Clinical trial results:
A PHASE II/III, MULTI-CENTRE, PROSPECTIVE, EXPLORATORY, OPEN LABEL STUDY TO ASSESS THE EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG IN THE SYMPTOMATIC TREATMENT OF PATIENTS WITH REFRACTORY DIARRHEA (MEDICAL APPROACH OF REFRACTORY DIARRHEA)

Summary

EudraCT number	2009-009356-20
Trial protocol	BE
Global end of trial date	09 August 2013

Results information

Result version number	v2 (current)
This version publication date	27 February 2016
First version publication date	01 August 2015
Version creation reason	• Correction of full data set Review and correction.

Trial information

Trial identification

Sponsor protocol code	I-48-52030-223

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IPSEN NV
Sponsor organisation address	Guldensporenpark 87, Merelbeke, Belgium, 9820
Public contact	Medical Director, Gastroenterology, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Gastroenterology, 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	31 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2012
Global end of trial reached?	Yes
Global end of trial date	09 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to assess the effect of lanreotide autogel 120 mg on stool frequency in subjects with refractory diarrhea at day 28 (mean of last 7 days) compared to baseline.

Protection of trial subjects:

The Sponsor was responsible for monitoring this data to verify that the rights and well-being of subjects were protected, that trial data were accurate (complete and verifiable to source data) and that the trial was conducted in compliance with the protocol, GCP and regulatory requirements.
All measurements and methods used in the study were standard.
The QOL questionnaires (SF-36 and IBS) are standardized and validated

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2009
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	Belgium: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed as a multicentre study at 18 investigational sites in Belgium of which 11 recruited patients.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	42[1]
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/exclusion: 5
Reason: Number of subjects	Consent withdrawal: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Worldwide numbers reported are per Treatment, ITT group. However, pre-assignment period is reported per Screened group.

Period 1

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

Arms

Arm title	Lanreotide Autogel 120 mg

Arm description:

Lanreotide Autogel 120 mg one subcutaneous injection on Day 1 and Day 28.

Arm type	Experimental
Investigational medicinal product name	Lanreotides
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg of lanreotide. Open the case containing the prefilled syringe and remove the transparent plastic cover. Remove the needle sheath. Hold the syringe perpendicularly and inject deeply as a subcutaneous injection into the upper outer quadrant of the buttock.

Number of subjects in period 1	Lanreotide Autogel 120 mg
Started	36
Completed	27
Not completed	9
Adverse Event	2

Death	1
Lost to follow-up	1
Lack of efficacy	5

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
The Safety population was defined as all subjects who received at least one injection of the study medication.	

Reporting group values	Treatment	Total	
Number of subjects	36	36	
Age categorical			
Units: Subjects			
<30 years	2	2	
>=30 and <65 years	22	22	
>=65 years	12	12	
Age continuous			
Units: years			
arithmetic mean	55.2		
standard deviation	± 16.4	-	
Gender categorical			
Units: Subjects			
Female	24	24	
Male	12	12	
Race			
Units: Subjects			
Caucasian / White	36	36	
SF36 QOL: Physical Functioning			
SF36 QOL includes 1 multi-item scale measuring each of 8 health concepts. These scores are summed to produce raw scale scores for each health concept which are transformed to a 0–100 scale. There is in addition a single-item measure of Health Transition.			
Units: units on a scale			
arithmetic mean	60.5		
standard deviation	± 29.1	-	
SF36 QOL: Role Physical			
Units: units on a scale			
arithmetic mean	39.6		
standard deviation	± 30.9	-	
SF36 QOL: Role Emotional			
Units: units on a scale			
arithmetic mean	52.8		
standard deviation	± 38.7	-	
SF36 QOL: Vitality			
Units: units on a scale			
arithmetic mean	38.8		
standard deviation	± 24.1	-	
SF36 QOL: Mental Health			
Units: units on a scale			
arithmetic mean	47.6		
standard deviation	± 23.1	-	
SF36 QOL: Social Functioning			

