



Clinical trial results:

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 prolonged release formulation in subjects with acromegaly previously treated and controlled with either ocreotide Long Acting Release or lanreotide Autogel.

Summary

EudraCT number	2014-002389-62
Trial protocol	GB BE DE NL CZ LT ES IT PL
Global end of trial date	28 November 2017

Results information

Result version number	v1 (current)
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	8-55-52030-309
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02396953
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen
Sponsor organisation address	65 quai George Gorse, Boulogne Billancourt, France, 92100
Public contact	Medical Director, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2017
Global end of trial reached?	Yes
Global end of trial date	28 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was 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.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki in accordance with the International Council for Harmonisation Consolidated Guideline on Good Clinical Practice and in compliance with Independent Ethics Committees /Institutional Review Boards and informed consent regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	28
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label, dose-ascending study to assess the PK, pharmacodynamics (PD), safety and tolerability of a single dose of lanreotide PRF. 17 centres recruited adult subjects with acromegaly into 3 lanreotide PRF treatment cohorts (180 milligrams [mg], 270 mg and 360 mg).

Pre-assignment

Screening details:

Screening of subjects took place 28 to 42 days before administration of study treatment (Day -42 to Day -28). Overall, 60 subjects were screened during this run-in period; 32 of whom were screening failures and 28 subjects were enrolled and treated with lanreotide PRF.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	180 mg Lanreotide PRF

Arm description:

On Day 1, 3 initial subjects in Cohort 1 received a subcutaneous injection of 180 mg lanreotide PRF and a 12-week treatment period then commenced. The dose escalation proceeded with a 3+3+3 scheme. If 0 or 1 out of the 3 dosed subjects had experienced a Dose Limiting Toxicity (DLT), 3 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the Data Review committee (DRC) would have allowed the dose to be escalated to 270 mg (Cohort 2). At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until end of study (EOS) at Week 25 or early withdrawal (EW).

Arm type	Experimental
Investigational medicinal product name	Lanreotide PRF
Investigational medicinal product code	
Other name	Lanreotide acetate
Pharmaceutical forms	Prolonged-release solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock on Day 1 of the 12 week treatment period. The formulation was supplied in prefilled syringe and delivered 180 mg lanreotide base.

Arm title	270 mg Lanreotide PRF
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Arm description:

On Day 1, 1 initial subject in Cohort 2 received 270 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 2 subjects were treated and reviewed on a 1+2+2+2+2 scheme. If no DLT was experienced, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have stopped, and the dose was declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the DRC would have allowed dose to be escalated to 360 mg (Cohort 3).

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Arm type	Experimental
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Investigational medicinal product name	Lanreotide PRF
Investigational medicinal product code	
Other name	Lanreotide acetate
Pharmaceutical forms	Prolonged-release solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock on Day 1 of the 12 week treatment period. The formulation was supplied in a prefilled syringe and delivered 270 mg lanreotide base.

Arm title	360 mg Lanreotide PRF
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Arm description:

On Day 1, 2 initial subjects in Cohort 3 received 360 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 3 subjects were treated and reviewed on a 2+2+2+3 scheme. An additional subject was also dosed in this cohort as it was considered unethical to exclude an eligible subject. If 0 or 1 subject had experienced a DLT, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose was declared the maximum administered dose.

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Arm type	Experimental
Investigational medicinal product name	Lanreotide PRF
Investigational medicinal product code	
Other name	Lanreotide acetate
Pharmaceutical forms	Prolonged-release solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock on Day 1 of the 12 week treatment period. The formulation was supplied in a prefilled syringe and delivered 360 mg lanreotide base.

Number of subjects in period 1	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF
Started	9	9	10
Completed	5	6	7
Not completed	4	3	3
Consent withdrawn by subject	-	-	1
Insulin like Growth Factor-1 increased	3	2	2
Personal Reasons	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	180 mg Lanreotide PRF
Reporting group description:	
On Day 1, 3 initial subjects in Cohort 1 received a subcutaneous injection of 180 mg lanreotide PRF and a 12-week treatment period then commenced. The dose escalation proceeded with a 3+3+3 scheme. If 0 or 1 out of the 3 dosed subjects had experienced a Dose Limiting Toxicity (DLT), 3 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the Data Review committee (DRC) would have allowed the dose to be escalated to 270 mg (Cohort 2). At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until end of study (EOS) at Week 25 or early withdrawal (EW).	
Reporting group title	270 mg Lanreotide PRF
Reporting group description:	
On Day 1, 1 initial subject in Cohort 2 received 270 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 2 subjects were treated and reviewed on a 1+2+2+2+2 scheme. If no DLT was experienced, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have stopped, and the dose was declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the DRC would have allowed dose to be escalated to 360 mg (Cohort 3). At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.	
Reporting group title	360 mg Lanreotide PRF
Reporting group description:	
On Day 1, 2 initial subjects in Cohort 3 received 360 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 3 subjects were treated and reviewed on a 2+2+2+3 scheme. An additional subject was also dosed in this cohort as it was considered unethical to exclude an eligible subject. If 0 or 1 subject had experienced a DLT, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose was declared the maximum administered dose. At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.	

Reporting group values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF
Number of subjects	9	9	10
Age categorical			
Units: Subjects			
Adults (18-64 years)	8	9	7
From 65-84 years	1	0	3
Age continuous			
Units: years			
arithmetic mean	57.4	52.1	56.2
standard deviation	± 7.2	± 8.7	± 11.6
Gender categorical			
Units: Subjects			
Female	6	5	4
Male	3	4	6
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	9	9	10
More than one race	0	0	0
Inknown or Not Reported	0	0	0
Prior Acromegaly Medication			
Units: Subjects			
Octreotide Long Acting Release (LAR)	9	7	7
Lanreotide Autogel	0	2	3

Reporting group values	Total		
Number of subjects	28		
Age categorical			
Units: Subjects			
Adults (18-64 years)	24		
From 65-84 years	4		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	15		
Male	13		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	28		
More than one race	0		
Inknown or Not Reported	0		
Prior Acromegaly Medication			
Units: Subjects			
Octreotide Long Acting Release (LAR)	23		
Lanreotide Autogel	5		

End points

End points reporting groups

Reporting group title	180 mg Lanreotide PRF
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Reporting group description:

On Day 1, 3 initial subjects in Cohort 1 received a subcutaneous injection of 180 mg lanreotide PRF and a 12-week treatment period then commenced. The dose escalation proceeded with a 3+3+3 scheme. If 0 or 1 out of the 3 dosed subjects had experienced a Dose Limiting Toxicity (DLT), 3 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the Data Review committee (DRC) would have allowed the dose to be escalated to 270 mg (Cohort 2). At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until end of study (EOS) at Week 25 or early withdrawal (EW).

Reporting group title	270 mg Lanreotide PRF
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Reporting group description:

On Day 1, 1 initial subject in Cohort 2 received 270 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 2 subjects were treated and reviewed on a 1+2+2+2+2 scheme. If no DLT was experienced, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have stopped, and the dose was declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the DRC would have allowed dose to be escalated to 360 mg (Cohort 3).

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Reporting group title	360 mg Lanreotide PRF
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Reporting group description:

On Day 1, 2 initial subjects in Cohort 3 received 360 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 3 subjects were treated and reviewed on a 2+2+2+3 scheme. An additional subject was also dosed in this cohort as it was considered unethical to exclude an eligible subject. If 0 or 1 subject had experienced a DLT, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose was declared the maximum administered dose.

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Subject analysis set title	Lanreotide PK Set: 180 mg Lanreotide PRF
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The PK valid population consisted of subjects who received at least 1 dose and had no major protocol deviations affecting the PK variables, and who had a sufficient number of serum lanreotide concentrations to estimate the main PK parameters. The lanreotide PK dataset included the 9 subjects from the PK valid population who were not pre-treated with lanreotide and who received 1 deep subcutaneous injection of 180 mg lanreotide PRF.

Subject analysis set title	Lanreotide PK Set: 270 mg Lanreotide PRF
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The PK valid population consisted of subjects who received at least 1 dose and had no major protocol deviations affecting the PK variables, and who had a sufficient number of serum lanreotide concentrations to estimate the main PK parameters. The lanreotide PK dataset included the 7 subjects from the PK valid population who were not pre-treated with lanreotide and who received 1 deep subcutaneous injection of 270 mg lanreotide PRF. The 2 subjects previously treated with a stable dose of lanreotide Autogel were expected to have a detectable pre-dose concentration and it was considered relevant to exclude them.

Subject analysis set title	Lanreotide PK Set: 360 mg Lanreotide PRF
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The PK valid population consisted of subjects who received at least 1 dose and had no major protocol deviations affecting the PK variables, and who had a sufficient number of serum lanreotide

concentrations to estimate the main PK parameters. The lanreotide PK dataset included 6 subjects from the PK valid population who were not pre-treated with lanreotide and who received 1 deep subcutaneous injection of 360 mg lanreotide PRF. The 3 subjects previously treated with a stable dose of lanreotide Autogel were expected to have a detectable pre-dose concentration and it was considered relevant to exclude them.

Subject analysis set title	Glycofurol PK Set: 180 mg Lanreotide PRF
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK valid population consisted of subjects who received at least 1 dose and had no major protocol deviations affecting the PK variables, and who had a sufficient number of serum lanreotide concentrations to estimate the main PK parameters. This glycofurol dataset included 9 subjects from the PK valid population who had a sufficient number of serum glycofurol concentrations to estimate the main glycofurol PK parameters and who received 1 deep subcutaneous injection of 180 mg lanreotide PRF.

Subject analysis set title	Glycofurol PK Set: 270 mg Lanreotide PRF
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK valid population consisted of subjects who received at least 1 dose and had no major protocol deviations affecting the PK variables, and who had a sufficient number of serum lanreotide concentrations to estimate the main PK parameters. This glycofurol dataset included 9 subjects from the PK valid population who had a sufficient number of serum glycofurol concentrations to estimate the main glycofurol PK parameters and who received 1 deep subcutaneous injection of 270 mg lanreotide PRF.

Primary: Determination of the MTD by Number of Subjects With DLTs.

End point title	Determination of the MTD by Number of Subjects With DLTs. ^[1]
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End point description:

The MTD was defined based on the DLTs observed in each cohort. A DLT was defined as an adverse event (AE) (excluding anorexia and fatigue) or an abnormal laboratory value occurring within the first week (up to Week 2) following lanreotide PRF administration and during the entire study duration, assessed as unrelated to acromegaly, intercurrent illness or concomitant medications and which met any of the pre-established toxicity criteria. If no DLTs were reported then no MTD could be defined. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment.

End point type	Primary
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End point timeframe:

From Day 1 up to Week 25.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	10	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: PK Analysis of Lanreotide: Maximum Observed Serum Concentration (C_{max}).

End point title	PK Analysis of Lanreotide: Maximum Observed Serum Concentration (C _{max}). ^[2]
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End point description:

Blood samples for determination of lanreotide serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose, on Days 3 and 5 and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Mean serum lanreotide Cmax values were determined using non-compartmental analysis. Only subjects with data available for analysis and who were not pre-treated with lanreotide are presented.

End point type	Primary
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End point timeframe:

From Baseline (pre-dose) up to Day 85

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	Lanreotide PK Set: 180 mg Lanreotide PRF	Lanreotide PK Set: 270 mg Lanreotide PRF	Lanreotide PK Set: 360 mg Lanreotide PRF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	7	6	
Units: nanograms/millilitre (ng/mL)				
arithmetic mean (standard deviation)	19.0 (± 15.7)	14.0 (± 10.3)	20.5 (± 5.86)	

Statistical analyses

No statistical analyses for this end point

Primary: PK Analysis of Lanreotide: Time to Reach Maximum Serum Concentration (Tmax).

End point title	PK Analysis of Lanreotide: Time to Reach Maximum Serum Concentration (Tmax). ^[3]
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End point description:

Blood samples for determination of lanreotide serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose, on Days 3 and 5 and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Median serum lanreotide Tmax values were determined using non-compartmental analysis. Only subjects with data available for analysis and who were not pre-treated with lanreotide are presented.

End point type	Primary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	Lanreotide PK Set: 180 mg Lanreotide PRF	Lanreotide PK Set: 270 mg Lanreotide PRF	Lanreotide PK Set: 360 mg Lanreotide PRF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	7	6	
Units: days				
median (full range (min-max))	0.250 (0.167 to 1.00)	0.253 (0.167 to 1.00)	0.250 (0.167 to 0.333)	

Statistical analyses

No statistical analyses for this end point

Primary: PK Analysis of Lanreotide: Apparent Terminal Elimination Half-life (t_{1/2}).

End point title	PK Analysis of Lanreotide: Apparent Terminal Elimination Half-life (t _{1/2}). ^[4]
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End point description:

Blood samples for determination of lanreotide serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose, on Days 3 and 5 and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Mean serum lanreotide t_{1/2} values were determined using non-compartmental analysis. Only values fulfilling the determination rules for t_{1/2} were analysed. Only subjects with data available for analysis and who were not pre-treated with lanreotide are presented.

End point type	Primary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	Lanreotide PK Set: 180 mg Lanreotide PRF	Lanreotide PK Set: 270 mg Lanreotide PRF	Lanreotide PK Set: 360 mg Lanreotide PRF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	5	4	
Units: days				
arithmetic mean (standard deviation)	54.2 (± 17.0)	61.7 (± 13.9)	63.1 (± 13.3)	

Statistical analyses

No statistical analyses for this end point

Primary: PK Analysis of Lanreotide: Area Under the Serum Concentration-time Curve From Time 0 to 85 Days (AUC₀₋₈₅).

End point title	PK Analysis of Lanreotide: Area Under the Serum Concentration-time Curve From Time 0 to 85 Days (AUC ₀₋₈₅). ^[5]
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End point description:

Blood samples for determination of lanreotide serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose, on Days 3 and 5 and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Mean serum lanreotide AUC₀₋₈₅ values were determined using non-compartmental analysis. Only subjects with data available for analysis and who were not pre-treated with lanreotide are presented.

End point type	Primary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	Lanreotide PK Set: 180 mg Lanreotide PRF	Lanreotide PK Set: 270 mg Lanreotide PRF	Lanreotide PK Set: 360 mg Lanreotide PRF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	7	6	
Units: ng*day/mL				
arithmetic mean (standard deviation)	161 (± 97.6)	179 (± 54.2)	265 (± 87.1)	

Statistical analyses

No statistical analyses for this end point

Primary: PK Analysis of Lanreotide: Area Under the Serum Concentration-time Curve Extrapolated to Infinity (AUC0-∞).

End point title	PK Analysis of Lanreotide: Area Under the Serum Concentration-time Curve Extrapolated to Infinity (AUC0-∞). ^[6]
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End point description:

Blood samples for determination of lanreotide serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose, on Days 3 and 5 and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Mean serum lanreotide AUC0-∞ values were determined using non-compartmental analysis. Only values fulfilling the accuracy determination rules for AUC0-∞ were analysed. Only subjects with data available for analysis and who were not pre-treated with lanreotide are presented.

9999999 = not determined (i.e. when more than 1/3 of the values did not fulfil accuracy determination rules, the descriptive statistics were not calculated).

End point type	Primary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this was a dose ascending study, no comparative analyses were performed.

End point values	Lanreotide PK Set: 180 mg Lanreotide PRF	Lanreotide PK Set: 270 mg Lanreotide PRF	Lanreotide PK Set: 360 mg Lanreotide PRF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	2	3	
Units: ng*day/mL				
arithmetic mean (standard deviation)	9999999 (± 9999999)	9999999 (± 9999999)	9999999 (± 9999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Summary of Number of Subjects With AEs.

End point title	Overall Summary of Number of Subjects With AEs.
End point description: AEs reported by the investigators using the National Cancer Institute–Common Toxicity Criteria (NCI CTCAE) classification (Version 4.03) and incidence of all reported treatment emergent AEs (TEAEs) and serious AEs (SAEs) are presented by dose cohort for the safety population. AEs were assigned to a NCI CTCAE Grade from 1 through 5 as follows: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe or medically significant but not immediately life threatening or requiring hospitalisation; Grade 4: Life-threatening consequences; Grade 5: Death related to AE. TEAEs were defined as any AE that occurs during the active phase of the study (between the start of the 3 month treatment period and 3 months after the end of study treatment). The worst intensity of TEAEs at each grade are reported for all and for related TEAEs. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity and the most serious causality were reported.	
End point type	Secondary
End point timeframe: From Day -42 up to Week 25.	

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	10	
Units: Subjects				
TEAEs	6	7	7	
Related TEAEs	2	3	4	
TEAEs leading to study drug withdrawal	0	0	0	
SAEs	1	0	1	
Serious TEAEs	1	0	1	
Serious related TEAEs	0	0	0	
AEs leading to death	0	0	0	
Worst TEAE: Grade 1	1	3	5	
Worst TEAE: Grade 2	3	4	1	
Worst TEAE: Grade 3	2	0	1	
Worst TEAE: Grade 4	0	0	0	
Worst TEAE: Grade 5	0	0	0	
Worst related TEAE: Grade 1	0	1	3	
Worst related TEAE: Grade 2	2	2	1	
Worst related TEAE: Grade 3	0	0	0	
Worst related TEAE: Grade 4	0	0	0	
Worst related TEAE: Grade 5	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis of Glycofurol Excipients: Cmax.

End point title	PK Analysis of Glycofurol Excipients: Cmax.
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End point description:

Blood samples for determination of the excipients (N1-glycofurol and N2-glycofurol) serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose and on Days 3 and 5. Mean serum N1- glycofurol and N2-glycofurol Cmax values were determined using non-compartmental analysis. Only subjects with data available for analysis are presented. Due to bioanalytical issues, no results for the excipient N1-glycofurol and N2-glycofurol for 360 mg Lanreotide PRF (cohort 3) were available at the time of the PK analysis.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Day 5.

End point values	Glycofurol PK Set: 180 mg Lanreotide PRF	Glycofurol PK Set: 270 mg Lanreotide PRF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
N1-glycofurol	75.4 (± 65.6)	61.7 (± 17.2)		
N2-glycofurol	79.7 (± 72.1)	62.1 (± 18.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis of Glycofurol Excipients: Tmax.

End point title	PK Analysis of Glycofurol Excipients: Tmax.
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End point description:

Blood samples for determination of the excipients (N1-glycofurol and N2-glycofurol) serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose and on Days 3 and 5. Median serum N1-glycofurol and N2-glycofurol Tmax values were determined using non-compartmental analysis. Only subjects with data available for analysis are presented. Due to bioanalytical issues, no results for the excipient N1-glycofurol and N2-glycofurol for 360 mg Lanreotide PRF (cohort 3) were available at the time of the PK analysis.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Day 5.

End point values	Glycofurol PK Set: 180 mg Lanreotide PRF	Glycofurol PK Set: 270 mg Lanreotide PRF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: hours				
median (full range (min-max))				
N1-glycofurol	2.00 (1.00 to 3.92)	2.00 (1.00 to 4.00)		

N2-glycofurol	2.00 (1.00 to 3.92)	2.00 (1.00 to 4.00)		
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Statistical analyses

No statistical analyses for this end point

Secondary: PK Analysis of Glycofurol Excipients: AUC0-∞ and Area Under the Serum Concentration Time Curve From Time 0 to Last Quantifiable Timepoint (AUC0-t).

End point title	PK Analysis of Glycofurol Excipients: AUC0-∞ and Area Under the Serum Concentration Time Curve From Time 0 to Last Quantifiable Timepoint (AUC0-t).
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End point description:

Blood samples for determination of the excipients (N1-glycofurol and N2-glycofurol) serum concentrations were collected at Baseline (pre-dose), at 1, 2, 4, 6, 8, 12 and 24 hours post-dose and on Days 3 and 5. Mean serum N1-glycofurol and N2-glycofurol AUC0-∞ and AUC0-t values were determined using non-compartmental analysis. Only AUC0-∞ values fulfilling the accuracy determination rules were analysed. Due to bioanalytical issues, no results for the excipient N1-glycofurol and N2-glycofurol for 360 mg Lanreotide PRF (cohort 3) were available at the time of the PK analysis.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Day 5.

End point values	Glycofurol PK Set: 180 mg Lanreotide PRF	Glycofurol PK Set: 270 mg Lanreotide PRF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[7]	9 ^[8]		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AUC0-∞: N1-glycofurol	779 (± 205)	1049 (± 195)		
AUC0-∞: N2-glycofurol	1008 (± 268)	1359 (± 282)		
AUC0-t: N1-glycofurol	783 (± 193)	1082 (± 238)		
AUC0-t: N2-glycofurol	1007 (± 257)	1360 (± 285)		

Notes:

[7] - AUC0-∞: 8 subjects analysed.

[8] - AUC0-∞: 8 subjects analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: PD Analysis: Mean Change From Baseline in Insulin-like Growth Factor 1 (IGF-1).

End point title	PD Analysis: Mean Change From Baseline in Insulin-like Growth Factor 1 (IGF-1).
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End point description:

Blood samples were collected for the determination of IGF-1 in serum at Baseline (pre-dose), 6 hours

post-dose and at Weeks 5, 9 and 13. Samples were also collected during follow-up at Weeks 17, 21 and 25 (or EW). Serum concentrations of IGF-1 were calculated using the Immulite 2000 Platform for all subjects in the safety population. The production of the reagent kits was stopped by the vendor during the study. The old reagent kits were used for Cohorts 1 and 2 until their expiry date and then the kits were switched to a new reagent and used for remaining subjects in Cohorts 2 and 3. Summary data for serum concentrations of IGF-1 were obtained using both methods (old and new reagent) and the mean change from Baseline at each time point is presented. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment. Only subjects with data available for analysis are presented. 9999999 = not calculable.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[9]	9 ^[10]	10 ^[11]	
Units: ng/mL				
arithmetic mean (standard deviation)				
Old Reagent: 6 hours post-dose	-1.8 (± 18.9)	-7.1 (± 17.2)	-46.5 (± 46.7)	
Old Reagent: Week 5	2.4 (± 41.3)	27.9 (± 32.8)	-32.0 (± 49.5)	
Old Reagent: Week 9	72.3 (± 61.3)	71.4 (± 72.7)	9999999 (± 9999999)	
Old Reagent: Week 13	53.4 (± 67.9)	111.1 (± 129.3)	9999999 (± 9999999)	
Old Reagent: Week 17	48.3 (± 62.7)	96.2 (± 43.8)	9999999 (± 9999999)	
Old Reagent: Week 21	72.4 (± 84.4)	135.5 (± 80.5)	9999999 (± 9999999)	
Old Reagent: Week 25 (EOS/EW)	86.3 (± 81.4)	136.4 (± 83.5)	9999999 (± 9999999)	
New Reagent: 6 hours post-dose	9999999 (± 9999999)	6.0 (± 5.7)	-11.6 (± 15.9)	
New Reagent: Week 5	9999999 (± 9999999)	3.0 (± 8.5)	1.3 (± 38.4)	
New Reagent: Week 9	9999999 (± 9999999)	13.0 (± 9.9)	25.2 (± 33.6)	
New Reagent: Week 13	9999999 (± 9999999)	30.0 (± 43.8)	47.1 (± 43.9)	
New Reagent: Week 17	9999999 (± 9999999)	20.5 (± 17.7)	40.9 (± 46.8)	
New Reagent: Week 21	9999999 (± 9999999)	65.0 (± 58.0)	56.9 (± 35.6)	
New Reagent: Week 25 (EOS/EW)	9999999 (± 9999999)	45.5 (± 17.7)	64.1 (± 68.0)	

Notes:

[9] - Old : Weeks 13, 17 (n=7), 21 (n=5)

New: all weeks (n=0)

[10] - Old Reagent: 6 h (n=8) Weeks 17 (n=6), 21 (n=4)

New Reagent: all weeks (n= 2)

[11] - Old: 6 h (n=4) Weeks 5 (n=2), 9-25 (n=0)

New: 6 h & Weeks 9 (n=9), 17 (n=8), 21 (n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: PD Analysis: Mean Change From Baseline in Growth Hormone (GH).

End point title	PD Analysis: Mean Change From Baseline in Growth Hormone (GH).
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End point description:

GH cycle assessments were performed by taking 5 samples in the morning (with a sample taken every 30 minutes for 2 hours) at Baseline (pre-dose), Week 5 and Week 13. Summary data for the mean of the 5 samplings of the GH cycle were generated and the mean change from Baseline at each time point is presented. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment. Only subjects with data available for analysis are presented.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Week 13.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[12]	9	10	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 5	0.268 (± 0.344)	0.367 (± 0.926)	-0.228 (± 0.777)	
Week 13	0.667 (± 0.473)	0.684 (± 0.863)	0.003 (± 1.761)	

Notes:

[12] - Week 13 (n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: PD Analysis: Mean Change From Baseline in Free Triiodothyroxine (FT3) and Free Thyroxine (FT4).

End point title	PD Analysis: Mean Change From Baseline in Free Triiodothyroxine (FT3) and Free Thyroxine (FT4).
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End point description:

Blood samples were collected for the determination of FT3 and FT4 in serum at Baseline (pre-dose) and at Weeks 2, 5, 13 and 25 (or EW). Summary data for serum concentrations of FT3 and FT4 were calculated and the mean change from Baseline at each time point is presented. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment. Only subjects with data available for analysis are presented.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[13]	9 ^[14]	10 ^[15]	
Units: picomole/litre (L)				
arithmetic mean (standard deviation)				
FT3: Week 2	-0.278 (± 0.518)	-0.164 (± 0.517)	-0.374 (± 0.479)	
FT3: Week 5	-0.132 (± 0.429)	0.170 (± 0.705)	0.170 (± 0.452)	
FT3: Week 13	0.100 (± 0.590)	0.191 (± 0.912)	0.438 (± 0.481)	
FT3: Week 25 (EOS/EW)	0.268 (± 0.388)	0.295 (± 0.626)	0.396 (± 0.684)	
FT4: Week 2	0.50 (± 1.58)	-0.02 (± 1.43)	-0.68 (± 1.07)	
FT4: Week 5	1.18 (± 2.31)	0.33 (± 2.52)	-0.67 (± 2.19)	
FT4: Week 13	1.69 (± 2.16)	1.80 (± 3.59)	-0.46 (± 1.39)	
FT4: Week 25 (EOS/EW)	0.81 (± 2.5)	1.06 (± 2.39)	0.38 (± 2.03)	

Notes:

[13] - Week 13 (n=7)

[14] - FT4: Week 25 (n=8)

[15] - Weeks 2&5 (n=9)

Statistical analyses

No statistical analyses for this end point

Secondary: PD Analysis: Mean Change From Baseline in Thyroid Stimulating Hormone (TSH).

End point title	PD Analysis: Mean Change From Baseline in Thyroid Stimulating Hormone (TSH).
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End point description:

Blood samples were collected for the determination of TSH in serum at Baseline (pre-dose) and at Weeks 2, 5, 13 and 25 (or EW). Summary data for serum concentrations of TSH were calculated and the mean change from Baseline at each time point is presented. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment. Only subjects with data available for analysis are presented.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[16]	9 ^[17]	10 ^[18]	
Units: mIU/L				
arithmetic mean (standard deviation)				
Week 2	-0.222 (± 0.562)	0.119 (± 0.315)	0.047 (± 0.844)	
Week 5	-0.156 (± 0.577)	0.062 (± 0.670)	0.051 (± 0.534)	
Week 13	-0.404 (± 0.710)	-0.060 (± 0.897)	0.601 (± 1.080)	

Week 25 (EOS/EW)	-0.480 (\pm 0.593)	0.073 (\pm 0.450)	0.235 (\pm 0.671)	
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Notes:

[16] - Week 13 (n=7)

[17] - Week 25 (n=8)

[18] - Weeks 2&5 (n=9)

Statistical analyses

No statistical analyses for this end point

Secondary: PD Analysis: Mean Change From Baseline in Prolactin.

End point title	PD Analysis: Mean Change From Baseline in Prolactin.
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End point description:

Blood samples were collected for the determination of prolactin in serum at Baseline (pre-dose) and at Weeks 2, 5, 13 and 25 (or EW). Summary data for serum concentration of prolactin were calculated and the mean change from Baseline at each time point is presented. The safety population was all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment. Only subjects with data available for analysis are presented.

End point type	Secondary
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End point timeframe:

From Baseline (pre-dose) up to Week 25.

End point values	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[19]	9 ^[20]	10 ^[21]	
Units: mU/L				
arithmetic mean (standard deviation)				
Week 2	-33.2 (\pm 54.9)	37.6 (\pm 36.1)	1.0 (\pm 49.3)	
Week 5	-10.4 (\pm 53.2)	16.3 (\pm 81.2)	0.3 (\pm 50.7)	
Week 13	-1.9 (\pm 66.5)	33.9 (\pm 78.5)	-6.4 (\pm 47.1)	
Week 25 (EOS/EW)	19.3 (\pm 53.5)	58.3 (\pm 86.6)	-3.1 (\pm 55.9)	

Notes:

[19] - Week 13 (n=7)

[20] - Week 25 (n=8)

[21] - Week 2&5 (n=9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each subject was assessed for TEAEs over an approximate 6 month period. TEAEs were collected over the 32 month study duration.

Adverse event reporting additional description:

TEAEs were monitored for the safety population which was defined as all subjects who received the single dose of lanreotide PRF and had at least one post baseline safety assessment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	180 mg Lanreotide PRF
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Reporting group description:

On Day 1, 3 initial subjects in Cohort 1 received 180 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. The dose escalation proceeded with a 3+3+3 scheme. If 0 or 1 out of the 3 dosed subjects had experienced a DLT, 3 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have stopped, and the dose declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the DRC would have allowed the dose to be escalated to 270 mg (Cohort 2).

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Reporting group title	270 mg Lanreotide PRF
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Reporting group description:

On Day 1, 1 initial subject in Cohort 2 received 270 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 2 subjects were treated and reviewed on a 1+2+2+2+2 scheme. If no DLT was experienced, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have stopped, and the dose was declared the maximum administered dose. If ≤ 3 DLTs had been observed in the 9 treated subjects and the overall safety was in line with the known lanreotide safety profile, the DRC would have allowed dose to be escalated to 360 mg (Cohort 3).

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Reporting group title	360 mg Lanreotide PRF
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Reporting group description:

On Day 1, 2 initial subjects in Cohort 3 received 360 mg lanreotide PRF by a single deep subcutaneous injection in the superior, external quadrant of the buttock and a 12-week treatment period then commenced. Cohort 3 subjects were treated and reviewed on a 2+2+2+3 scheme. An additional subject was also dosed in this cohort as it was considered unethical to exclude an eligible subject. If 0 or 1 subject had experienced a DLT, 2 more subjects would have been dosed with the same dose. If more than 3 out of 9 subjects had experienced a DLT, dose escalation would have been stopped and the dose was declared the maximum administered dose.

At the end of the treatment period subjects continued to be assessed over a 12-week follow up period until EOS at Week 25 or EW.

Serious adverse events	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	180 mg Lanreotide PRF	270 mg Lanreotide PRF	360 mg Lanreotide PRF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	7 / 9 (77.78%)	7 / 10 (70.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Orthostatic Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vasculitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Influenza Like Illness			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Injection Site Haematoma			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Injection Site Induration subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Injection Site Pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1
Injection Site Swelling subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Reproductive system and breast disorders Breast Pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Postmenopausal Haemorrhage subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Oropharyngeal Pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Investigations Blood Bilirubin Increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 4	0 / 10 (0.00%) 0
Cardiac disorders Sinus Bradycardia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 3	0 / 10 (0.00%) 0
Nervous system disorders Dizziness			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	2 / 10 (20.00%) 3
Paraesthesia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Iron Deficiency Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Lymphopenia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Eye disorders			
Conjunctival Hyperaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Vision Blurred subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 2
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	3 / 9 (33.33%) 3	0 / 10 (0.00%) 0
Faeces Soft			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Flatulence subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Inguinal Hernia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 9 (22.22%) 2	2 / 10 (20.00%) 3
Renal and urinary disorders Renal Cyst subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Flank Pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal Pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0
Pain In Extremity subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0

Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2014	To provide clarification on questions received from the authorities associated with safety monitoring, the PK of lanreotide PRF, the dose escalation criteria and the dose selection rationale.
12 June 2015	<p>To extend the planned study period to January 2017.</p> <p>To include the option for home visits on Weeks 4, 7, 11, 15, 19 and 23.</p> <p>To increase the IGF-1 limit from within the normal range to $<1.3 \times$ upper limit of normal (ULN) and clarify that the assessment during the Screening period must be analysed by the central laboratory.</p> <p>To reduce the period in which the subject had had radiotherapy from 3 years to 2 years prior to study entry.</p> <p>To clarify that any significant renal abnormalities and/or creatinine values $\geq 1.5 \times$ ULN should be measured during the Screening period and must be analysed by the central laboratory.</p> <p>To include an opportunity to re-test the screening IGF-1 value once if it was just above the $1.3 \times$ ULN limit.</p> <p>To include an option for the Sponsor to conduct an interim analysis in relation to the clinical development of lanreotide PRF.</p>
27 July 2015	<p>To allow up to 3 subjects previously controlled on lanreotide Autogel to be enrolled per cohort of 9.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>To add the possibility not to perform Day 5, according to PK excipient data further to DRC review. If the $t_{1/2}$ of the excipient was short there was no need to follow it any longer. Also, the excipient PK may have also been removed on Day 3.</p> <p>To add a ± 2 day window for Day 1 and 2.</p>
22 March 2016	<p>To allow the addition of safety information gathered from the phase I study D-FR-52030-345 conducted with lanreotide PRF for transparency reasons.</p> <p>To increase the frequency of DRC meetings to ensure closer subject safety monitoring.</p> <p>To extend the study timelines and increase the number of participating sites.</p> <p>To allow more flexibility for the run-in period by extending the run-in period up to 6 weeks under specified circumstances.</p>
16 December 2016	<p>To allow inclusion of subjects with asymptomatic gallstones or sludge, and the re-screening of subjects who previously failed this exclusion criteria.</p> <p>To change the DRC frequency for Cohort 3 from 2+2+2+2+1 to 2+2+2+3.</p> <p>To better clarify the follow-up and reporting of AEs.</p> <p>To include details of withdrawal of consent for biobanking in the protocol for clarity and amend the procedure for the shipment of biobanking samples.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No glycofurol excipient PK results are available for 360mg Lanreotide PRF at this time. A total of 28 subjects were allowed to enrol rather than the 27 subjects planned as it was considered unethical not to enrol a consented eligible subject.
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Notes: