaly) during the follow-up period, the subject will be withdrawn from the study and will receive treatment according to routine practice. Additional information regarding risks and benefits to human subjects may be found in the IB.	**half-life (t½ ~35 days) of lanreotide PRF corresponds to 175 days (i.e. ~6 months). Therefore a 6-month follow up should be sufficient to cover more than 95% of the profile if the half-life in dogs is similar in human.** **The rationale for a follow up of 3 months after the potential 3 months treatment period is based on the need for the study subjects to resume treatment with their approved somatostatin analogue to control acromegaly and GH / IGF1 levels. Given the similar class of active ingredient, the sponsor believes it is reasonable to let the participants go back to their regular treatment after three months follow up as longer periods off therapy may be associated with unnecessarily higher rates of symptoms. Furthermore after a single dose of lanreotide PRF, anticipated to provide 3 months treatment and after 3 months additional follow-up, it is reasonable to consider that the residual lanreotide concentrations are low enough not to trigger any new safety concern when standard treatment is resumed. Should any concern about this residual concentration arise during the study the sponsor will notify the investigators about the level of residual concentration which would allow to adjustadjusting the restart of octreotide treatment.** The risk of reactivation of the disease with clinical symptoms within the 3 month follow up period is taken into consideration. IGF-1 and GH concentrations will be monitored monthly during this period. If the investigator judges that the subject requires any treatment for acromegaly (reappearance of clinical or biochemical symptoms of

			acromegaly) during the follow-up period, the subject will be withdrawn from the study and will receive treatment according to routine practice. Additional information regarding risks and benefits to human subjects may be found in the IB.
22	1.5	Lanreotide PRF will be injected via the deep subcutaneous route in the superior, external quadrant of the buttock according to the recommendations detailed in Section 6.1.	Lanreotide PRF will be injected via the deep subcutaneous route in the superior, external quadrant of the buttock according to the recommendations detailed in Section 6.1. **The three dose levels proposed for lanreotide PRF (180 mg, 270 mg and 360 mg) are targeted as three times the common doses of lanreotide Autogel used for the treatment of acromegaly (60, 90 and 120 mg).** **A robust PK/PD model developed with lanreotide Autogel in acromegalic patients which relates lanreotide trough concentrations (at 1 month for Autogel) to GH and IGF-1 concentrations, has proven that if the lanreotide concentration remains above a target therapeutic level over the whole dosing interval, acromegalic patients remain controlled in terms of GH and IGF-1.** **Therefore, the trough concentrations (C_{trough}) observed at 3 months with lanreotide PRF were compared to the target therapeutic levels reached at 1 month with lanreotide Autogel (using a 'translation' from human data to dogs). In dogs, the C_{trough} achieved with lanreotide PRF 240, 270 and 450 mg were comparable to those achieved with the corresponding dose of lanreotide Autogel (i.e., lanreotide PRF dose divided by 3), which justifies the selected doses of lanreotide PRF.** **From a safety point of view, the C_{max} and AUC of lanreotide PRF in dogs were carefully reviewed and compared to the commercial**

			formulation lanreotide Autogel 120 mg and a previous development formulation of lanreotide Autogel$^{23\%}$ 240 mg. The mean C_{max} of 58 ng/mL observed with the highest dose tested in dogs (PRF 450 mg) is increased by 60-70% compared to the mean C_{max} of 36 ng/nL observed with lanreotide Autogel 120 mg (highest dose commercially available of the 1-month formulation) and in dogs the mean exposure over 3 months after a single injection of lanreotide PRF 450 mg (706 ng.day/mL) is similar to the exposure over 3 months after three injections of lanreotide Autogel 120 mg every 4 weeks (737 ng.day/mL). Therefore, if the PK profile of lanreotide PRF in human is consistent with dog data, comparable safety ratios to those observed with lanreotide Autogel 120 mg (200- to 400-fold in rats and 16- to 23-fold in dogs) could be anticipated with lanreotide PRF. Moreover the mean C_{max} of lanreotide PRF tested in dogs is 2-fold lower than that observed with a dose of 240 mg of lanreotide Autogel$^{23\%}$ (a previous development formulation tested in a Phase 1 study in healthy volunteers) which was not well tolerated in healthy subjects. Furthermore, in the dog PK study performed with lanreotide PRF, assessment of the local tolerance of lanreotide PRF containing glycofurol showed a s.c. granulomatous inflammation at the injection site at the end of the 3-month and 6-month periods. These histological findings have already been described for lanreotide Autogel in dogs thus the excipient glycofurol does not aggravate the local tolerance of the therapeutic compound.

			In conclusion, the choice of the lanreotide PRF doses as 3 times the doses of Autogel is confirmed, from an efficacy perspective, by the C_{trough} reached at 3 months. In terms of safety, the selected doses of lanreotide PRF are expected to show similar or lower exposure than with the highest dose of the commercially available 1-month formulation (lanreotide Autogel 120 mg). Consequently, no change in the safety ratios is expected. Moreover, the local tolerance of the lanreotide PRF in dog was not different from that observed with lanreotide Autogel.
24	1.7	The choice of octreotide stable subjects as the study population, instead of lanreotide stable subjects, was guided by the fact that a 4 month washout period before lanreotide PRF administration would be avoided and no cross interference in lanreotide and octreotide measurements would occur.	The choice of octreotide stable subjects as the study population, instead of lanreotide stable subjects, was guided by the fact that a 4 month washout period before lanreotide PRF administration would be avoided and no cross interference in lanreotide and octreotide measurements **by the bioanalytical assay** would occur.
25	2.1	A first-in-man lanreotide PRF safety and PK/PD study in healthy volunteers was not planned because, given the previous extent of lanreotide use, it was not expected that any new information on lanreotide would be obtained to justify such a phase I study. In addition, it did not appear ethical to expose healthy volunteers to high doses of lanreotide.	~~A first-in-man lanreotide PRF safety and PK/PD study in healthy volunteers was not planned because, given the previous extent of lanreotide use, it was not expected that any new information on lanreotide would be obtained to justify such a phase I study. In addition, it did not appear ethical to expose healthy volunteers to high doses of lanreotide.~~ **A modified lanreotide autogel formulation has been studied in a single Phase 1 study in healthy volunteers, however its profile was not compatible with adequate exposure for a 3 month dosing interval and exaggerated adverse effects were observed in the study subjects (Study 2-55-52030-724).**
26	3.1	The occurrence of ≥2 dose limiting toxicities (DLTs) would trigger the organisation of an intermediate	The occurrence of ~~≥~~2 dose limiting toxicities (DLTs) would trigger the organisation of an intermediate

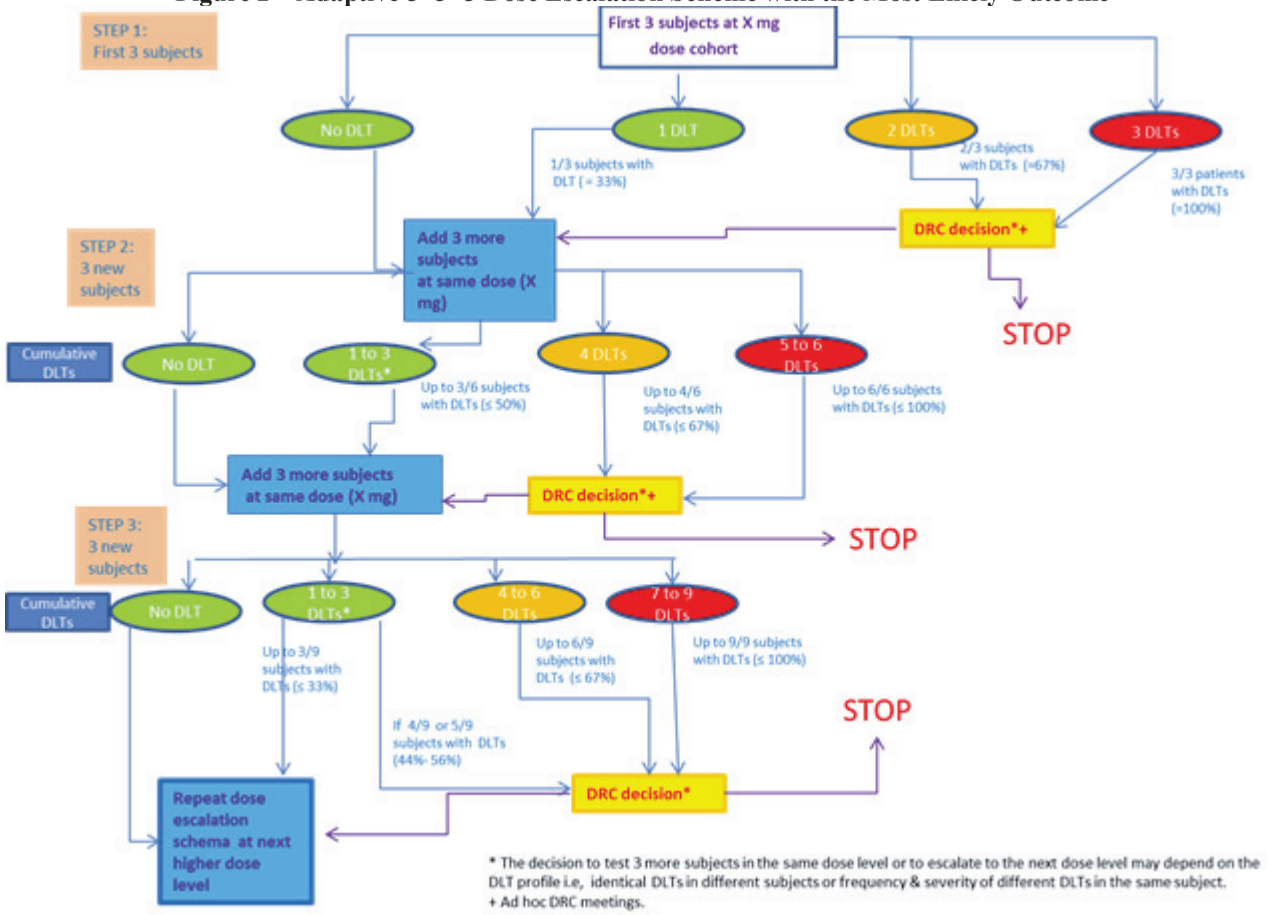
		DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level (see Section 6.1.1).	DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level (see Section 6.1.1).
31	3.6.2	The pre established stopping rules for the DRC decision for study discontinuation and/or inclusion of the subsequent treatment cohort include the occurrence of any DLT occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration (see Section 3.6.3).	The pre established stopping rules for the DRC decision for study discontinuation and/or inclusion of the subsequent treatment cohort include the occurrence of ~~any~~ DLT**s** occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration (see Section 3.6.3).
43, 44, 45	5.2.3, 5.2.4.1, 5.2.4.2	• Clinical laboratory assessments	• **Central** clinical laboratory assessments
47	6.1.1	The dose escalation will proceed with a 3+3+3 scheme. At each dose level, a total of 9 subjects will be enrolled if ≤2 DLT are reported. See Section 3.6.3 for the definition of DLT. Subject enrolment into the study will begin at Dose Level 1 (180 mg). Starting with the 180 mg dose cohort, the first 3 subjects will be enrolled into the study. If none or one (1/3; 33%) subject experiences a DLT, 3 more subjects will be enrolled at the same dose (180 mg). However, if 2 (2/3; 67%) or 3 (3/3; 100%) subjects experience DLTs, the DRC will convene immediately (ad hoc meeting) to evaluate the decision to test 3 more subjects at this dose level. This will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject. Based on the decision of the DRC, 3 more subjects will be enrolled into the 180 mg dose cohort. Of the 6 subjects enrolled at this dose level, if up to 3/6 (≤50%) experiences a DLT, 3 more subjects will be enrolled at the same dose (180 mg). However, if at least 4/6 (≤ 67%) to 6/6 (100%) subjects experience DLTs, the DRC will convene immediately (ad	The dose escalation will proceed with a 3+3+3 scheme. At each dose level, a total of 9 subjects will be enrolled if ≤~~2~~**3** DLT**s** are reported. See Section 3.6.3 for the definition of DLT. Subject enrolment into the study will begin at Dose Level 1 (180 mg). ~~Starting with the 180 mg dose cohort, the first 3 subjects will be enrolled into the study. If none or one (1/3; 33%) subject experiences a DLT, 3 more subjects will be enrolled at the same dose (180 mg). However, if 2 (2/3; 67%) or 3 (3/3; 100%) subjects experience DLTs, the DRC will convene immediately (ad hoc meeting) to evaluate the decision to test 3 more subjects at this dose level. This will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject.~~ ~~Based on the decision of the DRC, 3 more subjects will be enrolled into the 180 mg dose cohort. Of the 6 subjects enrolled at this dose level, if up to 3/6 (≤50%) experiences a DLT, 3 more subjects will be enrolled at the same dose (180 mg). However, if at least 4/6 (≤ 67%) to 6/6 (100%) subjects experience DLTs, the DRC will convene immediately (ad~~

		hoc meeting) to evaluate the decision to test 3 more subjects at this dose level. Again, this will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject. Based on the decision of the DRC, 3 more subjects will be enrolled into the 180 mg dose cohort to give a total of 9 subjects. The DRC will evaluate the safety of lanreotide PRF after all 9 subjects have been treated at this dose level before authorising treatment to the next highest dose (270 mg). If up to 3/9 (≤33%) subjects experience a DLT, dose escalation to the next highest dose (270 mg) will proceed. However, if at least 4/9, 5/9 up to 6/9 or up to 9/9 (44%, 56%, ≤67% or ≤100%, respectively) subjects experience DLTs, the DRC will evaluate the decision to escalate to the next highest dose. Again, this will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject. These rules will apply for the recruitment of subjects into the 270 mg dose cohort and for further escalation and recruitment of subjects into the 360 mg dose cohort. Details of the adaptive 3+3+3 dose escalation scheme with the most likely outcome are provided in Figure 2.	~~hoc meeting) to evaluate the decision to test 3 more subjects at this dose level. Again, this will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject.~~ ~~Based on the decision of the DRC, 3 more subjects will be enrolled into the 180 mg dose cohort to give a total of 9 subjects. The DRC will evaluate the safety of lanreotide PRF after all 9 subjects have been treated at this dose level before authorising treatment to the next highest dose (270 mg). If up to 3/9 (≤33%) subjects experience a DLT, dose escalation to the next highest dose (270 mg) will proceed. However, if at least 4/9, 5/9 up to 6/9 or up to 9/9 (44%, 56%, ≤67% or ≤100%, respectively) subjects experience DLTs, the DRC will evaluate the decision to escalate to the next highest dose. Again, this will be dependent on the DLT profile (i.e. identical DLTs in different subjects) or the frequency and severity of DLTs in the same subject.~~ ~~These rules will apply for the recruitment of subjects into the 270 mg dose cohort and for further escalation and recruitment of subjects into the 360 mg dose cohort.~~ **Dose level: 180 mg. The study will start dosing 3 subjects. If none or 1 out of the 3 dosed subjects experiences a DLT, 3 more subjects will be dosed at the same time. If 2 out of the 3 dosed subjects experiences a DLT, the DRC will decide whether 3 more subjects may be dosed. If all 3 subjects have experienced a DLT, dosing will be stopped and the dose will be declared the maximum administered dose.** **If none or 1 of the 6 dosed subjects experience a DLT, 3 more subjects can be dosed at**

			the same dose. If 2 of the 6 dosed subjects experience a DLT, and one or both of the DLTs occured in the second group of 3 patients, the DRC will decide whether 3 more subjects may be dosed. If a total of 3 or more out of 6 subjects experience a DLT, dosing will be stopped and the dose will be declared the maximum administered dose. Dose escalation: If more than 3 out of 9 subjects experience a DLT, dose escalation will be stopped and the dose will be declared the maximum administered dose. If ≤3 DLTs have been observed in the 9 treated subjects, then the dose may be escalated to 270 mg. The DRC will determine if progression to the next dose cohort should occur after reviewing data from the preceding cohort. The same rules will be applied to the next dose level and the decision to escalate to 360 mg will be done in the same way. Details of the adaptive 3+3+3 dose escalation scheme with the most likely outcome are provided in Figure 2.
48	6.1.1	Figure 2 (see below)	Figure 2 was adapted in line with the changes to the Dose Escalation Criteria outlined above.
49	6.2	• Hormone replacement therapy (HRT) with oestrogens, • Dopamine agonist and GH receptor antagonist, or pituitary surgery within 3 months prior to study entry, • Radiotherapy at any time prior to study entry.	• Hormone replacement therapy (HRT) with oestrogens, • Dopamine agonist and GH receptor antagonist, or pituitary surgery ~~within 3 months prior to study entry,~~ • Radiotherapy ~~at any time prior to study entry.~~
66	10.6	However, ad hoc DRC meetings would take place if ≥2 DLTs occur during cohort accrual.	However, ad hoc DRC meetings would take place if ≥2 DLTs occur during cohort accrual.

WAS: Version Final: 01 September 2014

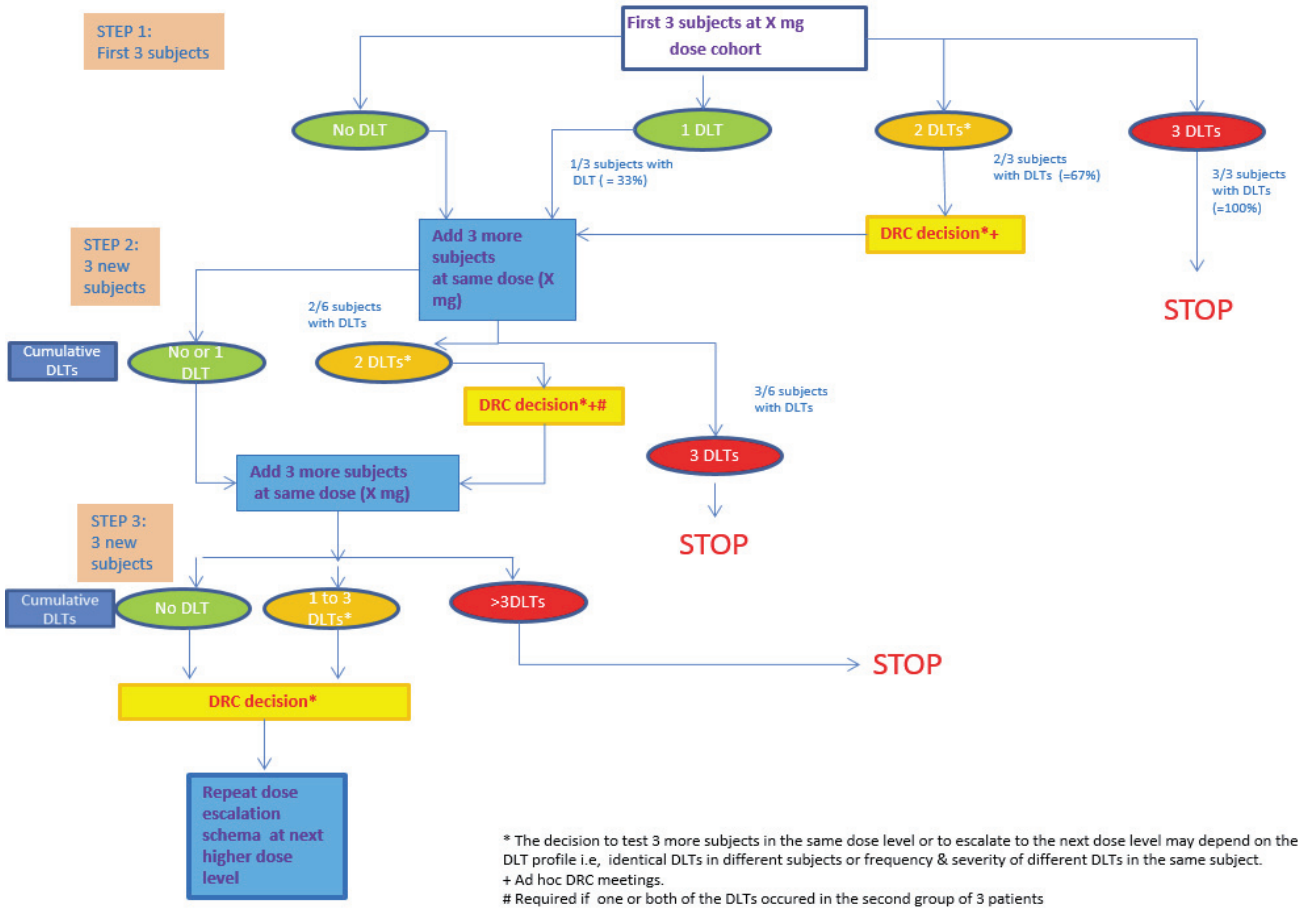
Figure 2 Adaptive 3+3+3 Dose Escalation Scheme with the Most Likely Outcome



DLT=dose limiting toxicity; DRC=Data Review Committee.

IS: Amendment 1.0 Version 2.0: 19 November 2014

Figure 2Adaptive 3+3+3 Dose Escalation Scheme with the Most Likely Outcome



DLT=dose limiting toxicity; DRC=Data Review Committee.

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 1.0 Version 2.0: 19 November 2014	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	To provide clarification on questions received from the authorities associated with safety monitoring, the pharmacokinetics of lanreotide PRF, the dose escalation criteria, and the dose selection rationale.	
Other Action Required?	CRF Update	Yes ☐ No ☒ (tick one)
	Local Consent Form Update	Yes ☒ No ☐ (tick one)
	Database Update	Yes ☐ No ☒ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☐ No ☒ (tick one)

Appendix 4 Protocol Amendment 2 (18 February 2015)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Octreotide LAR
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 2.0 Version 3.0: 18 February 2015

The following amendment(s) is/are proposed:

Version Date		**19 November 2014**	**18 February 2015**
Page	**Section**	**WAS**	**IS**
1	Title page	**Sponsor's Medically Responsible Person:** PPD Ipsen Innovation Ipsen Research and Development 5 avenue du Canada Les Ulis Cedex (France) PPD	**Sponsor's Medically Responsible Person:** PPD ~~Ipsen Innovation~~ ~~Ipsen Research and Development~~ ~~5 avenue du Canada~~ ~~Les Ulis Cedex (France)~~ PPD PPD **Ipsen Biosciences, Inc.** **650 East Kendal Street** **Cambridge, MA 02142 (USA)** PPD
1	Title page	**Monitoring Office:** PPD Ipsen Innovation 5 avenue du Canada 91966 Les Ulis Cedex (France) PPD	**Monitoring Office:** PPD PPD Ipsen Innovation 5 avenue du Canada 91966 Les Ulis Cedex (France) PPD
1	Title page	**Pharmacovigilance/ Emergency Contact:** PPD Central Department of Pharmacovigilance, Ipsen Group, 190 Bath Road, Slough, Berkshire SL1 3XE, England	**Pharmacovigilance/ Emergency Contact:** PPD PPD Central Department of Pharmacovigilance, Ipsen Group, 190 Bath Road, Slough, Berkshire SL1 3XE, England
38	Table 4, footnote 'f'	f evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, fasting and postprandial glycaemia, insulinaemia.	f evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, ~~fasting and~~ postprandial glycaemia, **and postprandial** insulinaemia.

40	Table 6, footnote 'a'	a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, fasting and postprandial blood glucose, fasting and postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.	a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, ~~fasting and~~ postprandial blood glucose, ~~fasting and~~ postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.
42	5.2.3	• Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, international normalised ratio (INR), fasting and postprandial glycaemia, insulinaemia) at 6 hours postdose	• Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, international normalised ratio (INR), ~~fasting and~~ postprandial glycaemia, **and postprandial** insulinaemia) at 6 hours postdose
49	6.2	The following concomitant medications are permitted during this study, but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study. • Bradycardia inducing drugs (e.g. beta blockers), • Substrate of CYP3A4 (e.g. quinidine, erythromycin, simvastatin).	The following concomitant medications are permitted during this study, but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study. • Bradycardia inducing drugs (e.g. beta blockers), • Substrate of CYP3A4 (e.g. quinidine, erythromycin, simvastatin). **For information regarding the effects on blood glucose and the need for monitoring and adjustment of anti-diabetic agents, as well as information about the possible effects on cyclosporine bioavailability, please refer to the IB (Summary of Data and Guidance for the Investigator, Section 6.4.4 Glycoregulation and Section 6.4.7 Drug Interactions).**

53	8.1.3	Follow up is required until the AE or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.	Follow up is required until the AE or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative. **For information on actions to be taken, monitoring and/or follow-up procedures in case of cardiac disorders, pancreatic and renal abnormalities, hyperglycaemia, and gallstones please refer to the IB (Summary of Data and Guidance for the Investigator, Section 6.4.1 Cardiac Safety, Section 6.4.3 Effects on Gallbladder and Pancreas, Section 6.4.4 Glycoregulation, and Section 6.4.6 Special Patient Populations).**
56	8.2.3	• albumin total protein, total cholesterol, triglycerides, fasting and postprandial glucose, and fasting and postprandial insulin	• albumin total protein, total cholesterol, triglycerides, ~~fasting and~~ postprandial glucose, ~~and fasting~~ and postprandial insulin

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 2.0 Version 3.0: 18 February 2015	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
Reason(s) for changes	To update the contact details of the Sponsor's medically responsible person, the monitoring office, and the pharmacovigilance/emergency contact. At the 6 hours postdose timepoint, the postprandial assessment was considered as the most clinically relevant. Therefore the fasting glucose and fasting insulin assessments were removed from Visit 2 (postdose) to Visit 12. To add a reference to the IB for information regarding the effects on blood glucose and the need for monitoring and adjustment of anti-diabetic agents, as well as information about the possible effects on cyclosporine bioavailability. To add a reference to the IB for information regarding the action to be taken and the patient monitoring and follow-up procedures to be used in cases of cardiac disorders, pancreatic and renal abnormalities, hyperglycaemia, and gallstones.	
Other Action Required?	CRF Update	Yes ☐ No ☒ (tick one)
	Local Consent Form Update	Yes ☐ No ☒ (tick one)
	Database Update	Yes ☐ No ☒ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☐ No ☒ (tick one)

Appendix 5 Protocol Amendment 3 (12 June 2015)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Octreotide LAR
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 3.0 Version 4.0: 12 June 2015

The following amendment(s) is/are proposed:

Version Date		**18 February 2015**	**12 June 2015**
Page	**Section**	**WAS**	**IS**
1	Title page	**Sponsor's Medically Responsible Person:** PPD Ipsen Biosciences, Inc. 650 East Kendal Street Cambridge, MA 02142 (USA) PPD	**Sponsor's Medically Responsible Person:** PPD Ipsen Biosciences, Inc. 650 East Kendal Street Cambridge, MA 02142 (USA) PPD
1	Title page	**Sebastian J.C.M.M. Neggers, MD, PhD** Department of Medicine Section Endocrinology Eramus University MC PO Box 2040 3000 CA Rotterdam (The Netherlands)	**Sebastian J.C.M.M. Neggers, MD, PhD** Department of Medicine Section Endocrinology Erasmus University MC PO Box 2040 3000 CA Rotterdam (The Netherlands)
5	Synopsis	**Planned study period:** 02/2015 to 04/2016	**Planned study period:** 02/2015 to ~~04/2016~~**01/2017**
5	Synopsis, Methodology	Study visits will be performed on Days 1, 2, 3, and 5, and Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at Weeks 15, 17, 19, 21, 23 and 25 during follow up.	Study visits will be performed on Days 1, 2, 3, and 5, and Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at Weeks 15, 17, 19, 21, 23 and 25 during follow up. **All study visits can be performed at the study site. However, study visits on Weeks 4, 7, 11, 15, 19 and 23 can be performed at the study site and/or at the subjects home as per investigator's and subject's decision.**

6	Synopsis, Methodology	Assessments throughout the follow up period will evaluate the safety, tolerability and PK of lanreotide PRF. Levels of insulin like growth factor-1 (IGF-1) and growth hormone (GH) will also be evaluated. The proportion of subjects with age adjusted IGF-1 levels within the normal range, with GH ≤2.5 ng/mL and with GH ≤1.0 ng/mL will be recorded.	Assessments throughout the follow up period will evaluate the safety, tolerability and PK of lanreotide PRF. Levels of insulin like growth factor-1 (IGF-1) and growth hormone (GH) will also be evaluated. The proportion of subjects with age adjusted IGF-1 levels ~~within the normal range~~**<1.3 x upper limit of normal (ULN)**, with GH ≤2.5 ng/mL and with GH ≤1.0 ng/mL will be recorded.
6	Synopsis, Inclusion criterion #6	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <upper limit of normal (ULN)).	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <**1.3 x ULN, based on central laboratory results, during the Screening period**~~upper limit of normal (ULN)~~).
6	Synopsis, Exclusion criterion #1	Has undergone radiotherapy within 3 years prior to study entry.	Has undergone radiotherapy within ~~3~~**2** years prior to study entry.
7	Synopsis, Exclusion criterion #6	Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN.	Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN **during the Screening period (central laboratory results).**
28	3.1	Figure 1 (see below)	Figure 1 was adapted for clarification.
35	4.1	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <upper limit of normal (ULN)).	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <**1.3 x** upper limit of normal (ULN)**, based on central laboratory results, during the Screening period**).
35	4.2	Has undergone radiotherapy within 3 years prior to study entry.	Has undergone radiotherapy within ~~3~~**2** years prior to study entry.
35	4.2	Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN.	Has any significant renal abnormalities and/or creatinine ≥1.5 x ULN **during the Screening period (central laboratory results).**

38	5.1	Table 4 (see below)	Table 4 was updated to show Visits 7, 9 and 11 could be performed as home visits.
40	5.1	Table 5 (see below)	Table 5 was updated to show Visits 13, 15 and 17 could be performed as home visits.
41	5.1	The total volume of blood drawn for all evaluations throughout this study is approximately 410 mL for each subject.	The total volume of blood drawn for all evaluations throughout this study is approximately ~~410~~**571** mL for each subject.
41	5.1	Table 6 (see below)	Table 6 was updated with new blood volumes for the treatment period. Table 7 was created to show the blood volumes for the follow-up period.
41	5.1	A volume of 10 to 12 mL of urine will be collected at each of the visits that includes a clinical laboratory assessment.	A volume of **approximately** ~~10 to 12~~ **14** mL of urine will be collected at each of the visits that includes a clinical laboratory assessment.
42	5.2.1	Under no circumstances will subjects be screened more than once.	Under no circumstances will subjects be screened more than once**, except for the IGF-1 assessment. IGF-1 may be re-tested once if the screening value is just above the 1.3 x ULN limit (analysis by central laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN.**
44	5.2.3	The following procedures will be performed at Visit 6 (Week 3±2 days) and Visit 7 (Week 4±2 days).	The following procedures will be performed at Visit 6 (Week 3±2 days) and Visit 7 (Week 4±2 days). **Visit 7 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.**
45	5.2.3	The following procedures will be performed at Visit 9 (Week 7±2 days) and Visit 11 (Week 11±2 days).	The following procedures will be performed at Visit 9 (Week 7±2 days) and Visit 11 (Week 11±2 days). **Visits 9 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.**

46	5.2.4.1	The following procedures will be performed at Visit 13 (Week 15±3 days), Visit 15 (Week 19±3 days) and Visit 17 (Week 23±3 days).	The following procedures will be performed at Visit 13 (Week 15±3 days), Visit 15 (Week 19±3 days) and Visit 17 (Week 23±3 days). **Visits 13 and 15 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.**
58	8.2	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.	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. **Any unscheduled test (indication and results) will be recorded on the dedicated page in the eCRF.**
58	8.2.2	Blood samples (2 mL) will be collected to assess the following coagulation parameters: activated partial thromboplastin time, prothrombin time and its derived measures of prothrombin ratio and INR.	Blood samples (~~2~~**4.5** mL) will be collected to assess the following coagulation parameters: activated partial thromboplastin time, prothrombin time and its derived measures of prothrombin ratio and INR.
58	8.2.3	Blood samples (5 mL) will be collected to assess the following parameters: • urea, creatinine, total bilirubin, conjugated bilirubin • chloride, bicarbonate, sodium, potassium, calcium, phosphate • AP, AST, ALT, GGT • albumin total protein, total cholesterol, triglycerides, postprandial glucose, and postprandial insulin • pancreatic enzymes, glucagon Blood samples (2 mL) will also be collected to assess HbA1c. Any unscheduled test (indication and results) will be recorded on the dedicated page in the eCRF.	Blood samples (~~5~~**6** mL) will be collected to assess the following parameters: • urea, creatinine, total bilirubin, conjugated bilirubin • chloride, bicarbonate, sodium, potassium, calcium, phosphate • AP, AST, ALT, GGT • albumin**,** total protein, total cholesterol, triglycerides, postprandial glucose, and postprandial insulin • pancreatic enzymes, glucagon Blood samples (2 mL) will also be collected to assess HbA1c. ~~Any unscheduled test (indication and results) will be recorded on the dedicated page in the eCRF.~~

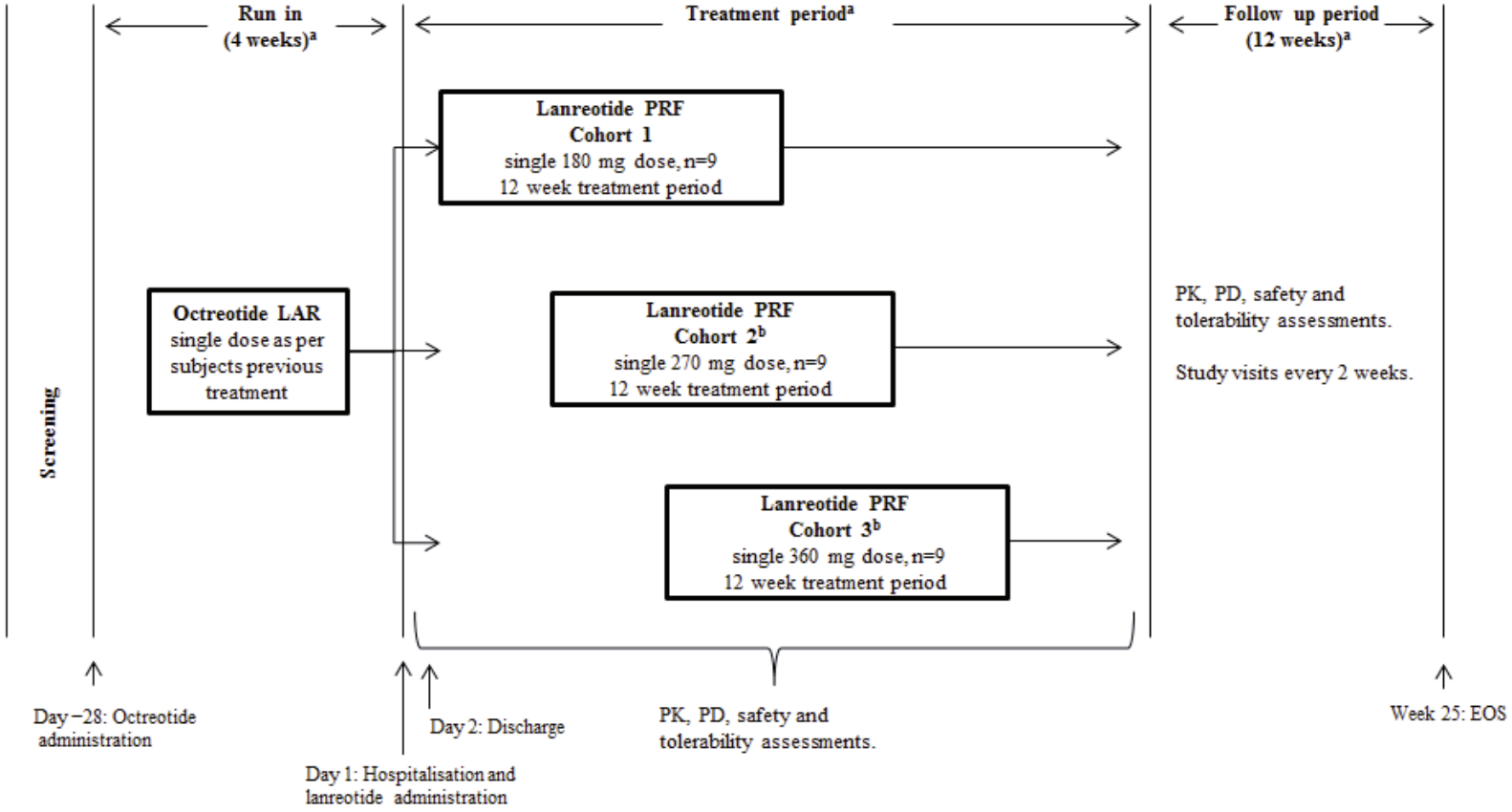
58	8.2.4	Fresh urine samples (10 to 12 mL) will be collected to assess the following parameters: chloride, bicarbonates, sodium, potassium, calcium, pH, proteins, ketones, glucose, blood, bilirubin and urobilinogen.	Fresh urine samples (~~10 to 12~~ **approximately 14** mL) will be collected to assess the following parameters: chloride, bicarbonates, sodium, potassium, calcium, pH, proteins, ketones, glucose, blood, bilirubin and urobilinogen.
59	8.2.5	Blood samples (3 mL) will be collected for the assay of putative antibodies to lanreotide. The tubes should be left to stand for 30 minutes and then centrifuged at 1000 g to 1300 g for 10 minutes at 4°C. The resulting serum will be stored as two 500 µL aliquots at 20°C in polypropylene tubes prior to shipment to the analysis laboratory PPD	Blood samples (~~3~~**4** mL) will be collected for the assay of putative antibodies to lanreotide. The tubes should be left to stand for 30 minutes and then centrifuged at 1000 g to 1300 g for 10 minutes at 4°C. The resulting serum will be stored as two **1 mL** ~~500 µL~~ aliquots at 20°C in polypropylene tubes prior to shipment to the analysis laboratory PPD
59	8.2.5	Full details regarding the requirements for processing, labelling and shipment of these samples will be provided in the study manual and archived in the TMF.	Full details regarding the requirements for processing, labelling and shipment of these samples will be provided in the ~~study~~**central laboratory** manual and archived in the TMF.
59	8.3	Details of the sample handling methodology and reference ranges will be provided in the study manual and archived in the TMF.	Details of the sample handling methodology and reference ranges will be provided in the ~~study~~**central laboratory** manual and archived in the TMF.
60	8.8	Injection sites will be evaluated by the investigator for appearance and local symptoms according to NCI CTCAE criteria at the timepoints specified in the study schedule (Table 4 and Table 5).	Injection sites will be evaluated by the investigator **(or appropriately trained healthcare professional)** for appearance and local symptoms according to NCI CTCAE criteria at the timepoints specified in the study schedule (Table 4 and Table 5).

61	9.1.1	Blood samples (3 mL each) for determination of lanreotide and excipient serum concentrations will be collected at the timepoints indicated in Table 4 and Table 5. Although the sample collection procedures for lanreotide and the excipient are the same, separate blood samples will be collected for each analyte. During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, and lanreotide PRF administration must be recorded in the eCRF. The tubes will be left to stand for 30 minutes and will then be centrifuged at 1000 g to 1300 g for 10 minutes at 4ºC. For each analyte, the resulting serum will be stored as two 500 µL aliquots at -20°C in polypropylene tubes prior to shipment to the analysis laboratory. Aliquots will be shipped on dry ice. Details of the sample handling methodology and reference ranges will be provided in the study manual and archived in the TMF.	Blood samples (~~3~~**4** mL each) for determination of lanreotide and excipient serum concentrations will be collected at the timepoints indicated in Table 4 and Table 5. Although the sample collection procedures for lanreotide and the excipient are the same, separate blood samples will be collected for each analyte. During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, and lanreotide PRF administration must be recorded in the eCRF. The tubes will be left to stand for 30 minutes and will then be centrifuged at 1000 g to 1300 g for 10 minutes at 4ºC. For each analyte, the resulting serum will be stored as two **1 mL**~~500 µL~~ aliquots at –20°C in polypropylene tubes prior to shipment to the analysis laboratory. Aliquots will be shipped on dry ice. Details of the sample handling methodology and reference ranges will be provided in the ~~study~~**central laboratory** manual and archived in the TMF.
61	9.1.2	Serum will be analysed to determine concentrations of lanreotide using a validated, specific and sensitive radioimmunoassay (RIA) method PPD Concentrations of excipient will be analysed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method at a CRO under the supervision of Ipsen's Pharmacokinetics and Drug Metabolism (PDM) Department.	Serum will be analysed to determine concentrations of lanreotide using a validated, specific and sensitive radioimmunoassay (RIA) method PPD Concentrations of excipient will be analysed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method PPD under the supervision of Ipsen's Pharmacokinetics and Drug Metabolism (PDM) Department.

62	9.2.1	Blood samples (3.5 mL) will also be collected to assess endocrinology parameters (FT3, FT4, TSH and PRL) according to the study schedule (Table 4 and Table 5).	Blood samples (~~3.5~~**2** mL) will also be collected to assess endocrinology parameters (FT3, FT4, TSH and PRL) according to the study schedule (Table 4 and Table 5).
62	9.2.1	Details of the sample handling methodology and reference ranges will be provided in the study manual and archived in the TMF.	Details of the sample handling methodology and reference ranges will be provided in the ~~study~~ **central laboratory** manual and archived in the TMF.
62	9.2.2	Measurement of IGF-1 and GH concentrations will be performed by a central laboratory using a validated method (see Laboratory Manual for further details).	Measurement of IGF-1 and GH concentrations will be performed by a central laboratory using a validated method (see **the central laboratory manual** ~~Laboratory Manual~~ for further details).
63	9.2.3.1	Time to escape (defined as time from lanreotide PRF administration to the time when the IGF-1 ≥ULN) will be summarised by dose cohort.	Time to escape (defined as time from lanreotide PRF administration to the time when the IGF-1 ≥**1.3 x** ULN) will be summarised by dose cohort.
67	10.6	Details regarding stopping boundaries and early stopping rules will be described in the charter.	Details regarding stopping boundaries and early stopping rules will be described in the charter. **Interim analyses may be performed by the Sponsor to faciliatate the planning of future clinical studies of lanreotide PRF.**

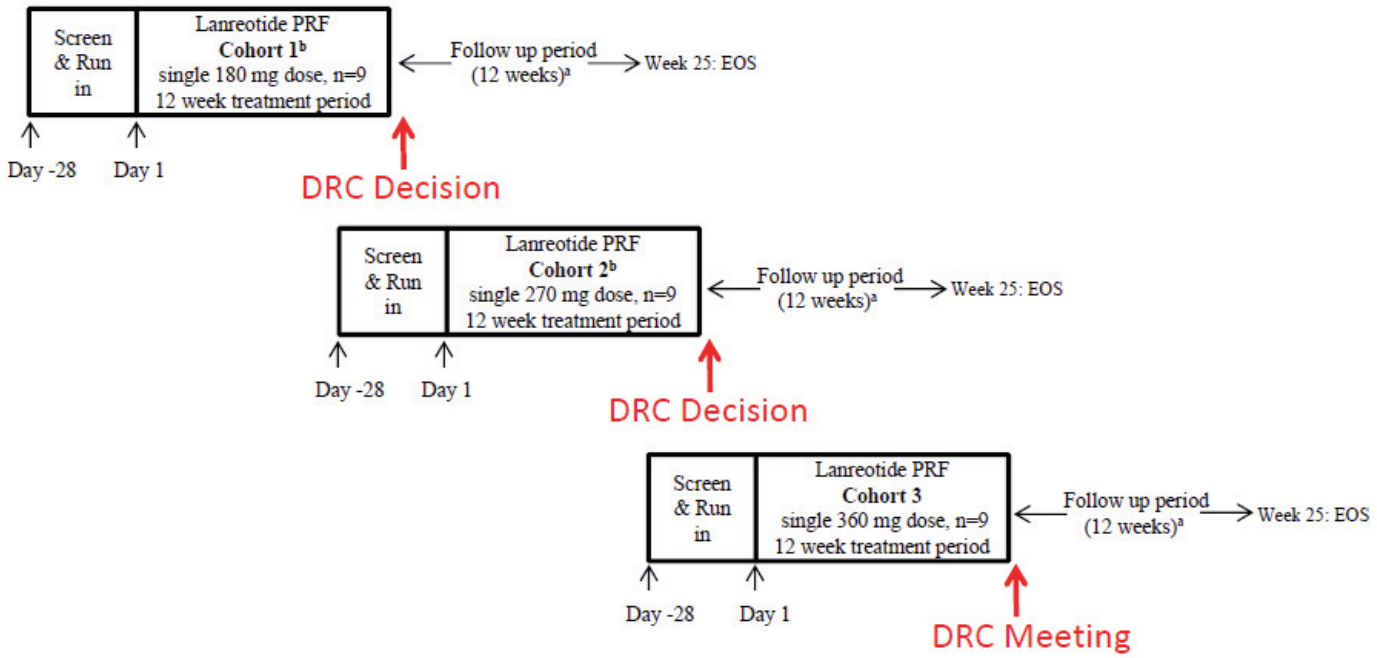
WAS: Amendment 2.0 Version 3.0: 18 February 2015

Figure 1 Study Design



IS: Amendment 3.0 Version 4.0: 12 June 2015

Figure 1 Study Design



For each patient:
- Day -28: Octreotide LAR as per subjects previous treatment and start of 4 week run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

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Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3	4	5	6	7	8	9	10	11	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [b]	0	1	2	4	6	8	12	24										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide administration [c]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X	X	X								
PD assessments																				
IGF-1	X	X					X									X		X		X
GH cycle [d]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [e]	X	X					X [f]				X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [g]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X

Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) *(Cont.)*

Visit	1 [a]	2	3	4	5	6	7	8	9	10	11	12

Week		**1**											**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Day	**−28**	**1**								**2**	**3**	**5**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**
Hour		**Predose [b]**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**										
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [h]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit..
b Baseline.
c after Screening, subjects will enter a 4 week run in period and will receive a single dose of octreotide LAR at the same dose as their previous octreotide dose.
d five sampling times in the morning, with a sample every 30 minutes for 2 hours.
e blood and urine samples taken for clinical laboratory tests.
f evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.
g measured by MDRD formula [1].
h Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

IS: Amendment 3.0 Version 4.0: 12 June 2015

Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3	4	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [~~b~~c]	0	1	2	4	6	8	12	24										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide administration [~~e~~d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X	X	X								
PD assessments																				
IGF-1	X	X					X									X		X		X
GH cycle [~~d~~e]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [~~e~~f]	X	X					X [~~f~~g]				X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [~~g~~h]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X

Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) ***(Cont.)***

Visit	**1 [a]**	**2**									**3**	**4**	**5**	**6**	**7 [b]**	**8**	**9 [b]**	**10**	**11 [b]**	**12**
Week		**1**											**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Day	**−28**	**1**								**2**	**3**	**5**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**
Hour		**Predose [~~b~~c]**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**										
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [~~h~~i]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit.

b **Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.**

~~**b**~~**c** Baseline.

~~**c**~~**d** after Screening, subjects will enter a 4 week run in period and will receive a single dose of octreotide LAR at the same dose as their previous octreotide dose.

~~**d**~~**e** five sampling times in the morning, with a sample every 30 minutes for 2 hours.

~~**e**~~**f** blood and urine samples taken for clinical laboratory tests.

~~**f**~~**g** evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.

~~**g**~~**h** measured by MDRD formula [1].

~~**h**~~**i** Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

WAS: Amendment 2.0 Version 3.0: 18 February 2015

Table 5 Study Procedures and Assessments (Follow Up; Weeks 15 to 25)

Visit	**13**	**14**	**15**	**16**	**17**	**18 (EOS or EW)[a]**
Week [b]	**15**	**17**	**19**	**21**	**23**	**25/EW**
Acromegaly symptoms						X
Concomitant medications	x----------x					
PK blood samples						
Lanreotide PRF		X		X		X
PD assessments						
IGF-1		X		X		X
Random GH sample		X		X		X
FT_3, FT_4, TSH , PRL						X
Safety assessments						
AEs	x----------x					
Physical examination	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X	X	X	X
HbA1c						X
eGFR [c]		X		X		X
Vital signs	X	X	X	X	X	X
Gallbladder echography						X
Evaluation of injection site reactions	X	X	X	X	X	X
Putative antibodies to lanreotide						X

AE=adverse event; eGFR=estimated glomerular filtration rate; EOS=end of study; EW=early withdrawal; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a EOS for subjects completing the follow up period or EW visit for subjects who withdraw from the study during the follow up period.

b follow up visits will be conducted every 2 weeks (±3 days).

c measured by MDRD formula [1].

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Table 5 Study Procedures and Assessments (Follow Up; Weeks 15 to 25)

Visit	13 [a]	14	15 [a]	16	17 [a]	18 (EOS or EW)[~~a~~b]
Week [~~b~~c]	**15**	**17**	**19**	**21**	**23**	**25/EW**
Acromegaly symptoms						X
Concomitant medications	x----------x					
PK blood samples						
Lanreotide PRF		X		X		X
PD assessments						
IGF-1		X		X		X
Random GH sample		X		X		X
FT_3, FT_4, TSH , PRL						X
Safety assessments						
AEs	x----------x					
Physical examination	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X	X	X	X
HbA1c						X
eGFR [~~e~~d]		X		X		X
Vital signs	X	X	X	X	X	X
Gallbladder echography						X
Evaluation of injection site reactions	X	X	X	X	X	X
Putative antibodies to lanreotide						X

AE=adverse event; eGFR=estimated glomerular filtration rate; EOS=end of study; EW=early withdrawal; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a **Study visits on Weeks 15, 19 and 23 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.**

~~**a**~~**b** EOS for subjects completing the follow up period or EW visit for subjects who withdraw from the study during the follow up period.

~~**b**~~**c** follow up visits will be conducted every 2 weeks (±3 days).

~~**e**~~**d** measured by MDRD formula [1].

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Table 6 Blood Volume Calculation

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	16	12	192
PD	9 IGF-1 20 GH Cycle 5 random GH	2	68
PK	18 for lanreotide; 10 for excipient	3	84
HbA1c	3	2	6
FT_3, FT_4, TSH and PRL	6	3.5	21
Antibody testing	3	3	9
Biobanking [b]	3	10	30
Total	93	35.5	410

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

IS: Amendment 3.0 Version 4.0: 12 June 2015

Table 6 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	~~16~~**10**	~~12~~**20.5 mL for 9 visits and 14.5 mL for 1 visit (Vist 2 postdose)**	~~192~~**199**
PD	~~9~~**6** IGF-1 20 GH Cycle ~~5~~**2** random GH	2 **2** **2**	~~68~~**56**
PK	~~18~~**15** for lanreotide; 10 for excipient	~~3~~**4** **4**	~~112~~**100**
HbA1c	~~3~~**2**	2	~~6~~**4**
FT_3, FT_4, TSH and PRL	~~6~~**5**	3.5	~~2~~**17.5**
Antibody testing	~~3~~**2**	~~3~~**4**	~~9~~**8**
Biobanking [b]	3	10	30
Total	~~93~~**75**	~~35.5~~**Up to 132.5 mL per visit (Visit 2)**	~~410~~**414.5**

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

Table 7 Blood Volume Calculation for Follow Up Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	**6**	**20.5 mL**	**123**
PD	**3 IGF-1** **3 random GH**	**2** **2**	**12**
PK	**3 for lanreotide**	**4**	**12**
HbA1c	**1**	**2**	**2**
FT_3, FT_4, TSH and PRL	**1**	**3.5**	**3.5**
Antibody testing	**1**	**4**	**4**
Total	**18**	**Up to 38 per visit (Visit 18)**	**156.5**

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 3.0 Version 4.0: 12 June 2015	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	To update the Sponsor's medically responsible person and contact details. To extend the planned study period to January 2017. To include the option for home visits on Weeks 4, 7, 11, 15, 19 and 23. To increase the IGF-1 limit from within the normal range to <1.3 x ULN and clarify that the assessment during the Screening period must be analyzed by the central laboratory. To reduce the period in which the patient has had radiotherapy from 3 years to 2 years prior to study entry. To clarify that any significant renal abnormalities and/or creatinine values ≥1.5 x ULN should be measured during the Screening period must be analyzed by the central laboratory. To update Figure 1 for clarification of the DRC decisions. To update the Schedule of Assessments to include the option of home visits. To update the blood and urine volumes to be collected according to the central laboratory manual. To include an opportunity to re-test the screening IGF-1 value once if it is just above the 1.3 x ULN limit. To ensure the central laboratory manual is referred to consistently throughout the protocol. To include an option for the Sponsor to conduct an interim analysis in relation to the clinical development of lanreotide PRF.	
Other Action Required?	CRF Update	Yes ☒ No ☐ (tick one)
	Local Consent Form Update	Yes ☒ No ☐ (tick one)
	Database Update	Yes ☒ No ☐ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☒ No ☐ (tick one)

Appendix 6 Protocol Amendment 4 (27 July 2015)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Either Octreotide LAR or Lanreotide Autogel
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 4.0 Version 5.0: 27 July 2015

The following amendment(s) is/are proposed:

Version Date		**12 June 2015**	**27 July 2015**
Page	**Section**	**WAS**	**IS**
1	Title page	PROTOCOL TITLE: PHASE IIA, OPEN LABEL, DOSE ASCENDING STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, SAFETY AND TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A SINGLE DOSE OF LANREOTIDE PRF IN SUBJECTS WITH ACROMEGALY PREVIOUSLY TREATED AND CONTROLLED WITH OCTREOTIDE LAR	PROTOCOL TITLE: PHASE IIA, OPEN LABEL, DOSE ASCENDING STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, SAFETY AND TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A SINGLE DOSE OF LANREOTIDE PRF IN SUBJECTS WITH ACROMEGALY PREVIOUSLY TREATED AND CONTROLLED WITH **EITHER** OCTREOTIDE LAR **OR LANREOTIDE AUTOGEL**
5	Synopsis	**Title of study:** Phase IIa, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with octreotide LAR	**Title of study:** Phase IIa, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with **either** octreotide LAR **or lanreotide Autogel**
5	Synopsis	**Number of planned centres:** 20 to 25	**Number of planned centres:** ~~20 to 25~~ **up to 30**

5	Synopsis, Methodology	Subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR) will be recruited to this open label study. Eligible subjects will enter a 4 week run in period, during which they will receive the same single dose of octreotide LAR as their previous treatment (Day −28). A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR administration).	Subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR) **or lanreotide Autogel** will be recruited to this open label study. Eligible subjects will enter a 4 week run in period, during which they will receive the same single dose of **either** octreotide LAR **or lanreotide Autogel** as their previous treatment (Day −28). A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR **or lanreotide Autogel** administration).
5	Synopsis, Methodology	It is planned to include three cohorts of subjects; Cohort 1 will receive lanreotide PRF 180 mg, Cohort 2 will receive 270 mg and Cohort 3 will receive 360 mg. Nine subjects will be allocated to each lanreotide PRF treatment cohort.	It is planned to include three cohorts of subjects; Cohort 1 will receive lanreotide PRF 180 mg, Cohort 2 will receive 270 mg and Cohort 3 will receive 360 mg. Nine subjects will be allocated to each lanreotide PRF treatment cohort. **Each cohort must enrol at least six subjects previously treated with octreotide LAR. Each cohort can enrol up to three subjects previously treated with lanreotide Autogel.**
5, 6, 9, 63	Synopsis, Methodology, Number of Subjects Planned, 10.2	9 subjects	~~9~~**nine** subjects
6	Synopsis, Diagnosis and criteria for inclusion	Subjects with acromegaly, well controlled by a stable dose of octreotide LAR for at least 3 months.	Subjects with acromegaly, well controlled by a stable dose of **either** octreotide LAR **or lanreotide Autogel** for at least 3 months.

6	Synopsis, Inclusion criterion #6	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on central laboratory results, during the Screening period).	Treatment with a stable dose of **either** octreotide LAR **or lanreotide Autogel** for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on ~~central~~ **local** laboratory results, during the Screening period**. Samples for analysis by central laboratory will also be collected during Screening**).
23	1.4.3	Should any concern about this residual concentration arise during the study the sponsor will notify the investigators about the level of residual concentration which would allow to adjustadjusting the restart of octreotide treatment.	Should any concern about this residual concentration arise during the study the sponsor will notify the investigators about the level of residual concentration which would allow ~~to adjust~~adjusting the restart of **either** octreotide **or lanreotide Autogel** treatment.

<table>
<tr><td>25</td><td>1.7</td><td>The study will enrol adult subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR).
The choice of octreotide stable subjects as the study population, instead of lanreotide stable subjects, was guided by the fact that a 4 month washout period before lanreotide PRF administration would be avoided and no cross interference in lanreotide and octreotide measurements by the bioanalytical assay would occur.</td><td>The study will enrol adult subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of either octreotide long acting release (LAR) or lanreotide Autogel. A minimum of six octreotide LAR subjects must be recruited in each cohort and up to three lanreotide Autogel subjects can be enrolled in each cohort.
The choice of ~~octreotide stable~~ subjects stable on octreotide LAR as the main study population, instead of ~~lanreotide stable~~ subjects stable on lanreotide Autogel, was guided by the ~~fact that a 4 month washout period before lanreotide PRF administration would be avoided and no cross interference in lanreotide and octreotide measurements by the bioanalytical assay would occur~~ need to avoid crossinterference between the different formulations of lanreotide in the primary PK analysis. The required PK analysis can be done with a minimum of six octreotide LAR subjects per cohort.
The inclusion of up to three lanreotide Autogel subjects per cohort will provide preliminary PK data from this population.
Possible subject combinations per cohort are shown in Table 3. (new Table 3 added; see below)</td></tr>
<tr><td colspan="4">Added new table:
Table 3 Possible Subject Combinations Per Cohort
<table>
<tr><th></th><th>Octreotide LAR</th><th>Lanreotide Autogel</th></tr>
<tr><td>Cohort 1, 2 and 3</td><td>6</td><td>3</td></tr>
<tr><td>Cohort 1, 2 and 3</td><td>7</td><td>2</td></tr>
<tr><td>Cohort 1, 2 and 3</td><td>8</td><td>1</td></tr>
<tr><td>Cohort 1, 2 and 3</td><td>9</td><td>0</td></tr>
</table></td></tr>
<tr><td>26</td><td>2.1</td><td>3 subjects</td><td>~~3~~ three subjects</td></tr>
</table>

27	3.1	This is an open label, dose ascending study to assess the PK, PD, safety and tolerability of a single dose of lanreotide PRF, a new sustained release formulation of lanreotide. Doses of 180 mg, 270 mg and 360 mg will be investigated in adults with acromegaly previously treated and controlled with a stable dose of octreotide LAR. A maximum of 27 adult subjects, aged 18 to 75 years will be treated in the study. Three cohorts of subjects will be included, with 9 subjects allocated to each lanreotide PRF treatment cohort (180 mg, 270 mg and 360 mg). Subjects in each cohort will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR administration). Specific details of the dose cohorts are given in Section 6.1.	This is an open label, dose ascending study to assess the PK, PD, safety and tolerability of a single dose of lanreotide PRF, a new sustained release formulation of lanreotide. Doses of 180 mg, 270 mg and 360 mg will be investigated in adults with acromegaly previously treated and controlled with a stable dose of **either** octreotide LAR **or lanreotide Autogel.** A maximum of 27 adult subjects, aged 18 to 75 years will be treated in the study. Three cohorts of subjects will be included, with ~~9~~nine subjects allocated to each lanreotide PRF treatment cohort (180 mg, 270 mg and 360 mg). Subjects in each cohort will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR **or lanreotide Autogel** administration). Specific details of the dose cohorts are given in Section 6.1. **Each cohort of nine subjects must be made up of at least six previously controlled on octreotide LAR. The remaining subjects can be up to three subjects previously controlled on lanreotide Autogel (see Table 3).**
27	3.1	Screening of subjects will take place 28 days before administration of study treatment (Day −28). Eligible subjects will receive the same single dose of octreotide LAR as their previous treatment and will enter a 4 week run in period.	Screening of subjects will take place 28 days before administration of study treatment (Day −28). Eligible subjects will receive the same single dose of octreotide LAR **or lanreotide Autogel** as their previous treatment and will enter a 4 week run in period.
29	3.1	Figure 1 (see below)	Figure 1 was adapted for clarification.

30	3.2.2	- At 1, 2, 4, 6, 8 and 12 hours postdose on thAll laboratory parameters will be analysed centrally to confirm subject eligibility against the inclusion and exclusion criteria. e day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration	- At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration **Note: If the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.**
25	4	All laboratory parameters will be analysed centrally to confirm subject eligibility against the inclusion and exclusion criteria.	All laboratory parameters will be analysed centrally to confirm subject eligibility against the inclusion and exclusion criteria**, with the exception of IGF-1. Age adjusted IGF-1 will be based on local laboratory results at Screening. Samples for analysis of IGF-1 by central laboratory will also be collected during Screening.**
36	4.1	Treatment with a stable dose of octreotide LAR for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF 1 <1.3 x upper limit of normal (ULN), based on central laboratory results, during the Screening period).	Treatment with a stable dose of **either** octreotide LAR **or lanreotide Autogel** for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF 1 <1.3 x upper limit of normal (ULN), based on ~~central~~ **local** laboratory results, during the Screening period **Samples for analysis by central laboratory will also be collected during Screening**).
39	5.1	Table 4 (see below)	Table 5 (previously Table 4) was updated to add lanreotide Autogel as a previous treatment option and to include a footnote regarding DRC review of PK data from the excipient.

41	5.1	Table 5 (see below)	Table 6 (previously Table 5) Added footnote **[d]** to the IGF-1 PD assessment. **d during follow up visits, IGF-1 testing will be conducted by a central laboratory using a validated method.**
42	5.1	Table 6 (see below)	Table 7 (previously Table 6) was updated with the number of IGF-1 blood samples and the total blood volumes.
43	5.2.1	Under no circumstances will subjects be screened more than once, except for the IGF-1 assessment. IGF-1 may be re-tested once if the screening value is just above the 1.3 x ULN limit (analysis by central laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN. Following confirmation of eligibility for the study, subjects will be enrolled into the study and allocated to one of the dose cohorts specified in Section 6.1. At the Screening visit, enrolled subjects will then receive their usual dose of octreotide LAR according to standard clinical practice.	Under no**rmal** circumstances ~~will~~ subjects **will not** be screened more than once**.**~~,~~ **There are two exceptions** ~~except for the IGF-1 assessment~~. **1).** IGF-1 may be re-tested once if the screening value is just above ~~the~~ 1.3 x ULN ~~limit~~ (analysis by ~~central~~ **local** laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN. **2). If the time elapsed between the original Screening visit (Visit 1) and Visit 2 is >28 days (±2 days) then re-screening of the subject for inclusion is permitted.** Following confirmation of eligibility for the study, subjects will be enrolled into the study and allocated to one of the dose cohorts specified in Section 6.1. At the Screening visit, enrolled subjects will then receive their usual dose of **either** octreotide LAR **or lanreotide Autogel** according to standard clinical practice.
43	5.2.2	On Day 1 (Visit 2), subjects will be admitted to the study centre where they will undergo Baseline assessments prior to the administration of study treatment. The following procedures will be performed at Baseline on Day 1 of the study, prior to the administration of study treatment:	On Day 1**±2 days** (Visit 2), subjects will be admitted to the study centre where they will undergo Baseline assessments prior to the administration of study treatment. The following procedures will be performed at Baseline on Day 1**±2 days** of the study, prior to the administration of study treatment

44	5.2.3	Following Baseline assessments on Day 1, study treatment will be administered. Subjects will remain at the study centre for 24 hours postdose, during which time further assessments will be performed. The following procedures will be performed at the indicated timepoints relative to administration of study treatment at Visit 2 (Day 1): The following procedures will be performed 24 hours after administration of study treatment at Visit 2 (Day 2): Following the assessments on Visit 2; Day 2	Following Baseline assessments on Day 1**±2 days**, study treatment will be administered. Subjects will remain at the study centre for 24 hours postdose, during which time further assessments will be performed. The following procedures will be performed at the indicated timepoints relative to administration of study treatment at Visit 2 (Day 1**±2 days**): The following procedures will be performed 24 hours after administration of study treatment at Visit 2 (Day 2**±2 days**): Following the assessments on Visit 2; Day 2**±2 days**
45	5.2.3	The following procedures will be performed at Visit 3 (Day 3±1 day): … • PK blood samples for lanreotide and excipient The following procedures will be performed at Visit 4 (Day 5±1 day): … • PK blood samples for lanreotide and excipient	The following procedures will be performed at Visit 3 (Day 3±1 day): … • PK blood samples for lanreotide and excipient **(if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then excipient PK may be removed for Visit 3).** The following procedures will be performed at Visit 4 (Day 5±1 day): … • PK blood samples for lanreotide and excipient **(if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected.)**

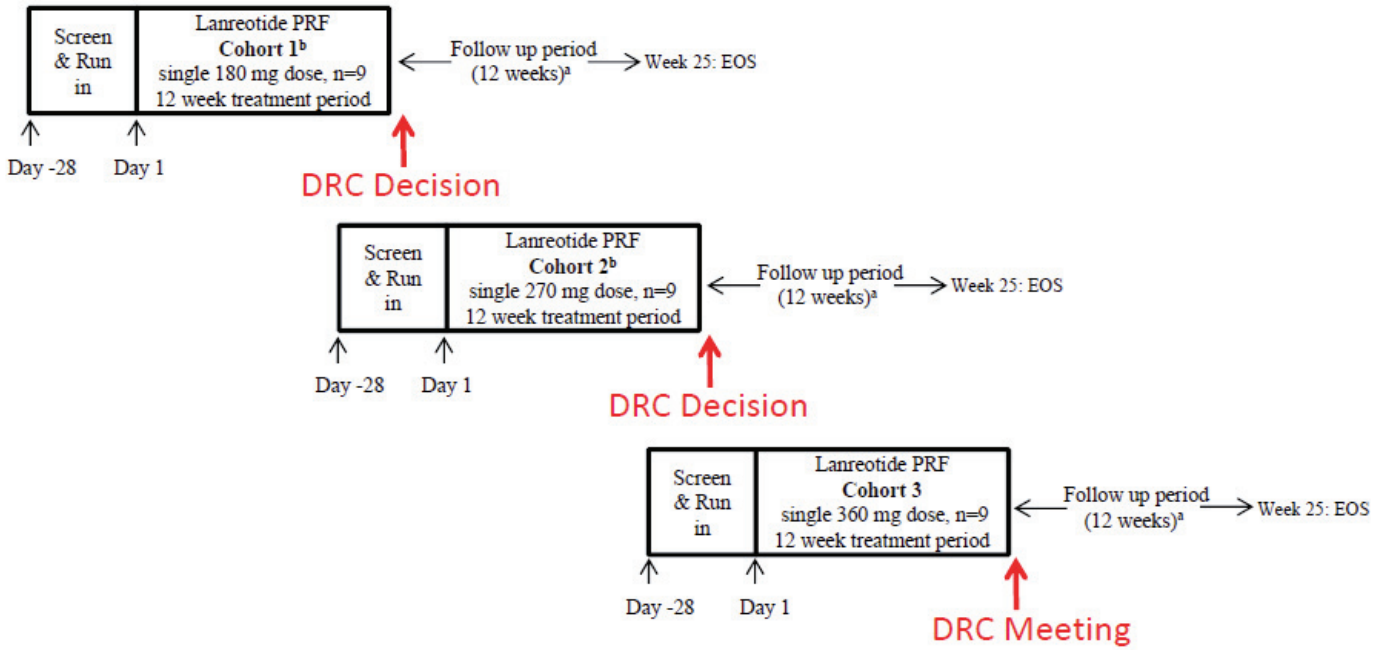
50	6.1.1	Dose level: 180 mg. The study will start dosing 3 subjects. If none or one out of the 3 dosed subjects experiences a DLT, 3 more subjects will be dosed at the same time. If 2 out of the 3 dosed subjects experiences a DLT, the DRC will decide whether three more subjects may be dosed. If all 3 subjects have experienced a DLT, dosing will be stopped and the dose will be declared the maximum administered dose. If none or 1 of the 6 dosed subjects experience a DLT, three more subjects can be dosed at the same dose. If 2 of the 6 dosed subjects experience a DLT, , and one or both of the DLTs occured in the second group of three patients, the DRC will decide whether three more subjects may be dosed. If a total of three or more out of six subjects experience a DLT, dosing will be stopped and the dose will be declared the maximum administered dose. Dose escalation: If more than 3 out of 9 subjects experience a DLT, dose escalation will be stopped and the dose will be declared the maximum administered dose. If ≤3 DLTs have been observed in the 9 treated subjects, then the dose may be escalated to 270 mg. The DRC will determine if progression to the next dose cohort should occur after reviewing data from the preceding cohort. The same rules will be applied to the next dose level and the decision to escalate to 360 mg will be done in the same way.	Dose level: 180 mg. The study will start dosing ~~3~~**three** subjects. If none or one out of the three dosed subjects experiences a DLT, ~~3~~**three** more subjects will be dosed at the same ~~time~~**dose**. If ~~2~~**two** out of the ~~3~~**three** dosed subjects experiences a DLT, the DRC will decide whether ~~3~~**three** more subjects may be dosed. If all ~~3~~**three** subjects have experienced a DLT, dosing will be stopped and the dose will be declared the maximum administered dose. If none or ~~1~~**one** of the ~~6~~**six** dosed subjects experience a DLT, ~~3~~**three** more subjects can be dosed at the same dose. If ~~2~~**two** of the ~~6~~**six** dosed subjects experience a DLT, , and ~~1~~**one** or both of the DLTs occured in the second group of ~~3~~**three** ~~patients~~**subjects**, the DRC will decide whether ~~3~~**three** more subjects may be dosed. If a total of ~~3~~**three** or more out of ~~6~~**six** subjects experience a DLT, dosing will be stopped and the dose will be declared the maximum administered dose. Dose escalation: If more than ~~3~~**three** out of ~~9~~**nine** subjects experience a DLT, dose escalation will be stopped and the dose will be declared the maximum administered dose. If ≤3 DLTs have been observed in the ~~9~~**nine** treated subjects, then the dose may be escalated to 270 mg. The DRC will determine if progression to the next dose cohort should occur after reviewing data from the preceding cohort. The same rules will be applied to the next dose level and the decision to escalate to 360 mg will be done in the same way.

62	9.2.2	Measurement of IGF-1 and GH concentrations will be performed by a central laboratory using a validated method (see the central laboratory manual for further details).	Measurement of IGF-1 and GH concentrations will be performed by a central laboratory using a validated method (see the central laboratory manual for further details). **Measurement of IGF-1 concentrations at the screening visit will be performed locally and centrally.**
66	10.5	If sufficient numbers of subjects are available to permit these analyses, descriptive statistics will be provided within each category of the following variables: previous dose of octreotide, sex, age (≤65, >65 years).	If sufficient numbers of subjects are available to permit these analyses, descriptive statistics will be provided within each category of the following variables: **Previous treatment amd dose (octreotide, lanreotide Autogel),** ~~previous dose of octreotide,~~ sex, age (≤65, >65 years).
66	10.6	The DRC will review safety data from each cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). At this time, if no DLT or unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort.	The DRC will review safety data from each cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). At this time, if no DLT or unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort. **The DRC will also review the PK data from the excipient when available and if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK will be removed.** **The DRC will also advise on any restriction on subject enrolment with regard to dose of pre-study octreotide or lanreotide Autogel for cohorts 2 and 3, based on considerations of safety and PK assessment of preceding cohort(s).**

73	14.2	The coding of an AE, medical history and concomitant medication terms will be performed by the contracted CRO/a CRO, directed by the sponsor's Biometry Group, and reviewed and approved by the sponsor.	**The coding of an AE, medical history and concomitant medication terms will be managed by the sponsor's Biometry Group.**

WAS: Amendment 3.0 Version 4.0: 12 June 2015

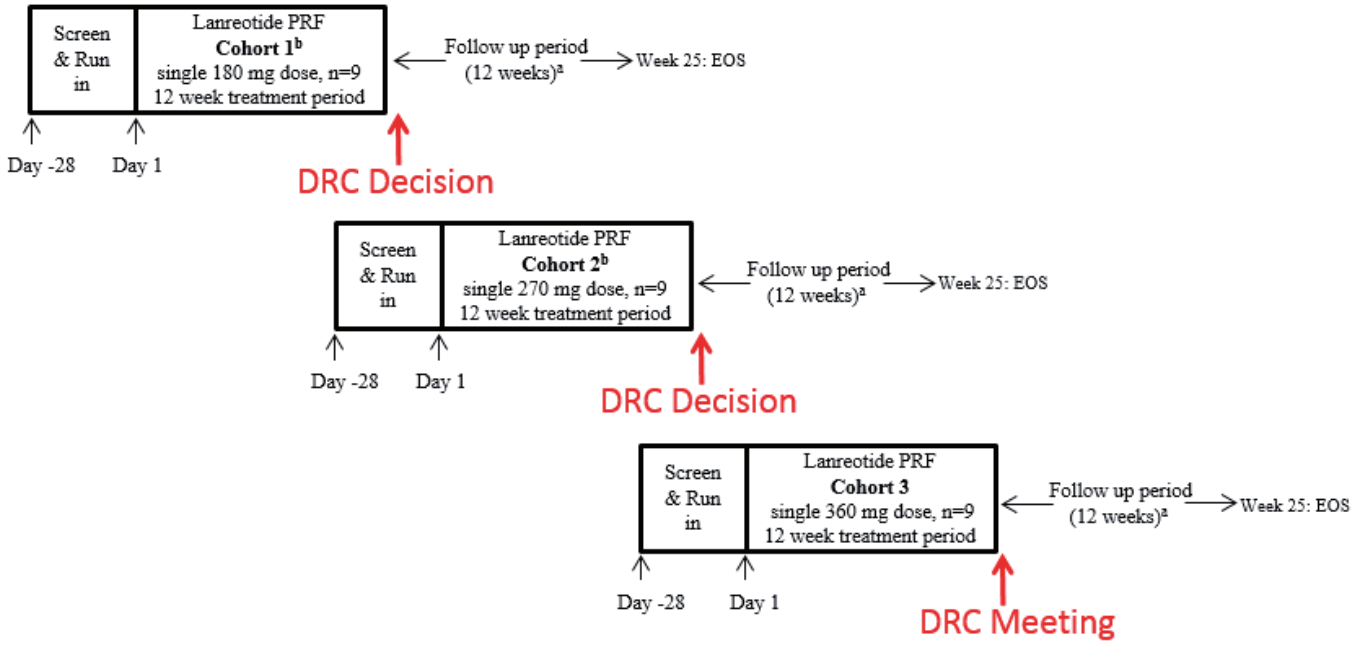
Figure 1 Study Design



For each patient:
- Day -28: Octreotide LAR as per subjects previous treatment and start of 4 week run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

IS: Amendment 4.0 Version 5.0: 27 July 2015

Figure 1 Study Design



For each patient:

- Day -28: Octreotide LAR or lanreotide Autogel as per subjects previous treatment and start of 4 week run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

WAS: Amendment 3.0 Version 4.0: 12 June 2015

Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	**1 [a]**	**2**									**3**	**4**	**5**	**6**	**7 [b]**	**8**	**9 [b]**	**10**	**11 [b]**	**12**
Week		**1**											**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Day	**−28**	**1**								**2**	**3**	**5**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**
Hour		**Predose [c]**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide administration [d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X	X	X								
PD assessments																				
IGF-1	X	X					X									X		X		X
GH cycle [e]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [f]	X	X					X [g]				X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [h]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X

Table 4 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) *(Cont.)*

Visit	**1 [a]**	**2**									**3**	**4**	**5**	**6**	**7 [b]**	**8**	**9 [b]**	**10**	**11 [b]**	**12**
Week		**1**											**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**
Day	**−28**	**1**								**2**	**3**	**5**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**
Hour		**Predose [c]**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**										
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [i]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit.
b Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.
c Baseline.
d after Screening, subjects will enter a 4 week run in period and will receive a single dose of octreotide LAR at the same dose as their previous octreotide dose.
e five sampling times in the morning, with a sample every 30 minutes for 2 hours.
f blood and urine samples taken for clinical laboratory tests.
g evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.
h measured by MDRD formula [1].
i Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

IS: Amendment 4.0 Version 5.0: 27 July 2015

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3 [e]	4 [e]	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------x																			
Eligibility criteria	X	X																		
Octreotide **or lanreotide Autogel** administration [d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------x																		
PK blood samples																				
Lanreotide **PRF**		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X [e]	X [e]	X [e]								
PD assessments																				
IGF-1 **[f]**	X	X					X									X		X		X
GH cycle [~~eg~~]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------x																			

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) *(Cont.)*

Visit	1 [a]	2									3 [e]	4 [e]	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										

Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [~~f~~**h**]	X	X					X [~~g~~**i**]				X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [~~h~~**j**]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [~~i~~**k**]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit.

b Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.

c Baseline.

d after Screening, subjects will enter a 4 week run in period and will receive a single dose of octreotide LAR at the same dose as their previous octreotide dose.
after Screening, subjects will enter a 4 week run in period and will receive a single dose of **either** octreotide LAR **or lanreotide Autogel** at the same dose as ~~their previous octreotide dose~~ **they received previously.**

e **if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.**

f **IGF-1 testing will be conducted by a central laboratory using a validated method. During the Screening period, IGF-1 will be analysed locally and centrally.**

g five sampling times in the morning, with a sample every 30 minutes for 2 hours.

h blood and urine samples taken for clinical laboratory tests.

i evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.

j measured by MDRD formula [1].

k Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

WAS: Amendment 3.0 Version 4.0: 12 June 2015

Table 6 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	10	20.5 mL for 9 visits and 14.5 mL for 1 visit (Vist 2 postdose)	199
PD	6 IGF-1 20 GH Cycle 2 random GH	2 2 2	56
PK	15 for lanreotide; 10 for excipient	4 4	100
HbA1c	2	2	4
FT_3, FT_4, TSH and PRL	5	3.5	17.5
Antibody testing	2	4	8
Biobanking [b]	3	10	30
Total	75	Up to 132.5 mL per visit (Visit 2)	414.5

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

IS: Amendment 4.0 Version 5.0: 27 July 2015

Table 7 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	10	20.5 mL for 9 visits and 14.5 mL for 1 visit (Vist 2 postdose)	199
PD	~~6~~**7** IGF-1 20 GH Cycle 2 random GH	2 2 2	~~56~~**58**
PK	15 for lanreotide; 10 for excipient	4 4	100
HbA1c	2	2	4
FT_3, FT_4, TSH and PRL	5	3.5	17.5
Antibody testing	2	4	8
Biobanking [b]	3	10	30
Total	75	Up to 132.5 mL per visit (Visit 2)	~~414.5~~**416.5**

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 4.0 Version 5.0: 27 July 2015	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	To allow up to three subjects previously controlled on lanreotide Autogel to be enrolled per cohort of nine. The choice of subjects stable on octreotide LAR as the main study population, instead of subjects stable on lanreotide Autogel, was guided by the need to avoid crossinterference between the different formulations of lanreotide in the primary PK analysis. The required PK analysis can be done on a minimum of six octreotide LAR subjects per cohort. The inclusion of up to three lanreotide Autogel subjects per cohort will provide preliminary PK data from the intended indication of switch from lanreotide Autogel to lanreotide PRF. To amend the title of the protocol to reflect this change to the subjects enrolled from just octreotide LAR to either octreotide LAR or lanreotide Autogel. To allow the screening for subject enrolment regarding IGF-1 levels to be assessed on an IGF-1 level analysed at a local laboratory instead of only at the central laboratory. This is because of the known variability in the different IGF-1 assays used at local and central laboratories. We want to avoid an eligible subject (whom the investigator knows is stable) being excluded from the study due to a higher reading from the central lab when the IGF-1 levels have been well controlled as analysed by local laboratories. The subject must comply with all inclusion criteria and be well controlled according to the experienced investigator. All subsequent IGF-1 analysis in the study will be performed at the central laboratory. This change is just for entry criteria only. To update the number of IGF-1 samples and total blood volumes to account for the additional sample collected during screening for assessment by local laboratory. To add an additional subgroup analysis due to the change in subjects eligible for the study - from only octreotide LAR to either octreotide LAR or lanreotide Autogel. The additional subgroup analysis will be performed to assess the PK and safety of these two groups of subjects depending on their prior treatment. To add the possibility not to perform Visit 4 Day 5 according to PK excipient data further to DRC review. Indeed if the half life of the excipient is short there is no need to follow it any longer and adding blood sampling and visits to the subject if it is not needed. Also the excipient PK may also be removed at Visit 3 Day 3. To add a ±2 day window for Visit 2 Day 1 and 2.	
Other Action Required?	CRF Update	Yes ☒ No ☐ (tick one)
	Local Consent Form Update	Yes ☒ No ☐ (tick one)

	Database Update	Yes ☒ No ☐ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☒ No ☐ (tick one)

Appendix 7 Protocol Amendment 5 (22 March 2016)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Either Octreotide LAR or Lanreotide Autogel
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 5.0 Version 6.0: 22 March 2016

The following amendment(s) is/are proposed:

Version Date		**27 July 2015**	**22 March 2016**
Page	**Section**	**WAS**	**IS**
1	Title page	**Sponsor's Medically Responsible Person:** PPD Ipsen Biosciences, Inc. 650 East Kendal Street Cambridge, MA 02142 (USA) PPD	**Sponsor's Medically Responsible Person:** **David Rich, MPhil** **Ipsen Biopharm Limited** **190 Bath Road** **Slough, SL1 3XE (UK)** PPD PPD ~~Ipsen Biosciences, Inc.~~ ~~650 East Kendal Street~~ ~~Cambridge, MA 02142 (USA)~~ PPD
5	Synopsis	**Number of planned centres:** up to 30	**Number of planned centres:** up to **40** ~~**30**~~
5	Synopsis	**Planned study period:** 02/2015 to 01/2017	**Planned study period:** 02/2015 to ~~01/2017~~ **06/2018**
5	Synopsis, Methodology	Subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR) or lanreotide Autogel will be recruited to this open label study. Eligible subjects will enter a 4 week run in period, during which they will receive the same single dose of either octreotide LAR or lanreotide Autogel as their previous treatment (Day −28). A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR or lanreotide Autogel administration).	Subjects with acromegaly who have been well controlled for at least 3 months on a stable dose of octreotide long acting release (LAR) or lanreotide Autogel will be recruited to this open label study. Eligible subjects will enter a 4 week run in period **(or up to 6 weeks under certain circumstances)**, during which they will receive the same single dose of either octreotide LAR or lanreotide Autogel as their previous treatment ~~(Day −28)~~. A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks **or up to 6 weeks under certain circumstances** after the last octreotide LAR or lanreotide Autogel administration).

5	Synopsis, Methodology	Progression to each ascending dose cohort will be dependent upon a review of data from the preceding cohort during meetings of the data review committee (DRC). The DRC will review the safety data from each cohort after all subjects in the cohort completed Visit 5 (Week 2 postdose). At this time, if no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next treatment cohort. The dose escalation will proceed with a 3+3+3 scheme in order to enrol nine subjects within each dose cohort.	Progression to each ascending dose cohort **(or groups of subjects)** will be dependent upon a review of data from the preceding cohort **(or groups of subjects)** during meetings of the data review committee (DRC). The DRC will review the safety data from each cohort after all subjects in the cohort completed Visit 5 (Week 2 postdose). At this time, if no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next treatment cohort **(or groups of subjects)**. The dose escalation will proceed with a 3+3+3 scheme in order to enrol nine subjects within each dose cohort. **In Cohort 2 subjects will be reviewed on a 1+2+2+2+2 scheme and in Cohort 3 on a 2+2+2+2+1 scheme.**
6	Synopsis, Methodology	The occurrence of 2 DLTs would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level.	The occurrence of 2 DLTs would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects **(2 more subjects for Cohort 2 and Cohort 3)** at the same dose level.
6	Synopsis, Methodology	The overall duration of the study will be approximately 13 to 14 months. Each subject will participate in the study for approximately 7 months.	The overall duration of the study will be approximately ~~13 to 14~~ **32** months. Each subject will participate in the study for **up to 7.5** ~~approximately 7~~ months.

6	Synopsis, Inclusion criteria	(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (maximum of 7 months). (6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on local laboratory results, during the Screening period. Samples for analysis by central laboratory will also be collected during Screening).	(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (~~maximum of 7~~ **up to 7.5** months). (6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on local laboratory results, during the Screening period. ~~Samples for analysis by central laboratory will also be collected during Screening~~).
8	Synopsis, Duration of treatment	Overall study duration: Approximately 13 to 14 months for three dose levels. Subject study participation: Approximately 7 months (4 week run in period, 12 week treatment period and 12 week follow up period without treatment).	Overall study duration: Approximately ~~13 to 14~~**32** months for three dose levels. Subject study participation: **Up to 7.5** ~~Approximately 7~~ months (4 week run in period **or up to 6 weeks under certain circumstances**, **a** 12 week treatment period and **a** 12 week follow up period without treatment).
8	Synopsis, Safety variables	• Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, Day 3, and Weeks 2, 3, 4, 5, 9 and 13 of the treatment period.	• Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, **24 hours postdose on Day 2,** Day 3, and Weeks 2, 3, 4, 5, 9 and 13 of the treatment period.
9	Synopsis, Statistical methods	Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule focussing a priori on the subject safety.	Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule **(in Cohort 2 on a 1+2+2+2+2 and in Cohort 3 on a 2+2+2+2+1 decision rule)** focussing a priori on the subject safety.

21	1.3	Consequently, the local effects that were recorded in the toxicology studies were considered without clinical relevance.	Consequently, the local effects that were recorded in the toxicology studies were considered without clinical relevance. **Lanreotide PRF has been tested in a parallel phase I study where the participants were healthy volunteers with cholecystectomy (study DFR-52030-345 and EUDRACT number: 2015-004338-85). Four healthy volunteers received a single injection of lanreotide PRF 180 mg in February 2016. Two of the volunteers had no side effects but two experienced abdominal pain on the day of the injection and their blood biochemistry revealed elevated hepatic and pancreatic enzymes. These levels returned to within normal ranges by Day 5. These elevations met the protocol-defined criteria for DLT. As a result, no further healthy volunteers were entered into that study. A full safety analysis for the subjects in this study (309) was performed and no similar trends were seen in Cohort 1 or the first subject dosed in Cohort 2. The study DRC on 29th February 2016 recommended to continue study 309 as planned with some precautionary changes that were included in amendment 5.**
22	1.4.2	Eligible subjects are expected to participate for a duration of up to 7 months.	Eligible subjects are expected to participate for a duration of up to 7**.5** months.
27	3.1	The study consists of a 4 week run in period, followed by a 12 week treatment period, and then a 12 week follow up period.	The study consists of a 4 week **(or up to 6 weeks under certain circumstances)** run in period, followed by a 12 week treatment period, and then a 12 week follow up period.
27	3.1	Subjects in each cohort will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR or lanreotide Autogel administration).	Subjects in each cohort will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks **(or up to 6 weeks if extended)** after the last octreotide LAR or lanreotide Autogel administration).

27	3.1	Progression to each ascending dose cohort will be dependent upon a review of data from the preceding cohort by a data review committee (DRC; see Section 10.6). The DRC will review the safety data for each dose cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). If no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort. The occurrence of 2 dose limiting toxicities (DLTs) would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects at the same dose level (see Section 6.1.1).	Progression to each ascending dose cohort **(or groups of subjects)** will be dependent upon a review of data from the preceding cohort **(or groups of subjects)** by a data review committee (DRC; see Section 10.6). The DRC will review the safety data for each dose cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). If no unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort **(or groups of subjects)**. The occurrence of 2 dose limiting toxicities (DLTs) would trigger the organisation of an intermediate DRC meeting (ad hoc meeting) to evaluate the decision to test 3 more subjects **(2 more subjects for Cohort 2 and Cohort 3)** at the same dose level (see Section 6.1.1).

27	3.1	Screening of subjects will take place 28 days before administration of study treatment (Day −28). Eligible subjects will receive the same single dose of octreotide LAR or lanreotide Autogel as their previous treatment and will enter a 4 week run in period.	Screening of subjects will take place 28 **to 42** days before administration of study treatment (**Day −42 to** Day −28). Eligible subjects will receive the same single dose of octreotide LAR or lanreotide Autogel as their previous treatment and will enter a 4 week run in period. **The 4 week run in period (28 days) can be extended to up to 6 weeks (42 days) under the following circumstances and only in specific cases:** **(1) When there is a delay in receiving blood results or having to re-collect a blood sample e.g. due to a clotted sample being received by the central laboratory.** **(2) The data review of the group of 2 prior subjects is ongoing and not completed by the end of a 4 week run in. In this circumstance, the run in period can be extended by a further 2 weeks. This would make the run in a maximum of 6 weeks in total.** **(3) At the investigator's discretion after discussion with the sponsor.** **Any extension to the run in period will be done in close consultation with the investigator to ensure that there is no safety risk to the subject.**
29	3.1	Figure 1 (see below)	Figure 1 was adapted for clarification.
30	3.2.1	• Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Days 1, 3, at Weeks 2, 3, 4, 5, 9 and 13 of the treatment period, and at each follow up visit.	• Clinical laboratory assessments: haematology, coagulation, clinical biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day~~s~~ 1**, 24 hours postdose (Day 2),** ~~and~~ **48 hours postdose (Day** 3**)**, at Weeks 2, 3, 4, 5, 9 and 13 of the treatment period, and at each follow up visit.

31	3.2.2	• Excipient serum concentration at the following timepoints after administration of lanreotide PRF: - Baseline (predose on Day 1 of lanreotide PRF administration) - At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration Note: If the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.	• Excipient serum concentration at the following timepoints after administration of lanreotide PRF: - Baseline (predose on Day 1 of lanreotide PRF administration) - At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration ~~Note: If the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.~~
32	3.5	This study will consist of a Screening visit, followed by a 4 week run in period, a 12 week open label treatment period and a 12 week follow up period. Subjects are expected to participate in this study for approximately 7 months. The overall duration of the study will be approximately 13 to 14 months.	This study will consist of a Screening visit, followed by a 4 week run in period **(or up to 6 weeks under certain circumstances)**, a 12 week open label treatment period and a 12 week follow up period. Subjects are expected to participate in this study for ~~approximately~~ **up to** 7**.5** months. The overall duration of the study will be approximately ~~13 to 14~~ **32** months.
36	4.1	(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (maximum of 7 months). (6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on local laboratory results, during the Screening period. Samples for analysis by central laboratory will also be collected during Screening).	(5) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (~~maximum of 7~~ **up to 7.5** months). (6) Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 <1.3 x ULN, based on local laboratory results, during the Screening period. ~~Samples for analysis by central laboratory will also be collected during Screening~~).

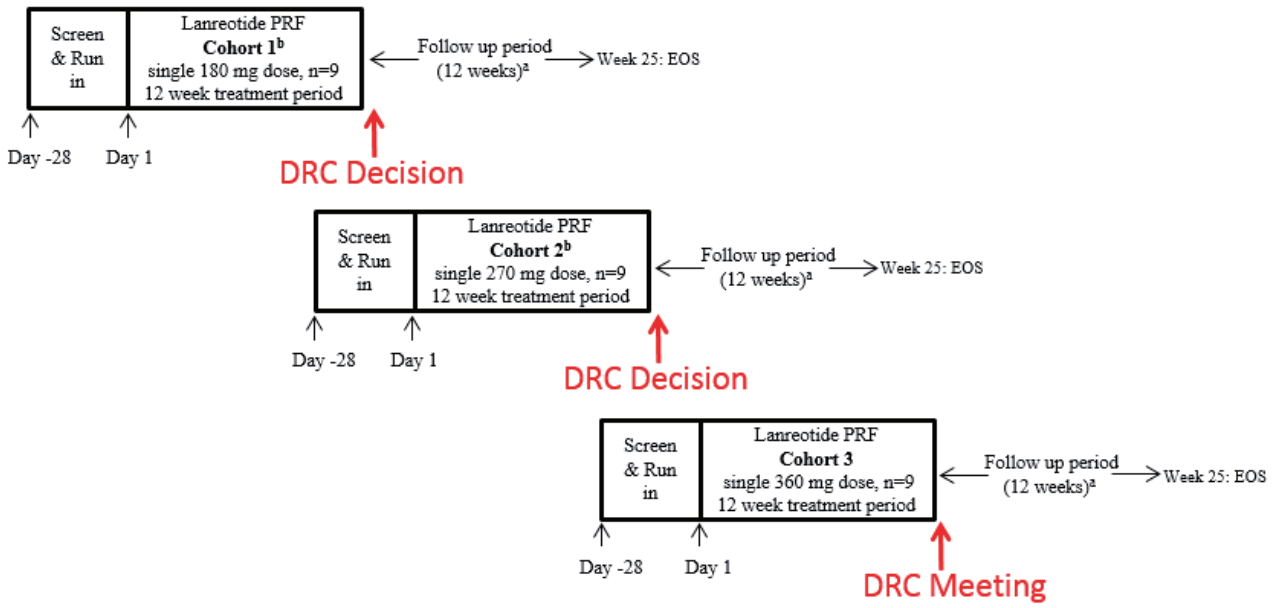
39	5.1	Table 5 (see below)	Table 5 was updated to include the option to extend the run in period; to add an additional blood sample at 24 hours postdose (before hospital discharge); to state that a reduced physical examination would be performed at home visits and weight would not be measured; IGF-1 will not be measured centrally during the screening period.
42	5.1	Table 6 (see below)	Table 6 was updated to state that a reduced physical examination would be performed at home visits and weight would not be measured.
43	5.1	The total volume of blood drawn for all evaluations throughout this study is approximately 571 mL for each subject.	The total volume of blood drawn for all evaluations throughout this study is approximately 57**9** mL for each subject.
43	5.1	Table 7 (see below)	Table 7 was updated with the additional blood volume taken at 24 hours postdose.
44	5.2.1	The Screening visit (Visit 1) will take place 28 days prior to the start of treatment with lanreotide PRF.	The Screening visit (Visit 1) will take place 28 **to 42** days prior to the start of treatment with lanreotide PRF **(Day −42 to −28)**.
45	5.2.2	• Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis)	• Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, **creatine kinase (CK),** serum electrolytes and urinalysis)
45	5.2.3	• Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, international normalised ratio (INR), postprandial glycaemia, and postprandial insulinaemia) at 6 hours postdose	• Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, international normalised ratio (INR), postprandial glycaemia, and postprandial insulinaemia**, CK**) at 6 hours postdose

45	5.2.3	The following procedures will be performed 24 hours after administration of study treatment at Visit 2 (Day 2±2 days): • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • PK blood samples for lanreotide and excipient (24 (±2) hours)	The following procedures will be performed 24 hours after administration of study treatment at Visit 2 (Day 2±2 days)**, before hospital discharge**: • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • PK blood samples for lanreotide and excipient (24 (±2) hours) • **Central clinical laboratory assessments (including liver function (ALT, AST, bilirubin), pancreatic function (lipase, amylase), serum creatinine, CK and GGT)**
46	5.2.3	The following procedures will be performed at Visit 3 (Day 3±1 day): • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis) • PK blood samples for lanreotide and excipient (if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then excipient PK may be removed for Visit 3). The following procedures will be performed at Visit 4 (Day 5±1 day): • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • PK blood samples for lanreotide and excipient (if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected.)	The following procedures will be performed at Visit 3 (Day 3±1 day): • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • Central clinical laboratory assessments (haematology, clinical biochemistry including hepatic, pancreatic and renal function tests, serum electrolytes and urinalysis) • PK blood samples for lanreotide and excipient ~~(if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then excipient PK may be removed for Visit 3).~~ The following procedures will be performed at Visit 4 (Day 5±1 day): • Review of AEs • New or changed concomitant medications/therapies/nondrug therapies/ surgeries • PK blood samples for lanreotide and excipient ~~(if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subjects in cohorts 2 and 3 to perform Visit 4 at Day 5 since only PK data are collected.)~~

50	6.1.1	Details of the adaptive 3+3+3 dose escalation scheme with the most likely outcome are provided in Figure 2.	**At anytime the DRC can ask for an ad hoc review of the data prior to any dosing if it is judged necessary.** Details of the adaptive 3+3+3 **or 2+2+2+2+1** dose escalation scheme with the most likely outcome are provided in Figure 2 **and Figure 3**.
52	Figure 3	N/A	Addition of Figure 3 to show the adaptive 2 per 2 dose escalation scheme
60	8.2.3	Blood samples (6 mL) will be collected to assess the following parameters: • urea, creatinine, total bilirubin, conjugated bilirubin	Blood samples (6 mL) will be collected to assess the following parameters: • urea, creatinine, **CK,** total bilirubin, conjugated bilirubin
61	8.4	Physical examinations, including body weight, will be conducted according to the study schedule in Table 5 and Table 6. Height will be measured at Screening.	Physical examinations, including body weight, will be conducted according to the study schedule in Table 5 and Table 6. Height will be measured at Screening. **A reduced physical examination will be performed at home visits and weight will not be measured.**
63	9.2.2	Measurement of IGF-1 concentrations at the screening visit will be performed locally and centrally.	Measurement of IGF-1 concentrations at the screening visit will be performed locally ~~and centrally~~.
67	10.6	The DRC will review safety data from each cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). At this time, if no DLT or unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort. The DRC will also review the PK data from the excipient when available and if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK will be removed.	The DRC will review safety data from each cohort after all subjects in the cohort have completed Visit 5 (Week 2 postdose). At this time, if no DLT or unexpected safety signals have been observed and the overall safety is in line with the known lanreotide safety profile, the DRC will decide whether to proceed with the next dose cohort. ~~The DRC will also review the PK data from the excipient when available and if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK will be removed.~~

WAS: Amendment 4.0 Version 5.0: 27 July 2015

Figure 1 Study Design



For each patient:
- Day -28: Octreotide LAR or lanreotide Autogel as per subjects previous treatment and start of 4 week run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

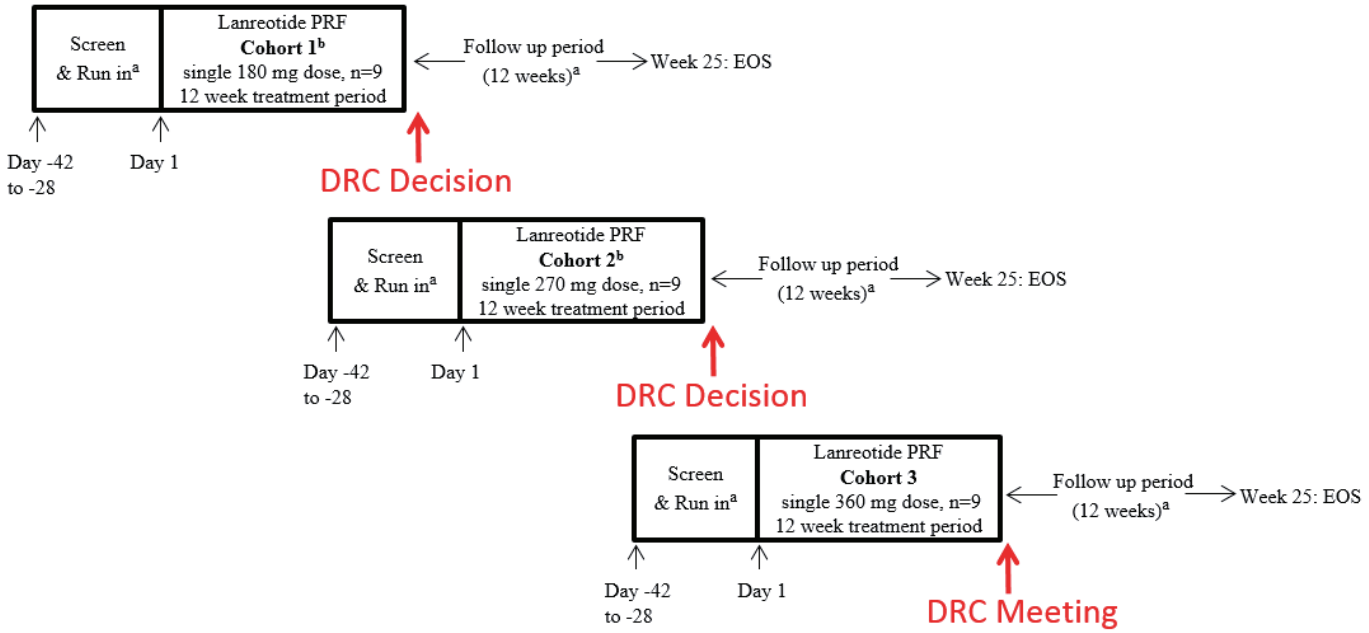
DRC=Data Review Committee; EOS=end of study; LAR=long acting release; PD=pharmacodynamic; PK=pharmacokinetic; PRF=prolonged release formulation.

a each cohort will undergo a 4 week run in period and two subsequent 12 week periods for treatment and follow up unless the subject withdraws from the study prematurely.

b each successive dose increase will proceed only on the recommendation of the DRC after review of the safety data for the preceding dose cohort after all subjects in the cohort have reached Visit 5 (Week 2 postdose).

IS: Amendment 5.0 Version 6.0: 22 March 2016

Figure 1 Study Design



For each patient:
- Day -42 to -28: Octreotide LAR as per subjects previous treatment and start of 4 week (or up to 6 weeks if extended) run-in period
- Day 1: hospitalisation and Lanreotide PRF administration
- Day 2: discharge
- During the 12 Week Treatment Period: PK, PD, safety and tolerability assessments.
- Week 13 (Visit 5): end of treatment period & study endpoints
- Week 25 (Visit 18): end of follow-up period
- Study visits every 2 weeks in follow-up period

DRC=Data Review Committee; EOS=end of study; LAR=long acting release; PD=pharmacodynamic; PK=pharmacokinetic; PRF=prolonged release formulation.

a each cohort will undergo a 4 week run in period **(or, if extended, the run in can be up to a maximum of 6 weeks)** and two subsequent 12 week periods for treatment and follow up unless the subject withdraws from the study prematurely.

b each successive dose increase will proceed only on the recommendation of the DRC after review of the safety data for the preceding dose cohort after all subjects in the cohort have reached Visit 5 (Week 2 postdose). **The DRC will meet after every 2 subjects starting from Cohort 2 onwards instead of the 3 subject blocks.**

WAS: Amendment 4.0 Version 5.0: 27 July 2015

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3 [e]	4 [e]	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		**Predose [c]**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide or lanreotide Autogel administration [d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide PRF		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X [e]	X [e]	X [e]								
PD assessments																				
IGF-1 [f]	X	X					X									X		X		X
GH cycle [g]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) *(Cont.)*

Visit	1 [a]	2									3 [e]	4 [e]	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [h]	X	X					X [i]				X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [j]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [k]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit.
b Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.
c Baseline.
d after Screening, subjects will enter a 4 week run in period and will receive a single dose of either octreotide LAR or lanreotide Autogel at the same dose as they received previously.
e if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.
f IGF-1 testing will be conducted by a central laboratory using a validated method. During the Screening period, IGF-1 will be analysed locally and centrally.
g five sampling times in the morning, with a sample every 30 minutes for 2 hours.
h blood and urine samples taken for clinical laboratory tests.
i evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.
j measured by MDRD formula [1].
k Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

IS: Amendment 5.0 Version 6.0: 22 March 2016

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period)

Visit	1 [a]	2									3 ~~[e]~~	4 ~~[e]~~	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28 (up to −42)	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Informed consent	X																			
Demographic data	X																			
Medical history	X																			
Acromegaly symptoms	X																			X
Concomitant medications	x----------																			----------x
Eligibility criteria	X	X																		
Octreotide or lanreotide Autogel administration [d]	X																			
Lanreotide PRF administration			X																	
Hospitalisation		x----------								----------x										
PK blood samples																				
Lanreotide PRF		X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Excipient		X		X	X	X	X	X	X	X ~~[e]~~	X ~~[e]~~	X ~~[e]~~								
PD assessments																				
IGF-1 [~~f~~e]	X	X					X									X		X		X
GH cycle [~~g~~f]	X	X														X				X
Random GH sample							X											X		
FT_3, FT_4, TSH, PRL	X	X											X			X				X
Safety assessments																				
AEs	x----------																			----------x

Table 5 Study Procedures and Assessments (Screening to Week 13, Including Treatment Period) ***(Cont.)***

Visit	1 [a]	2									3 ~~[e]~~	4 ~~[e]~~	5	6	7 [b]	8	9 [b]	10	11 [b]	12
Week		1											2	3	4	5	7	9	11	13
Day	−28	1								2	3	5	8	15	22	29	43	57	71	85
Hour		Predose [c]	0	1	2	4	6	8	12	24										
Evaluation of injection site reactions				X			X			X			X	X	X	X	X	X	X	X
Physical examination	X	X					X			X			X	X	X	X	X	X	X	X
Clinical laboratory assessments [~~h~~g]	X	X					X [~~i~~h]			**X [i]**	X		X	X	X	X		X		X
HbA1c	X																			X
eGFR [j]	X	X											X			X		X		X
Vital signs	X	X					X			X			X	X	X	X	X	X	X	X
12-lead ECG	X	X					X			X			X			X				X
Gallbladder echography	X															X				X
Putative antibodies to lanreotide		X																		X
Biobanking																				
Blood sampling [k]		X														X				X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; INR=international normalised ratio; LAR=long acting release; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Screening visit. **Screening of subjects will take place 28 to 42 days before administration of study treatment (Day −42 to Day −28). The 4 week run in period (28 days) can be extended to up to 6 weeks (42 days) under certain circumstances.**

b Study visits on Weeks 4, 7 and 11 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. **A reduced physical examination will be performed at home visits and weight will not be measured.** More information on how those home visits are performed are described in the study manual.

c Baseline.

d after Screening, subjects will enter a 4 week run in period **(or up to 6 weeks under certain circumstances)** and will receive a single dose of either octreotide LAR or lanreotide Autogel at the same dose as they received previously.

~~e if the elimination half-life of glycofurol in all cohort 1 subjects is short (e.g. <5 hours), then there is no need for the subject to perform Visit 4 at Day 5 since only PK data are collected. In addition at Visit 3 (Day 3) excipient PK may be removed.~~

~~f~~**e** IGF-1 testing will be conducted by a central laboratory using a validated method. During the Screening period, IGF-1 will be analysed locally ~~and centrally~~.

~~g~~**f** five sampling times in the morning, with a sample every 30 minutes for 2 hours.

~~h~~**g** blood and urine samples taken for clinical laboratory tests.

~~i~~**h** evaluation of the following parameters during the first day after lanreotide administration: ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.

i **at 24 hours postdose before hospital discharge (Day 2) only blood chemistry will be analysed. A urine sample will not be collected.**

j measured by MDRD formula [1].

k Biobanking: samples will only be collected for those individuals who have signed a specific consent for the biobanking samples.

WAS: Amendment 4.0 Version 5.0: 27 July 2015

Table 6 Study Procedures and Assessments (Follow Up; Weeks 15 to 25)

Visit	13 [a]	14	15 [a]	16	17 [a]	18 (EOS or EW)[b]
Week [c]	**15**	**17**	**19**	**21**	**23**	**25/EW**
Acromegaly symptoms						X
Concomitant medications	x----------x					
PK blood samples						
Lanreotide PRF		X		X		X
PD assessments						
IGF-1 [d]		X		X		X
Random GH sample		X		X		X
FT_3, FT_4, TSH , PRL						X
Safety assessments						
AEs	x----------x					
Physical examination	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X	X	X	X
HbA1c						X
eGFR [e]		X		X		X
Vital signs	X	X	X	X	X	X
Gallbladder echography						X
Evaluation of injection site reactions	X	X	X	X	X	X
Putative antibodies to lanreotide						X

AE=adverse event; eGFR=estimated glomerular filtration rate; EOS=end of study; EW=early withdrawal; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Study visits on Weeks 15, 19 and 23 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. More information on how those home visits are performed are described in the study manual.

b EOS for subjects completing the follow up period or EW visit for subjects who withdraw from the study during the follow up period.

c follow up visits will be conducted every 2 weeks (±3 days).

d during follow up visits, IGF-1 testing will be conducted by a central laboratory using a validated method.

e measured by MDRD formula [1].

IS: Amendment 5.0 Version 6.0: 22 March 2016

Table 6 Study Procedures and Assessments (Follow Up; Weeks 15 to 25)

Visit	13 [a]	14	15 [a]	16	17 [a]	18 (EOS or EW)[b]
Week [c]	**15**	**17**	**19**	**21**	**23**	**25/EW**
Acromegaly symptoms						X
Concomitant medications	x----------x					
PK blood samples						
Lanreotide PRF		X		X		X
PD assessments						
IGF-1 [d]		X		X		X
Random GH sample		X		X		X
FT_3, FT_4, TSH , PRL						X
Safety assessments						
AEs	x----------x					
Physical examination	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X	X	X	X
HbA1c						X
eGFR [e]		X		X		X
Vital signs	X	X	X	X	X	X
Gallbladder echography						X
Evaluation of injection site reactions	X	X	X	X	X	X
Putative antibodies to lanreotide						X

AE=adverse event; eGFR=estimated glomerular filtration rate; EOS=end of study; EW=early withdrawal; FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1=insulin like growth factor-1; MDRD=modification of diet in renal disease; PRF=prolonged release formulation; PRL=prolactin; TSH=thyroid stimulating hormone.

a Study visits on Weeks 15, 19 and 23 can be performed at the study site and/or at the subject's home as per investigator's and subject's decision. **A reduced physical examination will be performed at home visits and weight will not be measured.** More information on how those home visits are performed are described in the study manual.

b EOS for subjects completing the follow up period or EW visit for subjects who withdraw from the study during the follow up period.

c follow up visits will be conducted every 2 weeks (±3 days).

d during follow up visits, IGF-1 testing will be conducted by a central laboratory using a validated method.

e measured by MDRD formula [1].

WAS: Amendment 4.0 Version 5.0: 27 July 2015

Table 7 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	10	20.5 mL for 9 visits and 14.5 mL for 1 visit (Vist 2 postdose)	199
PD	7 IGF-1 20 GH Cycle 2 random GH	2 2 2	58
PK	15 for lanreotide; 10 for excipient	4 4	100
HbA1c	2	2	4
FT_3, FT_4, TSH and PRL	5	3.5	17.5
Antibody testing	2	4	8
Biobanking [b]	3	10	30
Total	75	Up to 132.5 mL per visit (Visit 2)	416.5

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis.

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

IS: Amendment 5.0 Version 6.0: 22 March 2016

Table 7 Blood Volume Calculation for Treatment Period

Description	Number of samples	Volume (mL)	Total volume (mL)
Clinical laboratory assessments [a]	10	20.5 mL for **10**~~9~~ visits ~~and 14.5 mL for 1 visit (Vist 2 postdose)~~	~~199~~**205**
PD	7 IGF-1 20 GH Cycle 2 random GH	2 2 2	58
PK	15 for lanreotide; 10 for excipient	4 4	100
HbA1c	2	2	4
FT_3, FT_4, TSH and PRL	5	3.5	17.5
Antibody testing	2	4	8
Biobanking [b]	3	10	30
Total	75	Up to 132.5 mL per visit (Visit 2)	~~416.5~~**422.5**

FT_3=free triiodothyronine; FT_4=free thyroxine; GH=growth hormone; HbA1c=glycosylated haemoglobin; IGF-1; insulin like growth factor-1; PD=pharmacodynamic; PK=pharmacokinetic; PRL=prolactin; TSH=thyroid stimulating hormone.

a clinical laboratory assessments include: haematology, coagulation, clinical biochemistry, postprandial blood glucose, postprandial insulin, glucagon, liver function parameters, pancreatic enzymes, serum creatinine and electrolytes, and urinalysis. **Creatine kinase will only be measured at Baseline (predose) and 6 and 24 hours postdose.**

b the 10 mL sample blood volume collected will consist of 5 mL dry tube and 2 x 2.5 mL for RNA biobanking

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 5.0 Version 6.0: 22 March 2016	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	To allow the addition of safety information gathered from the phase I study D-FR-52030-345 conducted with Lanreotide PRF for transparency reasons. An additional blood sample at 24 hours postdose and the analysis of creatine kinase at Baseline (predose), 6 and 24 hours postdose have been implemented as precautions. To increase the frequency of DRC meetings to ensure closer subject safety monitoring. Respective figures and paragraphs in the study protocol have been updated to show the adaptive 2 per 2 dose escalation scheme. To update the Sponsor's medically responsible person and contact details. To extend the study timelines and increase the number of participating sites. To allow more flexibility for the run in period by extending the run in period up to 6 weeks under specified circumstances. To remove the central laboratory analysis of IGF-1 during Screening as this is assessed by the local laboratory. To clarify that a reduced physical examination would be performed at home visits and weight would not be measured.	
Other Action Required?	CRF Update	Yes ☒ No ☐ (tick one)
	Local Consent Form Update	Yes ☒ No ☐ (tick one)
	Database Update	Yes ☒ No ☐ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☒ No ☐ (tick one)

Appendix 8 Protocol Amendment 6 (20 May 2016)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Either Octreotide LAR or Lanreotide Autogel
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 6.0 Version 7.0: 20 May 2016

The following amendment(s) is/are proposed:

Version Date		**22 March 2016**	**20 May 2016**
Page	**Section**	**WAS**	**IS**
33	3.6.3	Taking into account the safety profile of lanreotide (detailed in the IB), a DLT is defined as an AE (excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre-established criteria listed in Table 4.	Taking into account the safety profile of lanreotide (detailed in the IB), a DLT is defined as an AE (excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which meets any of the pre-established criteria listed in Table 4. **In the event of hepatic enzyme (aminotransferases and/or bilirubin) increases, refer to Appendix 2 for an algorithm for safety management.**
34	3.6.3	Table 4 (see below)	The criteria for defining a pancreatic dose limiting toxicity was clarified in Table 4.
82	Appendix 2	N/A	Addition of liver safety algorithm to show the management of subjects with elevations in hepatic enzymes and/or bilirubin.

WAS: Amendment 5.0 Version 6.0: 22 March 2016

Table 4 Criteria for Defining Dose Limiting Toxicities

Toxicity	Any of the following criteria
Hepatic	NCI CTCAE grade ≥3 ALT, AST Total bilirubin ≥2.0 to <3.0 x ULN for >7 consecutive days NCI CTCAE grade ≥2 bilirubin and NCI CTCAE grade ≥2 ALT or AST
Renal	NCI CTCAE grade ≥3 serum creatinine Serum creatinine ≥2.0 to ≤3.0 x ULN for >7 consecutive days
Pancreatic	NCI CTCAE grade ≥3 amylase or lipase with symptoms NCI CTCAE grade ≥3 amylase or lipase for >7 consecutive days without symptoms
Endocrine/Metabolic	NCI CTCAE grade ≥4 hyperglycaemia (confirmed by a repeat FPG within 24 hours) that does not resolve to CTCAE grade ≤2 within 14 consecutive days despite optimal antidiabetic treatment (14 consecutive days counts from the day of initiation of antidiabetic treatment)
Cardiac	NCI CTCAE grade ≥3
Other AEs	Any event CTCAE ≥3 except for AP grade ≥4 NCI CTCAE grade ≥3 diarrhoea despite optimal antidiarrheal treatment NCI CTCAE grade ≥3 vomiting despite optimal antiemetic therapy In the view of the investigators and Ipsen, any other unacceptable toxicity encountered

AE=adverse event; ALT=alanine aminotransferase; AP=alkaline phosphatase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; ULN=upper limit of normal.

IS: Amendment 6.0 Version 7.0: 20 May 2016

Table 4 Criteria for Defining Dose Limiting Toxicities

Toxicity	Any of the following criteria
Hepatic	NCI CTCAE grade ≥3 ALT, AST Total bilirubin ≥2.0 to <3.0 x ULN for >7 consecutive days NCI CTCAE grade ≥2 bilirubin and NCI CTCAE grade ≥2 ALT or AST
Renal	NCI CTCAE grade ≥3 serum creatinine Serum creatinine ≥2.0 to ≤3.0 x ULN for >7 consecutive days
Pancreatic	NCI CTCAE grade ≥3 amylase or lipase with ~~symptoms~~ **abdominal pain** NCI CTCAE grade ≥3 amylase or lipase for >7 consecutive days without ~~symptoms~~ **abdominal pain** **If necrotising pancreatitis is suspected, the subject should be hospitalised**
Endocrine/Metabolic	NCI CTCAE grade ≥4 hyperglycaemia (confirmed by a repeat FPG within 24 hours) that does not resolve to CTCAE grade ≤2 within 14 consecutive days despite optimal antidiabetic treatment (14 consecutive days counts from the day of initiation of antidiabetic treatment)
Cardiac	NCI CTCAE grade ≥3
Other AEs	Any event CTCAE ≥3 except for A**L**P grade ≥4 NCI CTCAE grade ≥3 diarrhoea despite optimal antidiarrheal treatment NCI CTCAE grade ≥3 vomiting despite optimal antiemetic therapy In the view of the investigators and Ipsen, any other unacceptable toxicity encountered

AE=adverse event; ALT=alanine aminotransferase; A**L**P=alkaline phosphatase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; **FPG=fasting plasma glucose;** NCI=National Cancer Institute; ULN=upper limit of normal.

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 6.0 Version 7.0: 20 May 2016	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
Reason(s) for changes	To add a liver safety algorithm for the management of subjects with elevations in hepatic enzymes and/or bilirubin following a recommendation by the Competent Authority in France. To clarify the criteria for pancreatic dose limiting toxicities by specifying that 'abdominal pain' rather than 'symptoms' should accompany raised pancreatic enzymes (amylase and lipase). Clarification was also added that a subject should be hospitalised if necrotising pancreatitis is suspected.	
Other Action Required?	CRF Update	Yes ☐ No ☒ (tick one)
	Local Consent Form Update	Yes ☐ No ☒ (tick one)
	Database Update	Yes ☐ No ☒ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☐ No ☒ (tick one)

Appendix 9 Protocol Amendment 7 (16 December 2016)

STUDY NUMBER:	8-55-52030-309
PROTOCOL TITLE:	Phase IIa, Open Label, Dose Ascending Study to Determine the Maximum Tolerated Dose, Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of a Single Dose of Lanreotide PRF in Subjects with Acromegaly Previously Treated and Controlled with Either Octreotide LAR or Lanreotide Autogel
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 7.0 Version 8.0: 16 December 2016

The following amendment(s) is/are proposed:

Version Date		**20 May 2016**	**16 December 2016**
Page	**Section**	**WAS**	**IS**
1	Title Page	David Rich, MPhil Ipsen Biopharm Limited 190 Bath Road Slough, SL1 3XE (UK) PPD	David Rich, MPhil Ipsen Biopharm Limited **102 Park Drive** **Milton Park** **Oxfordshire, OX14 4RY (UK)** **Tel: +44 (0)7736 615866** ~~190 Bath Road~~ ~~Slough, SL1 3XE (UK)~~ PPD
1	Title Page	PPD, Central Department of Pharmacovigilance, Ipsen Group, 190 Bath Road, Slough, Berkshire SL1 3XE, England PPD	PPD, **Global Patient Safety,** ~~Central Department of Pharmacovigilance,~~ Ipsen **Biopharm Ltd** ~~Group~~, ~~190 Bath Road, Slough, Berkshire SL1 3XE, England~~ PPD **102 Park Drive, Milton Park, Oxfordshire, OX14 4RY (UK)** PPD
5	Synopsis	In Cohort 2 subjects will be reviewed on a 1+2+2+2+2 scheme and in Cohort 3 on a 2+2+2+2+1 scheme.	In Cohort 2 subjects will be reviewed on a 1+2+2+2+2 scheme and in Cohort 3 on a 2+2+2+**3**~~2+1~~ scheme.

7 and 37	Synopsis and Section 4.2	(10) Has a history of gallstones or any gallstones/sludge observed at Screening gallbladder echography (local assessment).	(10) ~~Has a history of gallstones or any gallstones/sludge observed at Screening gallbladder echography (local assessment).~~ **Has symptomatic gallstones/sludge at the Screening Visit echography (local assessment) OR is asymptomatic but has echography showing clear evidence of impending inflammation such as localised mucosal thickening suggesting the subject is at high risk of developing acute disease. Subjects with asymptomatic gallstones/sludge and otherwise normal echography may be entered at the discretion of the investigator.**
9	Synopsis	Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule (in Cohort 2 on a 1+2+2+2+2 and in Cohort 3 on a 2+2+2+2+1 decision rule)	Inclusion of nine subjects within a dose cohort (180, 270 or 360 mg) will be based on an adaptive 3+3+3 decision rule (in Cohort 2 on a 1+2+2+2+2 and in Cohort 3 on a 2+2+2+**3**~~2+1~~ decision rule)
29	Figure 1, footnote b	each successive dose increase will proceed only on the recommendation of the DRC after review of the safety data for the preceding dose cohort after all subjects in the cohort have reached Visit 5 (Week 2 postdose). The DRC will meet after every 2 subjects starting from Cohort 2 onwards instead of the 3 subject blocks.	each successive dose increase will proceed only on the recommendation of the DRC after review of the safety data for the preceding dose cohort after all subjects in the cohort have reached Visit 5 (Week 2 postdose). The DRC will meet after every 2 subjects starting from Cohort 2 onwards instead of the 3 subject blocks **and prior to the final 3 subjects in Cohort 3.**

37	Section 4.3	The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol.	The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol. **Subjects participating in the optional biobanking have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which the sample is kept). If a subject wishes to withdraw his consent for biobanking and the samples are still at the investigator site or at the central laboratory at this time, the investigator must first inform the study monitor in writing of the subject's decision and destroy the samples, respectively after informing the monitor the investigator will need to contact the central laboratory to destroy the samples. If the samples are already at Fisher BioServices (biobanking vendor), i.e. post-study, the investigator must inform Ipsen directly using the following e-mail address;** PPD **, mentioning only the ID of the subject in this e-mail. Ipsen will ensure destruction of the samples and all corresponding aliquots, issue confirmation of the withdrawal, and forward corresponding destruction certificate to the investigator.**

44	Section 5.2.1	Under normal circumstances subjects will not be screened more than once. There are two exceptions; (1) IGF-1 may be re-tested once if the screening value is just above 1.3 x ULN (analysis by local laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN. (2) If the time elapsed between the original Screening visit (Visit 1) and Visit 2 is >28 days (±2 days) then re-screening of the subject for inclusion is permitted.	Under normal circumstances subjects will not be screened more than once. There are **three**~~two~~ exceptions**:** (1) IGF-1 may be re-tested once if the screening value is just above 1.3 x ULN (analysis by local laboratory). The study treatment may only be administered if the re-test is <1.3 x ULN. (2) If the time elapsed between the original Screening visit (Visit 1) and Visit 2 is >28 days (±2 days) then re-screening of the subject for inclusion is permitted. **(3) If deemed acceptable by the investigator, the subject may be re-screened once for inclusion if they previously failed screening due to the presence of asymptomatic gallstones/sludge. This follows the change to exclusion criterion #10 in protocol amendment 7.**
50	Section 6.1.1	Details of the adaptive 3+3+3 or 2+2+2+2+1 dose escalation scheme with the most likely outcome are provided in Figure 2 and Figure 3.	Details of the adaptive 3+3+3 or **1+**2+2+2+2~~+1~~ **(Cohort 2) or 2+2+2+3 (Cohort 3)** dose escalation scheme with the most likely outcome are provided in Figure 2 and Figure 3.
56	Section 8.1.3	At each visit, the subject should be asked a non leading question such as: “How have you felt since starting the new treatment/last dose/the last assessment?”	**During the informed consent process and on an ongoing basis subjects should be reminded to report any AEs as soon as possible to their study site and not to wait until their next visit if they experience any unexpected medical symptoms.** At each visit, the subject should be asked a non leading question such as: “How have you felt since starting the new treatment/last dose/the last assessment?”

60	Section 8.7	Gallbladder echography will be conducted according to study site procedures. The results will be recorded in the eCRF. Any clinically significant abnormalities will be recorded as AEs.	Gallbladder echography will be conducted according to study site procedures. The results will be recorded in the eCRF. Any clinically significant abnormalities will be recorded as AEs. **In particular, sites should be aware of any subject who has gallstones or sludge present at baseline. In the case that a subject develops gallstone(s) during the study but they are asymptomatic, they can remain in the study and complete the protocol as planned. If a subject develops symptoms of either a pre-existing gallstone(s) or a newly developed gallstone, they may remain in the study at the discretion of the investigator. As this is a single-dose protocol, the subject will not be exposed to any additional IMP. In case of the development of (symptomatic) gallstones/sludge this will be treated according to the study sites' routine practice.**
79	Appendix 1	The samples will be stored at -80°C at the site. The samples will then be shipped regularly to the biobanking central laboratory, FISHER, in dry ice.	The samples will be **shipped to the central laboratory and** stored at -80°C at the site. **At the end of the study one shipment will be made by the central laboratory with all samples**~~The samples will then be shipped regularly~~ to the biobanking central laboratory, FISHER, in dry ice.

Summary & outcome of changes:

STUDY NUMBER	8-55-52030-309	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 7.0 Version 8.0: 16 December 2016	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
Reason(s) for changes	To allow inclusion of patients with asymptomatic gallstones or sludge, and the re-screening of patients who previously failed this exclusion criteria. This extension of the study population follows requests from investigators participating in the 8-55-52030-309 study, who asked to include these patients for two main reasons: (1) A significant proportion of acromegaly patients in clinical practice have gallstones, mostly being asymptomatic even when treated with somatostatin analogue for several years, (2) in the investigator's opinion, there is no reason to exclude these patients from a clinical study, as long as they are monitored regularly and as long as the gallstone(s) is(are) asymptomatic. These patients are prescribed somatostatin analogues in real world clinical practice in the same way as patients without gallstones. This decision follows a thorough review of all available safety data coming from both clinical investigations and the market use, which led to the conclusion that the benefit risk balance of lanreotide PRF for the above referenced patients is unchanged compared to the current study population. In addition to the monitoring measures already included in the study protocol (4 gallbladder echography and 18 face-to-face visits over 25 weeks) which provide a sufficient safety coverage to prevent the safety issues related to the gallstones, namely acute cholecystitis, the patients will be reminded to immediately report any AEs to their study team and not to wait until the next visit. Other changes include: To update the contact details for the Sponsor's Medically Responsible Person and Pharmacovigilance/Emergency contact. To change the DRC frequency for Cohort 3 from 2+2+2+2+1 to 2+2+2+3. To better clarify the follow-up and reporting of AEs. To include details of withdrawal of consent for biobanking in the protocol for clarity and amend the procedure in Appendix 1 for the shipment of biobanking samples.	
Other Action Required?	CRF Update	Yes ☒ No ☐ (tick one)
	Local Consent Form Update	Yes ☒ No ☐ (tick one)
	Database Update	Yes ☒ No ☐ (tick one)
	Reporting & Analysis Plan (RAP) Update	Yes ☒ No ☐ (tick one)