Units: units on a scale			
arithmetic mean	41.1		
standard deviation	± 31.2	-	
SF36 QOL: Bodily Pain			
Units: units on a scale			
arithmetic mean	48.7		
standard deviation	± 30.4	-	
SF36 QOL: General Health			
Units: units on a scale			
arithmetic mean	43.9		
standard deviation	± 22.8	-	
IBS QOL: Total Score			
IBS-QOL is a self-report QOL measure specific to IBS that can be used to assess impact of IBS and its treatment. This consists of 34 items, each with a 5 point response scale. Individual responses to 34 items are summed and averaged for a total score and transformed to a 0-100 scale with higher scores indicating better IBS specific QOL.			
Units: units on a scale			
arithmetic mean	47.4		
standard deviation	± 18.5	-	
Score of Stool Consistency (Bristol Stool Form Scale)			
Each patient scored his/her stool on the Bristol Stool Form Scale: Type 1 - Separate hard lumps, like nuts (hard to pass); Type 2 - Sausage-shaped but lumpy; Type 3 - Like a sausage but with cracks on its surface; Type 4 - Like a sausage or snake, smooth and soft; Type 5 - Soft blobs with clear-cut edges (passed easily); Type 6 - Fluffy pieces with ragged edges, a mushy stool; Type 7 - Water no solid pieces, Entirely liquid			
Units: units on a scale			
median	6		
full range (min-max)	5 to 7	-	
Mean Number of Stools			
Units: Number of Stools			
arithmetic mean	5.5		
standard deviation	± 2.3	-	

End points

End points reporting groups

Reporting group title	Lanreotide Autogel 120 mg
Reporting group description:	
Lanreotide Autogel 120 mg one subcutaneous injection on Day 1 and Day 28.	

Primary: Percentage of Patients Having Minimum Reduction of 50% or Normalization (≤3 Stools/ 24hours) in the Mean Number of Stools (mean of last 7 days)

End point title	Percentage of Patients Having Minimum Reduction of 50% or Normalization (≤3 Stools/ 24hours) in the Mean Number of Stools (mean of last 7 days)[1]
End point description:	
Intention to Treat (ITT) Population [All treated subjects with at least 3 Days of available primary efficacy variable data for both Baseline and post Baseline periods].	
End point type	Primary
End point timeframe:	
Day 28	

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: No statistical analysis derived for primary end point.

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percentage of patients				
number (not applicable)				
REDUCTION OF AT LEAST 50% OR NORMALIZATION - Yes	44.4			
REDUCTION OF AT LEAST 50% OR NORMALIZATION - No	55.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in QOL-Quality of Life {Assess Using Short Form (SF-36) and Irritable Bowel Syndrome (IBS-QOL)} Compared to Baseline

End point title	Change in QOL-Quality of Life {Assess Using Short Form (SF-36) and Irritable Bowel Syndrome (IBS-QOL)} Compared to Baseline

End point description:

SF36 QOL includes 1 multi-item scale measuring each of 8 health concepts. These scores are summed to produce raw scale scores for each health concept which are transformed to a 0-100 scale. The lower the score the more disability. The higher the score the less disability. There is in addition a single-item measure of Health Transition.

IBS-QOL is a self-report QOL measure specific to IBS that can be used to assess impact of IBS and its treatment. This consists of 34 items,each with a 5 point response scale.Individual responses to 34 items are summed and averaged for a total score and transformed to a 0-100 scale with higher scores indicating better IBS specific QOL.

ITT Population, Analysis based on number (n) of patients with a valid value.

End point type	Secondary
End point timeframe:	
Baseline (Day 1), Day 21, Day 28, Day 49 and Day 56	

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Units on a scale				
arithmetic mean (standard deviation)				
SF36 QOL: Physical Functioning (D21), n=33	-1.3 (± 20.5)			
SF36 QOL: Physical Functioning (D28), n=34	2.4 (± 19.6)			
SF36 QOL: Physical Functioning (D49), n=26	2.9 (± 18.9)			
SF36 QOL: Physical Functioning (D56), n=35	1.1 (± 23.3)			
SF36 QOL: Role Physical (D21), n=33	4.5 (± 19.6)			
SF36 QOL: Role Physical (D28), n=34	12.9 (± 21.8)			
SF36 QOL: Role Physical (D49), n=26	6.3 (± 28.3)			
SF36 QOL: Role Physical (D56), n=35	11.8 (± 23.5)			
SF36 QOL: Role Emotional (D21), n=33	-0.3 (± 34.8)			
SF36 QOL: Role Emotional (D28), n=34	3.4 (± 40.7)			
SF36 QOL: Role Emotional (D49), n=25	7 (± 35.2)			
SF36 QOL: Role Emotional (D56), n=35	5 (± 39.6)			
SF36 QOL: Vitality (D21), n=32	3.1 (± 22.1)			
SF36 QOL: Vitality (D28), n=33	5.9 (± 22.2)			
SF36 QOL: Vitality (D49), n=24	2.1 (± 24.6)			
SF36 QOL: Vitality (D56), n=34	7.2 (± 23.9)			
SF36 QOL: Mental Health (D21), n=32	5.8 (± 27.9)			
SF36 QOL: Mental Health (D28), n=33	8.3 (± 28.2)			
SF36 QOL: Mental Health (D49), n=24	8.3 (± 27.1)			
SF36 QOL: Mental Health (D56), n=34	10.1 (± 27.7)			
SF36 QOL: Social Functioning (D21), n=31	9.3 (± 27.8)			
SF36 QOL: Social Functioning (D28), n=33	16.7 (± 29.8)			
SF36 QOL: Social Functioning (D49), n=24	19.3 (± 34.8)			
SF36 QOL: Social Functioning (D56), n=33	14 (± 31.5)			
SF36 QOL: Bodily Pain (D21), n=33	-4.6 (± 31.5)			
SF36 QOL: Bodily Pain (D28), n=34	8.3 (± 28.6)			
SF36 QOL: Bodily Pain (D49), n=26	8.8 (± 29.2)			
SF36 QOL: Bodily Pain (D56), n=35	5.3 (± 30.7)			

