STATISTICAL AND ANALYSIS PLAN

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

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	ACROMEGALY PREVIOUSLY TREATED AND CONTROLLED WITH EITHER OCTREOTIDE LAR OR LANREOTIDE AUTOGEL
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Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

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

History of Changes				
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Page	Section	Was	Is	

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	Adverse Event
ADA:	Antidrug Antibodies
AP:	Alkaline phosphatase
ALT (SGPT):	Alanine aminotransferase
aPTT:	Activated Partial Thromboplastin Time
AST (SGOT):	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Class
AUC:	Area Under the Curve
BMI:	Body Mass Index
CK	Creatine Kinase
Cmax:	Maximum serum concentration
CRF:	Case Report Form
CRO:	Clinical Research Organisation
CS:	Clinically Significant
CSC:	Clinical Study Co-ordinator
CTCAE:	Common Terminology Criteria for Adverse Events
DLT:	Dose Limiting Toxicity
DM:	Data Management
DRC:	Data Review Committee
e:	Electronic
ECG:	Electrocardiogram
eGFR:	Estimated Glomerular Filtration Rate
EOS:	End of Study
EW:	Early Withdrawal
FT_3:	Free Triiodothyronine
FT_4:	Free Thyroxine
GCP:	Good Clinical Practices
GGT:	Gamma-Glutamyl Transferase
GLP:	Good Laboratory Practices
H:	High
HbA1c:	Glycosylated haemoglobin
IB:	Investigator Brochure
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio

ITT:	Intention-To-Treat
I.V.:	Intravenous
L:	Low
LAR:	Long Acting Release
LLN:	Lower Limit of Normal
LOCF:	Last Observation Carried Forward
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI-CTC:	National Cancer Institute – Common Toxicity Criteria
PD:	Pharmacodynamics
PDM:	Pharmacokinetics and Drug Metabolism
PK:	Pharmacokinetics
PP:	Per Protocol
PRF:	Prolonged Release Formulation
PRL:	Prolactin
PT:	Prothrombin Time
PV:	Pharmacovigilance
QC:	Quality Control
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QT_c:	Corrected QT interval
SAP:	Statistical and Analysis Plan
RBC:	Red blood cell
SAE:	Serious Adverse Event
SAS®	Statistical Analysis System®
SD:	Standard Deviation
SE:	Standard Error
SI:	Standard International
SOP:	Standard Operating Procedure
TEAE:	Treatment Emergent Adverse Event
T_{max}:	Time to maximum serum concentration
TFLs:	Tables, Figures and Listings
TSH:	Thyroid Stimulating Hormone
U:	Unscheduled
ULN:	Upper Limit of Normal

WBC:	White blood cell
WHO- DD:	World Health Organization – Drug dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

The primary objective of the study is to identify the maximum tolerated dose (MTD) and to investigate the pharmacokinetics (PK) of a single dose of lanreotide prolonged release formulation (PRF) in subjects with acromegaly.

1.1.2 Secondary objectives

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 pharmacodynamics (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.

1.2 Study design

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 long acting release (LAR) or lanreotide Autogel. The study consists of a 4 week run in period (or up to 6 weeks under certain circumstances), 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). 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.

Changes to the design or conduct of the study are mentioned in the Changes From Protocol (section 5).

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). 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.

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 either 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.

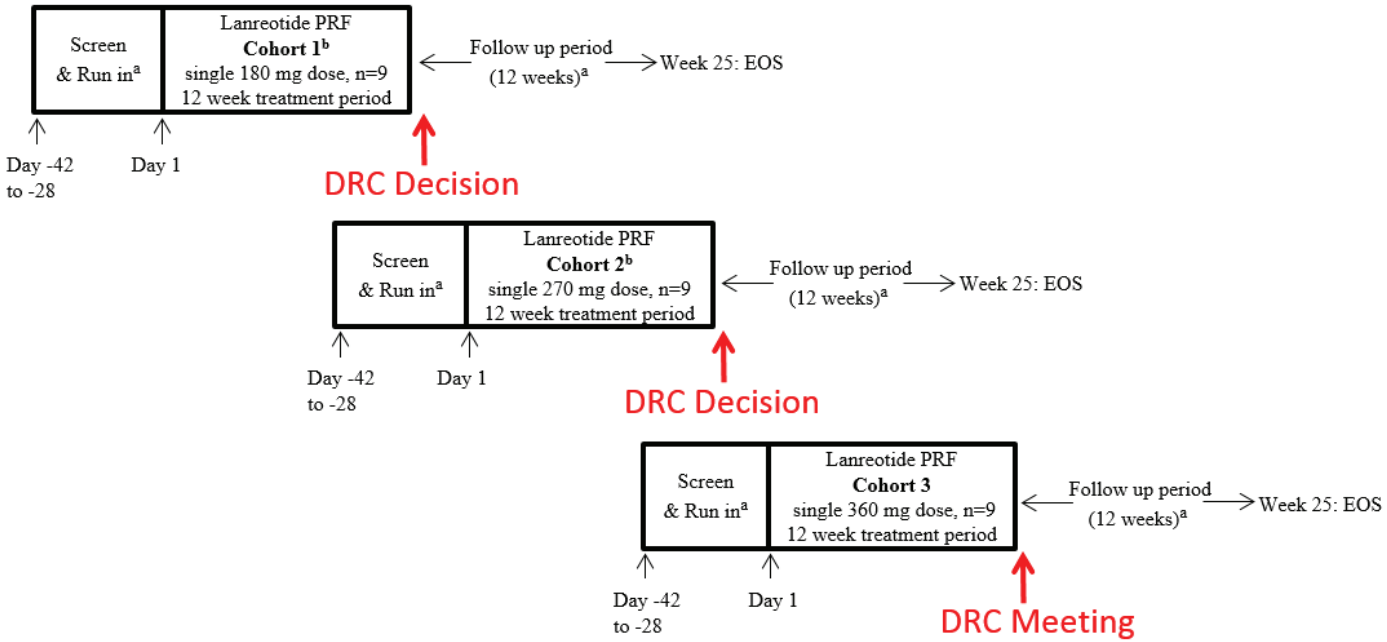
On Day 1, subjects will receive lanreotide PRF by deep subcutaneous injection in the superior, external quadrant of the buttock and a 12 week treatment period will then commence. Treatment will be administered at the study centre and subjects will remain at the study centre for 24 hours postdose. Throughout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

1.2.1 Study population

A maximum of 27 subjects will be treated with lanreotide PRF (9 subjects per cohort).

The target population are subjects with acromegaly, well controlled by a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months. 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.

Table 1 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

1.2.2 Study exposure

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

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

1.3.1.1 Subject identification

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.

1.3.1.2 Treatment of subjects

At Screening, subjects will be allocated a subject number.

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 informed consent and confirmation of eligibility for the study, subjects will be allocated to one of the following treatment cohorts:

Table 2 Treatment Cohorts

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.

1.3.1.3 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 (in Cohort 2 on a 1+2+2+2+2 and in Cohort 3 on a 2+2+2+3 decision rule). At each dose level, a total of

9 subjects will be enrolled if ≤3 DLTs are reported (see section 1.3.1.4 for the definition of DLT).

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

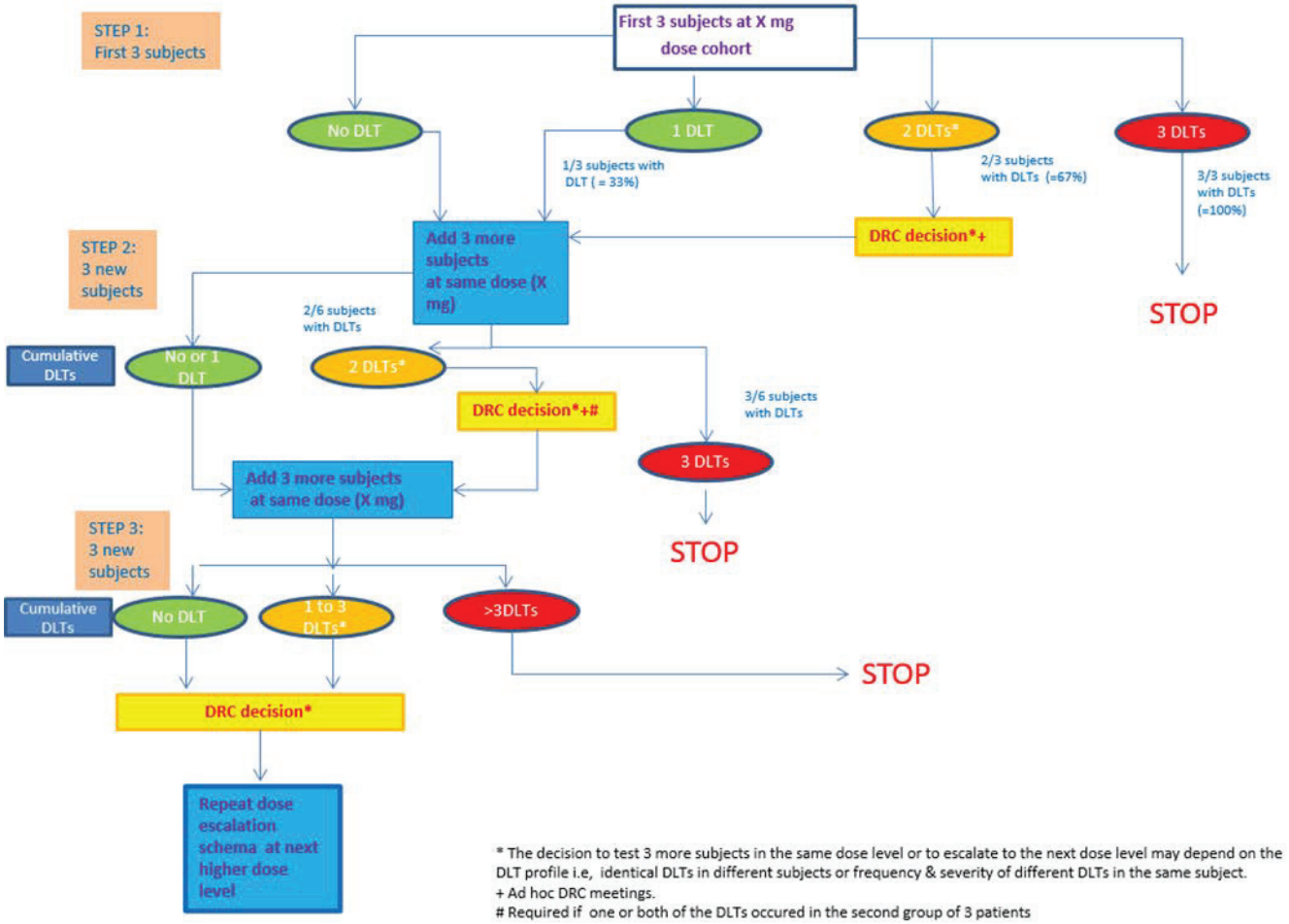
Dose level: 180 mg. The study will start dosing 3 subjects. If none or 1 out of the 3 dosed subjects experiences a DLT, 3 more subjects will be dosed at the same dose.

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 occurred in the second group of 3 subjects, 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.

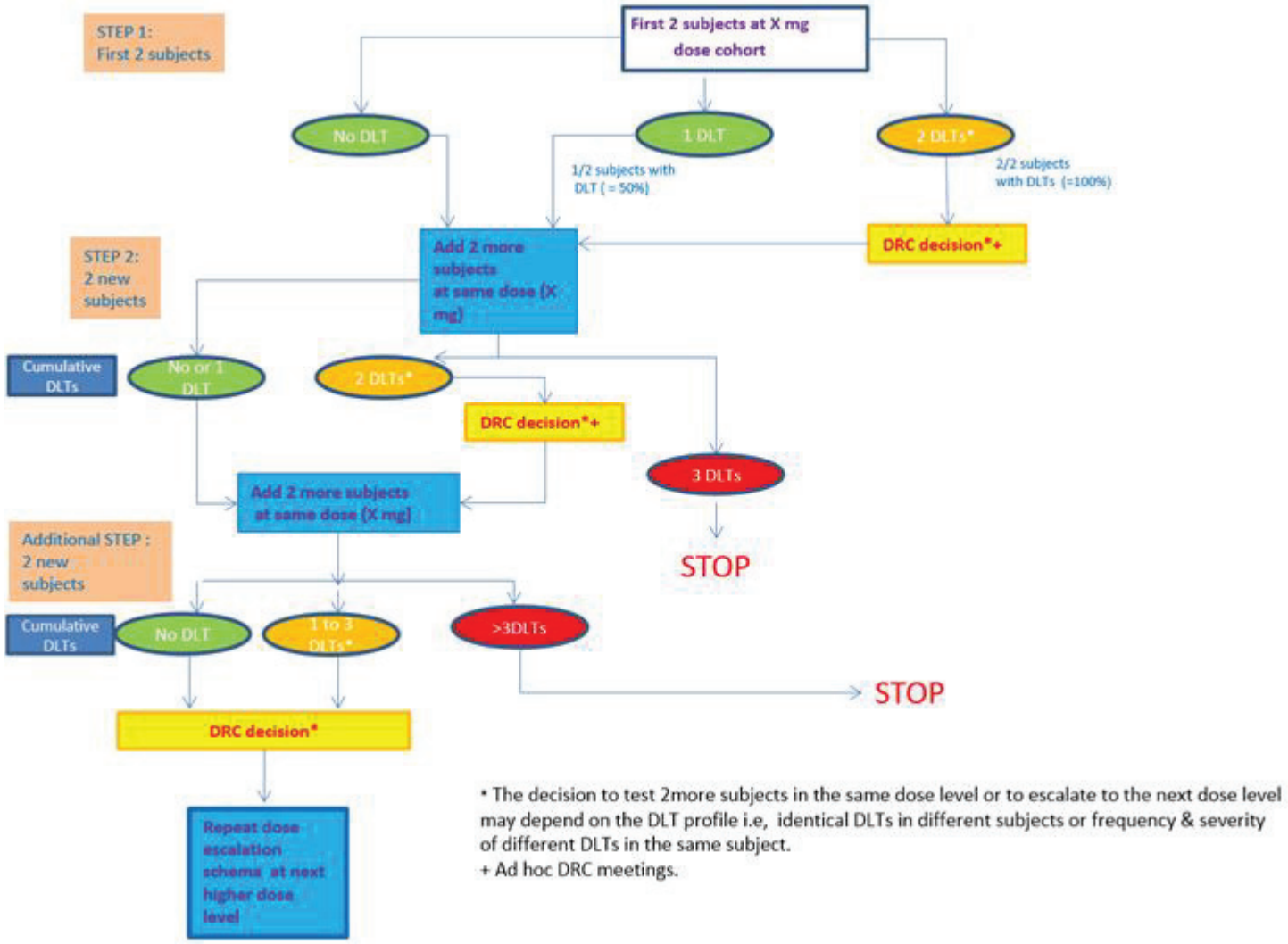
Dose escalation: If more than 3 out of 9 subjects experience a DLT, dose escalation will be stopped and the dose will be declared the maximum administered dose. If ≤3 DLTs have been observed in the 9 treated subjects, then the dose may be escalated to 270 mg. The DRC will determine if progression to 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. 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 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.

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



1.3.1.4 Definition of a Dose Limiting Toxicity

Taking into account the safety profile of lanreotide (detailed in the Investigator Brochure [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 3.

Table 3 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, i.e. of 4 weeks or more.

1.3.1.5 Definition of the 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).

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

Not applicable.

1.3.2.2 Safety assessments

The following safety parameters will be assessed during the study: adverse events, vital signs, physical examination, electrocardiography, clinical laboratory tests, glycosylated haemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), gallbladder echography, putative antibodies to lanreotide, evaluation of injection site reactions.

A post-baseline safety assessment is any assessment (i.e. assessment of absence or presence) of at least one of these parameters.

- **Adverse Events**

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study and will be elicited by direct, non-leading questioning or by spontaneous reports.

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

- **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 5 minutes rest in a supine position and after 1 minute standing.

Vital signs (supine and standing blood pressure and heart rate, and body temperature) will be measured at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at Weeks 15, 17, 19, 21, 23, 25 (or EW) of the follow up period.

- **Physical Examination**

Physical examinations, including body weight, will be conducted at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period, and at Weeks 15, 17, 19, 21, 23, 25 (or EW) of the follow up period. Height will be measured at Screening. A reduced physical examination will be performed at home visits and weight will not be measured.

- **Electrocardiography**

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.

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.

Automated ECG interval estimates taken from the ECG recorder will be used in this study. Any clinically significant abnormalities will be appropriately reported.

- **Clinical Laboratory Tests**

Blood samples for clinical laboratory tests and urine samples for urinalysis will be taken 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 Weeks 15, 17, 19, 21, 23, 25 (or EW) of the follow up period and will consist of the following:

Haematology – the following parameters will be assessed: 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.

Coagulation – activated partial thromboplastin time (aPTT), prothrombin time (PT) and its derived measures of prothrombin ratio and international normalised ratio (INR)**.**

Biochemistry – urea, creatinine, creatine kinase (CK), total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, Alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin total protein, total cholesterol, triglycerides, postprandial glucose, postprandial insulin, pancreatic enzymes and glucagon.

The following parameters will be evaluated during the first day after lanreotide administration (6 hours post-dose): ALT, AST, bilirubin, lipase, amylase, INR, serum creatinine, postprandial glycaemia, and postprandial insulinaemia.

Urinalysis – chloride, bicarbonates, sodium, potassium, calcium, pH, proteins, ketones, glucose, blood, bilirubin and urobilinogen.

- **Glycosylated haemoglobin (HbA1c)**

Glycosylated haemoglobin (HbA1c) at Screening, Week 13 and Week 25 (or early withdrawal).

- **Estimated glomerular filtration rate (eGFR)**

Estimated glomerular filtration rate (eGFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula [1], will be calculated 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**

Gallbladder echography will be performed 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), blood samples will be collected for the assay of putative antibodies to lanreotide in all subjects. The putative antilanreotide antibodies will be evaluated using a validated method by a Contract Research Organisation (CRO) in accordance with Good Laboratory Practices (GLP).

- **Evaluation of injection site reactions (appearance, local symptoms)**

Injection sites will be evaluated by the investigator for appearance and local symptoms according to NCI CTCAE criteria at the following timepoints: 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. Results will be recorded on a dedicated form in the eCRF.

Any clinically significant abnormalities will be recorded as AEs.

- **Acromegaly symptoms**

The following acromegaly symptoms will be graded by the subject at Screening, Week 13 and 25 (or EW):

- Headache
- Sweating
- Asthenia
- Swelling of extremities
- Joint pain
- Paresthesia
- Carpal tunnel syndrome
- Visual field defect
- Sleep apnea
- Backache
- Skin tags
- Potency decrease

Each symptom will be graded as absent (score=0), mild (score=1), moderate (score=2) or severe (score=3).

1.3.2.3 Other assessments

- **Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) analyses**

Pharmacokinetic and pharmacodynamics analyses will be described in a separate Data Analysis Plan. Biobanked samples will be analysed outside clinical study and analysis described in a separate data analysis plan.

1.3.2.4 Withdrawal/discontinuation

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.

The Investigator should use his/her clinical judgement to withdraw the subject at any time for safety reasons. The subject may decide to withdraw from the study for any reason and at any time.

In the event of a withdrawal, the Investigator must make every effort to convince the subject to return for a withdrawal visit for safety reasons. For any early termination of study treatment/withdrawal from the study, the reason must be documented in the electronic case report form (eCRF). Main reasons for discontinuation/withdrawal are as follows:

- Adverse event

- Lack of efficacy
- Physician decision
- Protocol deviation
- Consent withdrawn
- Lost to follow up
- Other reason

1.3.2.5 Stopping Rules

The DRC will review the safety data from each treatment cohort to determine whether the next treatment cohort should ensue (section 3.2.16). 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 within the first week (up to Week 2; Visit 5) following lanreotide PRF administration and during the entire study duration. If any serious adverse event (SAE) occurs, a relationship with the exposure to lanreotide PRF will be assessed.

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

1.3.3 Schedule of assessments

The schedule of procedures and assessments during the study is summarised in Table 4 (Screening to Week 13, including treatment period) and Table 5 (Follow up period; Weeks 15 to 25).

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 (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
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 5 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 (see section 5).

e measured by MDRD formula [1].

1.3.4 Planned sample size

Inclusion of 9 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 9 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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy

Not applicable

2.2 Safety

2.2.1 Screened population

The screened population is all subjects screened (i.e. who signed the informed consent form).

2.2.2 Safety population

The safety population is all subjects who receive the single dose of lanreotide PRF and have at least one post baseline safety assessment.

2.2.3 Intention-To-Treat population (ITT)

The Intent-to-Treat (ITT) population is all treated subjects.

2.2.4 Per Protocol population (PP)

The Per Protocol (PP) population is all subjects in the ITT population for whom no major protocol violations/deviations occur.

2.3 Pharmacokinetics

2.3.1 PK valid population

The PK valid population will consist of 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).

2.4 Primary population

The primary analysis based on the primary safety and PK will be performed on the Safety and PK valid populations, respectively.

2.5 Reasons for Exclusion from the Analysis Populations

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.

During the data review meeting, listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed by the study team. Based on minor or major protocol violations/deviations, subjects may be excluded from the Safety/ITT/PP population.

Subjects may be excluded from the PP population if one or more of the following violations/deviations occur:

- inclusion/exclusion criteria violations (see section 4 of the protocol)
- did not receive any Investigational Medicinal Product (IMP)
- non adequate compliance of IMP
- a prohibited medication/therapy/procedure was administered
- deviations from time windows (observed versus scheduled times)
- deviations from IMP administration
- other protocol violation/deviations

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [2] and will be based on the pooled data from the individual study sites, unless otherwise stated.

Statistical analyses will be performed by Chiltern, in accordance with their Standard Operating System (SOPs) and established QC and Validation plan for this study".

The PK data analysis will be performed independently by a CRO under Ipsen) Early Drug Development (EDD) department supervision.

3.1.1 Efficacy endpoint(s)

Not applicable

3.1.2 Primary safety endpoint

The primary safety endpoint is to identify the maximum tolerated dose (MTD) of a single dose of lanreotide PRF in subjects with acromegaly.

3.1.3 Secondary safety endpoints

Safety endpoints are adverse events, vital signs, physical examination, 12-lead ECG, QTc interval, clinical laboratory assessments (including haematology, coagulation, clinical biochemistry, urinalysis), glycosylated haemoglobin (HbA1c), eGFR, gallbladder echography, putative antibodies to lanreotide and evaluation of injection site reactions (appearance, local symptoms).

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

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

3.2 Analysis methods

3.2.1 Efficacy

Not applicable.

3.2.2 Safety

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

3.2.2.1 MTD determination

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

A summary of DLTs occurring during the first week (up to Visit 5 [Week 2]) and a summary of DLTs occurring during the entire study duration will be provided, presenting the number of subjects with DLTs, the total number of DLTs, the number of DTLs per dose cohort, and the type of DLTs.

Listings of DLTs will be presented and sorted by dose cohort and subject identifier.

3.2.2.2 Adverse events

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 19.0 or higher).

Listings will be presented and sorted by dose cohort, subject identifier, start time of AEs, primary system organ class, preferred term and verbatim text for all AEs recorded during the study.

Listings of deaths, serious adverse events (SAE), AEs leading to withdrawal, listing of lab findings: NCI-CTC grade 3 and 4 and prolonged (4 weeks or more) grade 2 haematological (respectively biochemistry) toxicities will also be presented.

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

A TEAE is defined as any AE that occurs during the active phase of the study (between the first date of IMP administration and 3 months after last IMP administration) 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 or became serious 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.

An overall summary table of all AEs will be presented.

All AEs and SAEs occurring during the Screening period will be listed; 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 per decreasing frequency, by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

TEAEs will be summarised by dose cohort and overall with the number and percentage of subjects with adverse events classified by primary system organ class and preferred term. The number of occurrences of a TEAE will also be presented.

Incidences tables of AEs will be provided with the number and percentage of subjects with adverse events classified by primary system organ class, preferred term (ordered alphabetically) 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) and the most serious causality (related>missing> not related) will be chosen.

A table presenting the duration (days) of grade 2 TEAEs by Preferred Term will be provided with the listing of prolonged grade 2 toxicities, i.e. of 4 weeks duration or more. If start and stop date are on the same day, this will be reported as < 1 day in the table.

3.2.2.3 Laboratory data

Clinical laboratory assessments (including haematology, coagulation, clinical biochemistry, urinalysis) will be listed in Standard International (SI) units in individual data listings by dose cohort, subject identifier and visit/timepoint.

Abnormal values will be flagged (High [H], Low [L], clinically significant [CS]) where applicable in the listings. A listing of CS abnormal values will be provided, additionally.

Any unscheduled laboratory assessments will be flagged [U] in the listings.

Baseline values will be defined as the last measurement of the specific laboratory parameter collected prior to the dose intake of the study drug (predose on Day 1 if available).

In cases where laboratory values are retested,

- For parameters with missing values, the last available value at each visit will be used of the analysis.
- For other parameters, the first value at each visit will be kept.

All laboratory values (including re-tested values) will be listed in the by-patient table and data listing.

Since all samples will be analysed by a central laboratory, the same reference value ranges apply to subjects from all study centres. For IGF-1, different normal ranges are provided by the central laboratory depending classically on age and gender but also here on assay method. They will all appear in the normal range listing.

Summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each dose cohort and overall.

Shift tables from Baseline to each post baseline visit of the number and percentages of subjects with low, normal, or high values will be presented by dose cohort and overall.

In addition, a graph of individual laboratory values over time from screening to end of study (or early withdrawal if applicable) will be performed for each dose cohort for the following

parameters: absolute neutrophils, gamma GT, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, amylase, lipase and glucose.

Haematology, biochemistry and urinalysis toxicities will be recorded and graded according to the NCI-CTC criteria, Version 4.03 (June, 2010). The NCI CTC grade of haematology and biochemistry by subject will be listed in Section 16.2.8. Listings of the laboratory parameters in section 14.3.4 will include listings of NCI-CTC grade 3 and 4 and prolonged (4 weeks or more) grade 2 haematological toxicities, listings of NCI-CTC grade 3 and 4 and prolonged (4 weeks or more) grade 2 biochemical toxicities and listings of out of range biochemistry parameters that could not be graded using NCI-CTC grade (below LLN – normal – above ULN).

For white blood cells (WBC), neutrophils, lymphocytes, platelets and haemoglobin, with associated grade 3 or 4 toxicities, nadir and day to nadir will be calculated (refer to section 7, Appendix 1, Derived data).

3.2.2.4 Vital signs

Vital signs (blood pressure and heart rate) will be listed at each assessment by treatment cohort and subject identifier. Any unscheduled vital signs will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the dose intake of the study drug (predose on Day 1 if available).

Summary statistics (mean, median, SD and range as appropriate) by dose cohort and overall will be presented with actual values and changes from Baseline to each post-baseline visit for each dose cohort and overall.

In addition, a graph of individual heart rate values (in both supine and standing positions) over time from screening to end of study (or early withdrawal if applicable) will be performed for each dose cohort.

3.2.2.5 Physical Examination

Physical examination and weight will be listed by dose cohort, subject identifier and visit. Any unscheduled physical examination will be flagged [U] in the listings.

Baseline values will be defined as the last physical examination performed prior to the dose intake of the study drug (predose on Day 1 if available).

A summary table of weight and BMI with actual values and changes from Baseline to each post-baseline visit will be presented for each dose cohort and overall.

3.2.2.6 ECG

ECG results (12-lead ECG, QT_c interval) will be listed at each assessment by treatment cohort and subject. Any unscheduled ECG will be flagged [U] in the listings.

Baseline will be defined as the last ECG measurement collected prior to the dose intake of the study drug (predose on Day 1 if available).

For continuous ECG parameters, summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each treatment cohort and overall.

For interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a shift table from Baseline to each post-baseline visit will be presented.

For ECG parameters, a listing of clinically significant findings will be provided by treatment cohort and overall.

3.2.2.7 Glycosylated haemoglobin (HbA1c)

Glycosylated haemoglobin (HbA1c) will be assessed by the central laboratory, therefore the same reference value ranges apply to subjects from all study centres. A separate listing of normal ranges for SI units will be provided by gender and age where appropriate.

HbA1c values will be listed in SI units in individual data listings by dose cohort, subject identifier and visit.

Baseline values will be defined as the last assessment of HbA1c collected prior to the dose intake of the study drug (Visit 1 if available).

Summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each dose cohort and overall.

3.2.2.8 Estimated glomerular filtration rate (eGFR)

Estimated glomerular filtration rate will be provided by the central laboratory and calculated from serum creatinine, age, gender and race, according to the Modification of Diet in Renal Disease (MDRD) formula [1].

The same reference value ranges apply to subjects from all study centres. A separate listing of normal ranges for SI units will be provided by gender and age where appropriate.

The eGFR values will be listed in SI units in individual data listings by dose cohort, subject identifier and visit.

Baseline values will be defined as the estimation made with the last measurement of serum creatinine collected prior to the dose intake of the study drug (predose on Day 1 if available).

Summary tables with actual values and changes from Baseline to each post-baseline visit will be presented for each dose cohort and overall, as well as a shift table from Baseline to each post-baseline visit.

3.2.2.9 Gallbladder echography

Gallbladder echography will be listed. Any unscheduled visits will be flagged [U] in the listings. A shift table from baseline (i.e. the assessment at screening) with number and percentage of subjects with presence and absence of lithiasis and sludge will be presented at each visit by dose cohort and overall.

Baseline values will be defined as the gallbladder echography performed prior the dose intake of the study drug (Visit 1 if available).

3.2.2.10 Putative antibodies to lanreotide

Baseline values will be defined as the last evaluation of putative antidrug antibodies (ADA) prior to the dose intake of the study drug (predose on Day 1 if available).

The number and 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).

For subject with putative anti-lanreotide antibodies, summary tables with actual titre values will be presented for each dose cohort and overall. Listing of individual results will also be provided.

3.2.2.11 Evaluation of injection site reactions

Evaluation of injection site reactions will be listed at each assessment by dose cohort and subject. Any unscheduled assessment will be flagged [U] in the listings.

Presence /absence of each symptoms of local tolerance at injection site at each timepoint will be summarized by dose cohort and overall, as well as length, width, and the estimated surface (mm^2) (see Section 7 Appendix 1: Derived Data).

3.2.2.12 Acromegaly symptoms

The number and percentage of subjects with at least one symptom of acromegaly (as described in section 1.3.2.2) at Week 13 and Week 25(EW), as well as the number and percentage of subjects manifesting these symptoms will be summarized by dose cohort and overall.
In addition, a shift table with acromegaly symptoms grade (Absent / Present - Mild / Present - Moderate / Present - Severe) from Baseline to each post-baseline visit will be presented, as well as the shift from baseline to the post-baseline period, i.e. with maximum intensity out of the two post-baseline visits.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

An assessment is considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

For adverse events with missing information for the intensity and causality the value will not be replaced and will be summarized as a separate category. Moreover, to summarize by maximum intensity / relationship when multiple events of the same AE occurs, missing data will not be imputed (section 3.2.2.2).

For all other variables, no imputations will be made for missing data.

3.2.3.2 Missing or incomplete dates

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

(1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

(2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

(3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: a medication with partial start and stop dates could be considered as prior and concomitant treatment).

(4) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

3.2.3.3 Outliers

A search of outliers should be performed before the unblinding and the impact may be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect. The decision of how to handle these outliers will be made during the Data Review Meeting and documented.

3.2.4 Subject disposition

The numbers and percentages of subjects screened, included in the study and included in each of the ITT, Safety and PP populations will be tabulated in total, by centre for each dose cohort

and overall. The reasons for subject exclusions from each of the populations will also be tabulated.

Reasons for exclusion from Per Protocol population will be presented in a summary table by dose cohort.

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

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

A summary table will present the extent of subject exposure in the study for each dose cohort. The definition of the length of exposure is the time interval between the first informed consent form signed to the last EOS or EW visit completed.

3.2.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who completed the study or withdrew from the study and the reasons for withdrawal will be presented by dose cohort and overall for the Safety population.

3.2.6 Demographic and baseline characteristics

All demographic and baseline characteristics, and the acromegaly history will be listed by dose cohort and subject identifier.

Summary statistics will be provided for demographic and baseline characteristics (specify parameters e.g. sex, race, age, age by category (≤ 65, > 65 with details for categories ≤ 30,]30, 65]), height, weight and BMI at screening, post-menopausal status) and for acromegaly history and acromegaly symptoms by dose cohort, for the Safety population.

Meal data at Day 1 will be listed on the Safety population.

No statistical testing between the dose cohorts to assess the homogeneity at baseline will be performed, however descriptive statistics together with 95% confidence intervals will be presented.

3.2.7 Medical and surgical history

Medical and surgical history will be coded using MedDRA Version 19.0 version or higher.

Listings will present the preferred term and verbatim text. The listings will be sorted by dose cohort, subject identifier, primary system organ class, preferred term and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term for each dose cohort and for the Safety population.

3.2.8 Subject compliance

A listing will be presented for drug administration (all captured data) by subject for each dose cohort.

3.2.9 Prior and concomitant therapies

All recorded data will be included in data listings.

3.2.9.1 Prior and Concomitant medications

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 and concomitant medications will be coded by using the World Health Organisation (WHO) Drug Dictionary (Version December 2016).

Medications which started before study entry but are continuing will be considered as both prior and concomitant medications.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by dose cohort, subject identifier, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant medications by drug class and preferred drug name for each dose cohort and overall on the Safety population.

3.2.9.2 Prior and Concomitant medications for acromegaly

Prior medications for acromegaly for the 3 months prior to study entry will be recorded on the eCRF on a specific page, as well as concomitant medications for acromegaly, and they will be coded by using the WHO Drug Dictionary (Version December 2016).

Medications which started after study entry will be considered as concomitant medications.

Listings will include the therapeutic class (i.e., the second level of ATC classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by dose cohort, subject identifier, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

Frequency tables of the number and percentage of subjects will be provided for prior medications for acromegaly and for concomitant medications for acromegaly by drug class and preferred drug name for each dose cohort and overall on the Safety population.

3.2.9.3 Prior and concomitant non-drug therapies

Concomitant non-drug therapies will be coded by using the WHO Drug Dictionary (Version December 2016). Therapies which started and stopped before start of study treatment are considered as prior therapies.

Therapies which started before start of study treatment but are continuing will be considered as both prior and concomitant therapies.

Listings will include the therapeutic class (i.e., the second level of ATC classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by dose cohort, subject identifier, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant therapies by therapeutic class and preferred name for each dose cohort and overall on the Safety population.

3.2.9.4 Concomitant surgical procedures

Concomitant surgical procedures will be recorded in the eCRF and coded by using the WHO Drug Dictionary (Version December 2016).

Listings will include the therapeutic class (i.e., the second level of ATC classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by dose cohort, subject identifier, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by therapeutic class and preferred name for each dose cohort and overall for the Safety population.

3.2.10 Pharmacokinetics and Pharmacodynamics

Analysis of pharmacokinetic and pharmacodynamics data will be performed by a CRO under IPSEN EDD team supervision.

A listing of PK and antibodies sampling time and any deviation from the scheduled time will be provided.

Summaries of the PD endpoints will be provided on the Safety Population, as well as the change from baseline:

- for FT3, FT4, TSH and PRL at Screening, Baseline (predose on Day 1), and at Weeks 2, 5, 13 and 25 (or EW).

- for IGF-1 per method of assessment (Liaison, Immulite 2000 old reagent, Immulite 2000 new standardized reagent) 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). IGF-1 summaries will be also performed using 2 units: SI unit (ng/mL) and percentage of upper limit according to gender and age (%ULN).

Note: In case the number of total data per method overall the study is deemed not sufficient (< 5), no summary statistics will be performed and corresponding data will be listed.

For these parameters, graphs of individual data at all sampling timepoints, and graphs of mean value (with 95% CI) at all sampling timepoints per dose cohort (and per unit and assessment method for IGF-1) as change from baseline will be provided.

In addition, a graph of IGF-1 values at all sampling timepoints per method of assessment and dose cohort will be provided for both units (SI and %ULN).

A graph of GH cycle will be provided for each subject showing the mean on the 5 GH samples along the study; the 5 sampling times being done every 30 minutes for 2 hours (i.e. T0, T0.5, T1.0, T1.5, T2.0) at the following visits: Screening (Visit 1), Baseline predose (Visit 2), and Week 5 (visit 8) and Week 13 (Visit 12).

Mean value (with 95% CI) at all sampling timepoints of the mean of five sampling will be provided per dose cohort as well as change from baseline, and corresponding graphs will be provided.

The corresponding listings will be provided.

In addition, for patients having performed IGF-1 assessments with both Immulite 2000 old reagent and new standardized reagent (see section 5), correlation between the two methods on

change from baseline to Visit 18(EOS or EW) using last observation carried forward (LOCF) will be studied for both units (SI and %ULN) by cohort (applicable for cohort 2 and 3 only) and overall, using Pearson's correlation coefficient. The corresponding overall correlation graph will be provided.

Additional correlation graphs will be provided per unit (SI and %ULN) overall and per cohort for IGF-1 assessments available for both methods.

Further details of the PK analysis will be provided in a separate document.

3.2.11 Derived data

The derived data are variables which are calculated from the raw data recorded in the eCRF or any other support and not included in the database. The derived data will be calculated to be included in tables and listings.

Some specifications of the data derivations necessary for this study are provided in Section 7 Appendix 1: Derived Data.

3.2.12 Visit windows

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

Study phase	Scheduled visit	Time interval (days, hours)
Pre treatment (Screening + Run in period)	Visit 1, Screening	Day -42 to Day -28
Treatment period	Visit 2, Baseline	Predose Day 1 (prior to dose intake)
		Day1, hour 0, **Lanreotide PRF administration**
		Visit 2, Day 1 ±2 days, 6 hours postdose (±10 min)
		Visit 2, Day 2 ±2 days, 24 hours postdose (±2h)
	Visit 3	Day 3±1 day
	Visit 4	Day 5±1 day
	Visit 5	Week 2±1 day
	Visit 6	Week 3±2 days
	Visit 7	Week 4±2 days
	Visit 8	Week 5±2 days
	Visit 9	Week 7±2 days
	Visit 10	Week 9±2 days
	Visit 11	Week 11±2 days
	Visit 12	Week 13±1 day
Follow up period (study visits conducted every 2 weeks (±3 days))	Visit 13	Week 15±3 days
	Visit 14	Week 17±3 days
	Visit 15	Week 19±3 days
	Visit 16	Week 21±3 days
	Visit 17	Week 23±3 days
End of Study Visit (or Early Withdrawal Visit)	Visit 18	Week 25

3.2.13 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number

of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

Summary statistics will be presented for continuous variables, by way of n, number of missing values, arithmetic mean, standard deviation (SD), median, range (minimum, maximum) and by way of group frequencies and percentages for categories of categorical variables.

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

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

Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean). In case a confidence interval is calculated for a parameter that can't be negative, the lower bound will be forced to 0.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, <4.5) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.14 Pooling of Centres

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

3.2.15 Interim analysis

One interim analysis will be performed to facilitate the planning of future clinical studies of lanreotide PRF. The cut-off date will be 3 months after patient #26 is treated, which is equivalent to the Visit 12 date.

3.2.16 Role of the Data Review Committee (DRC)

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 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).

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.

3.2.17 Covariates and analysis of subgroups

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). This will be discussed and decided during the Data Review Meeting.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows 7.

4.2 Software

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

4.3 Validation programs

SAS® programs are developed to produce clinical study output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Chiltern International SOP CCI "Programming specifications for analysis data sets" provides an overview of the development of such SAS® programs.

Chiltern SOP CCI "Verification of statistical programs and output" describes the quality control procedures that must be performed for all SAS® programs and outputs. Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical study output by checking for their logic, efficiency and commenting, and by inspection of the produced outputs. QC will be performed in accordance with Chiltern Standard Operating System (SOPs) and established QC and Validation plan for this study (Appendix 2 of the SAP).

Copies of the QC documentation produced as confirmation that the validation process has been followed will be provided by Chiltern and will be retained by the sponsor.

4.4 Restitution of the programs

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

5 CHANGES FROM PROTOCOL

It is stated in the section Study design of the protocol, section 1.2, that a maximum of 27 adult subjects, aged 18 to 75 years will be treated in the study.

During the study, the sponsor allowed an additional 28th patient to be dosed as it was considered unethical to not enrol a consented patient who was eligible for the study when the only reason not to include this patient was that the protocol total number of patients had been reached (27 patients). The sponsor also considered this to be a non-significant increase in the number of patients.

Before allowing the 28th patient to be included (dosed), the sponsor also took into consideration that there were no safety concerns during any of the previous Data Review Committee (DRC) meetings. This decision was reconsidered during the DRC meeting which took place on 06 June 2017 to review the data of cohort 3 up to patient #26 completed visit 5.

Two methods were used for IGF-1 measurements; Liaison platform and Immulite Platform.

Within the Immulite platform 2 kits were used (old and new).

- Liaison (first method, used on very few patients at screening, 3 screened (2 screen failure, one patient included measurement only at screening visit)
- Immulite 2000 with old reagent (second method, 1st kit). The reason for the platform change from Liaison to the Immulite 2000 was to align with the platform previously used for IGF-1 measurements and historical data so that there would be continuity in the data modelling by the PDM group
- Immulite 2000 with new standardized reagent (second method, 2nd kit). The reason for the use of this new method is that production of the kits of the previous method was stopped by the vendor, so the kits have been used until their expiry date and then kits switched to this new reagent.

Each one the Liaison, Immulite 2000 old reagent, Immulite 2000 new reagent will be referred to as “method”.

Summary statistics will not be performed on IGF-1 values obtained by Liaison methods data will only be listed.

For other methods, summary statistics will be performed by method type.

Also 2 units will be used: SI unit and IGF1 expressed as % of upper normal limit (according to age and gender).

The following sentence in the protocol section 10.4.7 Safety Evaluation:

“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” was changed in this SAP to include causality to:

“In the event of multiple occurrences of the same adverse events being reported by the same subject, the maximum intensity (grade 5 > grade 4 > grade 3 > grade 2 > grade 1 > missing > not applicable) and the most serious causality (related>missing> not related) will be chosen.”

6 REFERENCES

1 National Kidney Disease Education Program (NKDEP). GFR MDRD calculator for adults (SI units). Accessed 31 July 2014, from http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.asp

2 International Conference on Harmonisation (ICH) E9 Guidance on statistical principles for clinical trials. Federal register Vol 63, No. 179 (September 1998).

7 APPENDICES TO THE SAP TEMPLATE

Appendix 1: Derived Data

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

(1) **Age**

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

(2) **BMI**

BMI (kg/m^2) will be derived as Weight (kg)/[Height(cm)/100]^2 and rounded to the nearest decimal.

(3) **Estimated surface (for local tolerance)**

Estimated surface (mm^2) will be derived as length(mm)*width(mm) and rounded to one decimal.

(4) **Changes from baseline**

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

(5) **Percent change from baseline**

Percent change from baseline will be calculated as a percentage of change from baseline (e.g. 100*(assessment at the visit - assessment at baseline)/(assessment at baseline)).

(6) **Time since administration dose for adverse event**

If the start date of the adverse event is identical to the date of administration, then"<1" day will be presented with the time to onset in hh:mm recorded in the eCRF if it is available. If times are available, the time will be calculated as (start date/time –administration date/time) and presented in days hh:mm. If at least one time is missing and if the time to onset is greater than 24 hours then it will be calculated as (start date - administration date)+1 and presented in days. If the start date and the associated information do not allow to state about the dose received (partial start date or start at administration day without knowing if it started before or after the drug intake), all the time since dose intake will be "<1". If the start date is partial, the time since last dose will be presented as a superior inequality (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the time since dose intake will be as "≥2" days).

(7) **Study exposure**

Study exposure in days will be calculated as (last visit attended - screening date)+1.

(8) **Study day**

Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist). Thus, the study day for any assessment/event on or after study treatment administration will be calculated as:

Date of assessment/event – Date of study treatment +1.

If assessment was before study treatment administration then it will be calculated as:

Date of assessment/event – Date of study treatment.

(9) **Nadir**

A nadir for a subject is defined as the lowest laboratory value during the whole treatment period for that subject. The day to nadir is the number of days between the nadir and the date of study medication intake.

Appendix 2: List of TFLs

Tables

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Table 14.1.1.1	Subject Disposition (Screened Population)
Table 14.1.1.2	Subject Disposition by Study Site (All Included Subjects)
Table 14.1.2	Reasons for Exclusion from the Analysis Sets (Screened Population)
Table 14.1.3	Major Protocol Deviations (ITT Population)
Table 14.1.4	Attended Visits (ITT Population)
Table 14.1.5	Demographics (Safety Population)
Table 14.1.6	Acromegaly History (Safety Population)
Table 14.1.7	Acromegaly Symptoms with Intensity at Study Entry (Safety Population)
Table 14.1.8	Medical and Surgical History (Safety Population)
Table 14.1.9.1	Prior Medications for Acromegaly (Safety Population)
Table 14.1.9.2	Concomitant Medications for Acromegaly (Safety Population)
Table 14.1.9.3	Prior and Concomitant Medications (Safety Population)
Table 14.1.9.4	Prior and Concomitant non-drug Therapies (Safety Population)
Table 14.1.9.5	Concomitant Surgical Procedures (Safety Population)
Table 14.1.9.6	Study Administration and Study Exposure (Safety Population)

14.2 EFFICACY DATA

Non applicable

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

Table 14.3.1.1.1 Primary Safety Endpoint: Summary of DLTs occurring during the first week (up to visit 5 (week 2)) (Safety Population)

Table 14.3.1.1.2 Primary Safety Endpoint: Summary of DLTs occurring during the entire study duration (Safety Population)

Table 14.3.1.2.1 Overall Summary of Adverse Events (Safety Population)

Table 14.3.1.2.2 Treatment Emergent Adverse Events (TEAEs) by Primary System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.2.3 Treatment Emergent Adverse Events by Decreasing Frequency of Preferred Term (Safety Population)

Table 14.3.1.2.4 Related TEAEs by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.2.5 Non-Related TEAEs by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.2.6 TEAEs with Missing Relationship to Treatment by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.2.7 TEAEs by System Organ Class, Preferred Term and Maximum CTC Grade (Safety Population)

Table 14.3.1.2.8 TEAEs Leading to Study Withdrawal by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.2.9 Serious Adverse Events (SAEs) by Primary System Organ Class and Preferred Term (Safety Population)

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1 Listing of Deaths

Table 14.3.2.2 Listing of Serious Adverse Events

Table 14.3.2.3 Listing of AEs Leading To Study Withdrawal

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Listing of Lab Findings: NCI-CTC Grade 3 and 4 and prolonged (4 weeks or more) grade 2 Haematological Toxicities (Safety Population)

Table 14.3.4.2 Listing of Lab Findings: NCI-CTC Grade 3 and 4 and prolonged (4 weeks or more) grade 2 Biochemistry Toxicities (Safety Population)

14.3.5 Laboratory Measurements

Table 14.3.5.1.1 Haematology - Summary Statistics (Safety Population)

Table 14.3.5.1.2 Shift Table of Out of Normal Range Results – Haematology (Safety Population)

Table 14.3.5.1.3 Haematology - Nadir and Day to Nadir (Safety Population)

Table 14.3.5.2.1 Biochemistry - Summary Statistics (Safety Population)

Table 14.3.5.2.2 Biochemistry – Shift Table (Safety Population)

Table 14.3.5.2.3.1 Bilirubin by Normal Range (Safety Population)

Table 14.3.5.2.3.2 AST by Normal Range (Safety Population)

Table 14.3.5.2.3.3 ALT by Normal Range (Safety Population)

Table 14.3.5.2.3.4 Lipase by Normal Range (Safety Population)

Table 14.3.5.2.3.5 Alkaline phosphatase by Normal Range (Safety Population)

Table 14.3.5.3.1 Coagulation - Summary Statistics (Safety Population)

14.3.6 Other Safety Data

Listings

16.1.7 Randomisation Scheme and Codes
16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued Subjects

Listing 16.2.1.1 Informed Consent (All enrolled Subjects)
Listing 16.2.1.2 Visit Dates (All Screened Subjects)
Listing 16.2.1.3 Subject Disposition (All Screened Subjects)
Listing 16.2.1.4 Inclusion/Exclusion Criteria Descriptions
Listing 16.2.1.5 Inclusion/Exclusion Criteria Deviations

16.2.2 Protocol deviations

Listing 16.2.2.1: Protocol Deviations

16.2.3 Subjects excluded from the efficacy analysis

Non applicable

16.2.4 Demographic data

Listing 16.2.4.1 Subject Demography (all enrolled subjects)
Listing 16.2.4.2 Postmenopausal Status
Listing 16.2.4.3 Acromegaly History
Listing 16.2.4.4 Significant Medical and Surgical History
Listing 16.2.4.5 Acromegaly Symptoms
Listing 16.2.4.6 Prior Medications for Acromegaly
Listing 16.2.4.7 Concomitant Medications for Acromegaly
Listing 16.2.4.8 Prior and Concomitant Medications
Listing 16.2.4.9 Prior and Concomitant Non-Drug Therapies
Listing 16.2.4.10 Concomitant Surgical Procedures
Listing 16.2.4.11 Meal Data on Day 1

16.2.5 Compliance and/or drug concentration data (if available)

Listing 16.2.5.1 Study Treatment Administration
Listing 16.2.5.2 All Visit Dates
Listing 16.2.5.3 Pharmacokinetics Blood Sample Collection
Listing 16.2.5.4 Hospitalisation

16.2.6 Individual efficacy response data

Non applicable

16.2.7 Adverse event listings (each subject)

Listing 16.2.7.1 Summary of DLTs Occurring During the First Week (Up To Visit 5 (Week 2))

Listing 16.2.7.2 Summary of DLTs Occurring During the Entire Study Duration

Listing 16.2.7.3 Listing of AEs Defined as DLT

Listing 16.2.7.4 Listing of Abnormal Laboratory Values Defined as DLT

Listing 16.2.7.5 Listing of Relevant Toxicities: Grade ≥3 Cholelithiasis-Related Gallbladder Obstruction or Cholecystitis

Listing 16.2.7.6 Listing of Relevant Toxicities: Grade ≥3 Injection Site Reaction

Listing 16.2.7.7 Listing of Relevant Toxicities: Prolonged Grade 2 Toxicities or Investigation Abnormalities

Listing 16.2.7.8 Listing of all Adverse Events

Listing 16.2.7.9 Listing of Serious Adverse Events

Listing 16.2.7.10 Listing of AEs Leading To Death

Listing 16.2.7.11 Listing of AEs Leading To Study Withdrawal

16.2.8 Listing of individual laboratory measurements by subject

Listing 16.2.8.1: Normal Range for SI Units

Listing 16.2.8.2: Laboratory Results: Haematology

Listing 16.2.8.3: Laboratory Results: Biochemistry

Listing 16.2.8.4: Laboratory Results: Coagulation

Listing 16.2.8.5: Laboratory Results: Urinalysis

16.2.9 Listing of other safety data

Listing 16.2.9.1: Vital Signs

Listing 16.2.9.2: Weight and Body Mass Index

Listing 16.2.9.3: Physical Examination

Listing 16.2.9.4.1: Electrocardiogram

Listing 16.2.9.4.2: Electrocardiogram

Listing 16.2.9.5: Glycosylated Haemoglobin (HbA1c)

Listing 16.2.9.6: Estimated Glomerular Filtration (eGFR)

Listing 16.2.9.7: Gallbladder Echography

Listing 16.2.9.8.1: Putative Antibodies to Lanreotide

Listing 16.2.9.8.2: Putative Antibodies to Lanreotide Samples

Listing 16.2.9.9: Pharmacokinetic Blood Samples

Listing 16.2.9.10: Evaluation of Injection Site Reactions

Listing 16.2.11.1: PD Parameters - Central Laboratory Blood Data Samples - IGF-1

Listing 16.2.9.11.2: PD Parameters: IGF-1 Results

Listing 16.2.9.11.3: Other PD Parameters: FT3, FT4, TSH, PRL

Listing 16.2.9.11.4: PD parameters: Mean results by cohort