SF36 QOL: General Health (D21), n=33	-2.8 (± 16)			
SF36 QOL: General Health (D28), n=33	2.8 (± 16.8)			
SF36 QOL: General Health (D49), n=26	4.1 (± 19.1)			
SF36 QOL: General Health (D56), n=34	3.7 (± 19.9)			
IBS QOL: Total Score (D21), n=27	9.9 (± 21.5)			
IBS QOL: Total Score (D28), n=26	13.9 (± 22)			
IBS QOL: Total Score (D49), n=22	16.8 (± 22.5)			
IBS QOL: Total Score (D56), n=29	16.3 (± 22.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Median Score of Stool Consistency (Bristol Stool Form Scale) Compared to Baseline

End point title	Change in Median Score of Stool Consistency (Bristol Stool Form Scale) Compared to Baseline

End point description:

Each patient scored his/her stool on the Bristol Stool Form Scale: Type 1 - Separate hard lumps, like nuts (hard to pass); Type 2 - Sausage-shaped but lumpy; Type 3 - Like a sausage but with cracks on its surface; Type 4 - Like a sausage or snake, smooth and soft; Type 5 - Soft blobs with clear-cut edges (passed easily); Type 6 - Fluffy pieces with ragged edges, a mushy stool; Type 7 - Water no solid pieces, Entirely liquid.

ITT Population; Missing number of subjects = 1

End point type	Secondary

End point timeframe:

Baseline (day 1), day 28 and day 56

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Units on a scale				
median (full range (min-max))				
Change from Baseline to D28 (n=35)	0 (-3 to 1)			
Change from Baseline to D56 (n=35)	-0.5 (-4 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Mean Number of Stools Compared to Baseline

End point title	Percent Change in Mean Number of Stools Compared to Baseline

End point description:

ITT Population; Missing number of subjects = 1

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 28 and Day 56

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percent change				
arithmetic mean (standard deviation)				
Change from Baseline at D28 (n=35)	-25.9 (± 36.7)			
Change from Baseline at D56 (n=35)	-30.7 (± 38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Relative Frequency of Normalization (≤3 Stools) in Subjects

End point title	Change From Baseline in Relative Frequency of Normalization (≤3 Stools) in Subjects

End point description:

Normalization of stool frequency in subjects with refractory diarrhoea at Day 28 and Day 56 (mean of last 7 days) compared to Baseline.

ITT Population; Missing number of subjects = 1.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 28 and Day 56.

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of days per Week				
arithmetic mean (standard deviation)				
Change from Baseline to D28 (n=35)	27.5 (± 34.7)			
Change from Baseline to D56 (n=35)	33 (± 34.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Having Minimum Reduction of At Least 50% or Normalization of the Mean Number of Stools

End point title	Percentage of Patients Having Minimum Reduction of At Least 50% or Normalization of the Mean Number of Stools

End point description:

ITT Population; Missing number of subjects: 1.

End point type	Secondary

End point timeframe:

Day 56

End point values	Lanreotide Autogel 120 mg			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of participants				
number (not applicable)				
Reduction of at least 50% or normalization - Yes	54.3			
Reduction of at least 50% or normalization - No	45.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 56 (± 2)

Adverse event reporting additional description:

Treatment Emergent Adverse Event (TEAE)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Adverse Events

Reporting group description: -

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 36 (13.89%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Steatorrhoea			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal fistula			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 36 (83.33%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Injection site nodule			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 36 (25.00%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Steatorrhoea			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2009	. Trial is phase II/III instead of phase III . Oral contraception is not sufficient in view of the studied disease and should therefore be deleted form the eligibility criteria
25 January 2012	The main reason for the amendment was to clarify the inclusion criterium 01 and to prolong the inclusion period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported