



Clinical trial results:

Phase III, randomised, double-blind, stratified comparative, placebo controlled, parallel group, multicentre study to assess the effect of deep subcutaneous injections of lanreotide Autogel 120 mg administered every 28 days on tumour progression free survival in patients with non functioning entero-pancreatic endocrine tumour.

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2005-004904-35 |
| Trial protocol | GB NL BE DK CZ GR SE DE AT IT SK ES |
| Global end of trial date | 09 April 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 04 June 2016 |
| First version publication date | 04 June 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | Protocol2-55-52030-726 |
|-----------------------|------------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------|
| Sponsor organisation name | IPSEN PHARMA SAS |
| Sponsor organisation address | 65 quai Georges Gorse, Boulogne Billancourt Cedex , France, 92650 |
| Public contact | Medical Director, Gastroenterology, Ipsen Pharma S.A.S, clinical.trials@ipsen.com |
| Scientific contact | Medical Director, Gastroenterology, Ipsen Pharma S.A.S, 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 | 11 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 April 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 April 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the effect of lanreotide Autogel 120 mg administered every 28 days compared to placebo, on progression-free survival in patients with well or moderately differentiated non functioning entero-pancreatic endocrine tumour.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 22 June 2006 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 30 |
| Country: Number of subjects enrolled | Slovakia: 6 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Country: Number of subjects enrolled | Austria: 14 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Germany: 14 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | United States: 30 |
| Country: Number of subjects enrolled | India: 4 |
| Worldwide total number of subjects | 204 |
| EEA total number of subjects | 170 |

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) | 111 |
| From 65 to 84 years | 91 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

264 subjects were screened at 48 investigational sites in 14 countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, United Kingdom and the United States of America). 204 subjects were randomised to receive study treatment in the Intent to treat (ITT) population.

Pre-assignment

Screening details:

A total of 264 subjects were screened for this study. There were 101 subjects randomised to receive lanreotide Autogel 120 mg and 103 subjects randomised to receive placebo. These 204 randomised subjects form the ITT population for analysis.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Two sets of individual sealed code break envelopes were prepared by an Ipsen Randomisation Manager to enable code break procedures of individual subjects without compromising the blind of the study.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|----------------------------------|
| Arm title | Lanreotide (Autogel Formulation) |
|------------------|----------------------------------|

Arm description:

120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| | |
|----------------------------------------|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lanreotide Autogel 120 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

120 mg

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| | |
|----------------------------------------|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

NA

| Number of subjects in period 1 | Lanreotide (Autogel Formulation) | Placebo |
|---------------------------------------|----------------------------------|---------|
| Started | 101 | 103 |
| Completed | 56 | 34 |
| Not completed | 45 | 69 |
| Consent withdrawn by subject | 3 | 5 |
| Physician decision | 6 | 9 |
| Disease progression | 27 | 49 |
| Not otherwise specified | 4 | 1 |
| Adverse event | 3 | 3 |
| Protocol deviation | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Lanreotide (Autogel Formulation) |
|-----------------------|----------------------------------|

Reporting group description:

120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| Reporting group values | Lanreotide (Autogel Formulation) | Placebo | Total |
|------------------------|----------------------------------|---------|-------|
| Number of subjects | 101 | 103 | 204 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------|--------|--------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63 | 62 | - |
| standard deviation | ± 10 | ± 11 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 48 | 49 | 97 |
| Male | 53 | 54 | 107 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 2 | 5 | 7 |
| Black or African American | 2 | 2 | 4 |
| White | 97 | 96 | 193 |
| Neuroendocrine tumour (NET) origin | | | |
| Units: Subjects | | | |
| Pancreas | 42 | 49 | 91 |
| Midgut | 33 | 40 | 73 |
| Hindgut | 11 | 3 | 14 |
| Unknown/Other | 15 | 11 | 26 |
| Chromogranin A | | | |
| Chromogranin A is an NET marker. ULN: upper limit of normal | | | |
| Units: Subjects | | | |
| ≤1 × ULN | 33 | 34 | 67 |
| 1-2 × ULN | 25 | 18 | 43 |
| >2 × ULN | 41 | 48 | 89 |
| Unknown | 2 | 3 | 5 |
| Time since diagnosis | | | |
| Units: months | | | |
| arithmetic mean | 32.6 | 34.4 | - |
| standard deviation | ± 46.1 | ± 41.4 | - |
| 5-HIAA | | | |
| n= 44 and 37 | | | |

| | | | |
|--------------------------|-------------|-------------|---|
| Units: $\mu\text{mol/d}$ | | | |
| arithmetic mean | 163.2 | 285.8 | |
| standard deviation | ± 194 | ± 406.4 | - |
| Gastrin | | | |
| n = 33 and 35 | | | |
| Units: ng/L | | | |
| arithmetic mean | 258.4 | 450.3 | |
| standard deviation | ± 220 | ± 353.2 | - |
| Pancreatic polypeptide | | | |
| n = 29 and 34 | | | |
| Units: pmol/L | | | |
| arithmetic mean | 164.03 | 167.43 | |
| standard deviation | ± 35.53 | ± 38.81 | - |

End points

End points reporting groups

| | |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Reporting group title | Lanreotide (Autogel Formulation) |
| Reporting group description: | 120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks. |
| Reporting group title | Placebo |
| Reporting group description: | Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks. |

Primary: Progression-Free Survival (PFS)

| | |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression-Free Survival (PFS) ^{[1][2]} |
| End point description: | Time from randomization to first documentation of disease progression, or death. Disease progression centrally assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 |
| | Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects. |
| | For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study. |

| | |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point type | Primary |
| End point timeframe: | From randomisation up to the last tumour assessment (scheduled at 96 weeks). Radiological scans were performed every 12 weeks during the first year and every 24 weeks during the second year |

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: Due to system limitations, data is presented for single arm. Hence statistical analysis details could not be included.

Statistical analyses details: P-value: < 0.001, Method: Logrank, Hazard ratio (HR): 0.47, 95% Confidence interval level: (0.3, 0.73)

The log rank test was stratified according to progression status at baseline and prior therapy. No p-value adjustment for multiple comparisons.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study. Due to system limitations, data cannot be represented for this arm, hence this arm is not included.

| End point values | Placebo | | | |
|----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 | | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 72 (48.6 to 96) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Alive & Without Disease Progression

| | |
|-----------------|------------------------------------------------------------|
| End point title | Percentage of Patients Alive & Without Disease Progression |
|-----------------|------------------------------------------------------------|

End point description:

Percentage of patients still ongoing (or completing at Week 96) without centrally assessed disease progression or death at Weeks 48 and 96.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 48 & 96

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|-----------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 101 | 103 | | |
| Units: Percentage of participants | | | | |
| Week 48 | 66 | 49 | | |
| Week 96 | 53 | 25 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Profile of Lanreotide

| | |
|-----------------|------------------------------------------------------|
| End point title | Pharmacokinetic Profile of Lanreotide ^[3] |
|-----------------|------------------------------------------------------|

End point description:

Pharmacokinetic Profile of Lanreotide assessed by mean serum concentration at specified timepoints

Analysis based on the intent-to-treat (ITT) population which comprised 101 randomised subjects who received lanreotide

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4, 12, 24, 36, 48, 72, 96

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only to analyze the pharmacokinetic profile of the study drug and hence placebo arm is not included

| End point values | Lanreotide (Autogel Formulation) | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 101 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| At Week 4 predose (n=81) | 2.5 (± 0.46) | | | |
| At Week 12 predose (n=87) | 5 (± 0.42) | | | |
| At Week 24 predose (n=74) | 6.1 (± 0.44) | | | |

| | | | | |
|---------------------------|--------------|--|--|--|
| At Week 36 predose (n=67) | 6.2 (± 0.39) | | | |
| At Week 48 predose (n=62) | 6.6 (± 0.45) | | | |
| At Week 72 predose (n=52) | 6.8 (± 0.44) | | | |
| At Week 96 predose (n=48) | 6.6 (± 0.39) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Global Health Status Quality of Life Assessment

| | |
|-----------------|---------------------------------------------------------------|
| End point title | Change in the Global Health Status Quality of Life Assessment |
|-----------------|---------------------------------------------------------------|

End point description:

Analysis based on the intent-to-treat (ITT) population which comprised 193 randomised subjects with valid assessment.

Transformed scores from European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire responses (QLQ)-C30. Questionnaire response scores range from 0 to 100. Higher scores indicate best possible Quality of Life.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12 to Week 96 (last visit)

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|-------------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 98 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -5.2 (± 3.7) | -4.9 (± 3.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With a Greater Than or Equal to 50% Decrease in Plasma Chromogranin A (CgA) Levels

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Patients With a Greater Than or Equal to 50% Decrease in Plasma Chromogranin A (CgA) Levels |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Analysis based on the subgroup of subjects with an elevated plasma CgA values. Subjects with a gastrinoma were excluded from the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12 to Week 96 (last visit)

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|-----------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 42.2 | 4.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Still Alive Based on Available Overall Survival Data

| | |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Percentage of Patients Still Alive Based on Available Overall Survival Data |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Overall survival defined as the time from randomisation to death due to any cause. Subjects were followed for overall survival beyond study completion/withdrawal via annual telephone contact until the last subject completed the study.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation to death or last visit, up to 321 weeks

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|-----------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 101 | 103 | | |
| Units: percentage of participants | 84 | 77 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

| | |
|-----------------|--------------------------------------------|
| End point title | Time to Disease Progression ^[4] |
|-----------------|--------------------------------------------|

End point description:

The KM (Kaplan-Meier) estimates for the time to centrally assessed disease progression are presented.

Analysis based on the intent-to-treat (ITT) population which comprised 204 randomised subjects.

For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached fixed duration study.

| | |
|-----------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: up to 103 Weeks | |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: For the Lanreotide (Autogel Formulation) arm: Median (95% CI) was Not reached during the 96 week fixed duration study. Due to system limitations, data cannot be represented for this arm, hence this arm is not included.

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 | | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 72.1 (48.6 to 96.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for 5-Hydroxyindoleacetic acid (5-HIAA)

| | | | | |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--|--|--|
| End point title | Mean Change from baseline in Tumour Marker Levels for 5-Hydroxyindoleacetic acid (5-HIAA) | | | |
| End point description: ITT Subjects with Elevated Values at Baseline | | | | |
| End point type | Secondary | | | |
| End point timeframe: Baseline (visit 2) and 96 weeks (last post-baseline value) | | | | |

| | | | | |
|--------------------------------------|----------------------------------|-----------------|--|--|
| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 36 | | |
| Units: µmol/d | | | | |
| arithmetic mean (standard deviation) | -74 (± 136.2) | 148.1 (± 237.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for Gastrin

| | |
|------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title | Mean Change from baseline in Tumour Marker Levels for Gastrin |
| End point description: ITT Subjects with Elevated Values at Baseline | |
| End point type | Secondary |
| End point timeframe: Baseline (visit 2) and 96 weeks (last post-baseline value) | |

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|--------------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 35 | | |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | -91.1 (± 152.2) | -21.1 (± 287.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in Tumour Marker Levels for Pancreatic polypeptide

| | |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| End point title | Mean Change from baseline in Tumour Marker Levels for Pancreatic polypeptide |
| End point description: ITT Subjects with Elevated Values at Baseline | |
| End point type | Secondary |
| End point timeframe: Baseline (visit 2) and 96 weeks (last post-baseline value) | |

| End point values | Lanreotide (Autogel Formulation) | Placebo | | |
|--------------------------------------|----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 32 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | -107.59 (± 49.49) | -10.2 (± 59.6) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 96 weeks

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Lanreotide (Autogel Formulation) |
|-----------------------|----------------------------------|

Reporting group description:

120mg administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo: Saline solution 0.9% administered via deep subcutaneous injection every 28 days for a maximum period of 96 weeks.

| Serious adverse events | Lanreotide (Autogel Formulation) | Placebo | |
|---------------------------------------------------------------------|----------------------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 101 (24.75%) | 32 / 103 (31.07%) | |
| number of deaths (all causes) | 2 | 2 | |
| number of deaths resulting from adverse events | 2 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |

| | | | |
|-------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 3 / 103 (2.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 101 (2.97%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 101 (3.96%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Ileus | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Biliary fistula | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic necrosis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |

| | | | |
|--------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 101 (2.97%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Infected dermal cyst | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 101 (0.00%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |

| | | |
|-------------------------------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 101 (0.00%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hypokalaemia | | |
| subjects affected / exposed | 0 / 101 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Lanreotide (Autogel Formulation) | Placebo |
|--------------------------------------------------------------|----------------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | |
| subjects affected / exposed | 88 / 101 (87.13%) | 92 / 103 (89.32%) |
| Investigations | | |
| Weight decreased | | |
| subjects affected / exposed | 9 / 101 (8.91%) | 9 / 103 (8.74%) |
| occurrences (all) | 9 | 10 |
| Pancreatic enzymes decreased | | |
| subjects affected / exposed | 6 / 101 (5.94%) | 0 / 103 (0.00%) |
| occurrences (all) | 7 | 0 |
| Vascular disorders | | |
| Hypertension | | |
| subjects affected / exposed | 13 / 101 (12.87%) | 5 / 103 (4.85%) |
| occurrences (all) | 16 | 5 |
| Flushing | | |
| subjects affected / exposed | 4 / 101 (3.96%) | 6 / 103 (5.83%) |
| occurrences (all) | 4 | 6 |
| Nervous system disorders | | |
| Headache | | |
| subjects affected / exposed | 16 / 101 (15.84%) | 11 / 103 (10.68%) |
| occurrences (all) | 19 | 19 |
| Dizziness | | |
| subjects affected / exposed | 9 / 101 (8.91%) | 1 / 103 (0.97%) |
| occurrences (all) | 12 | 1 |
| Lethargy | | |

| | | | |
|-------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 13 | 4 / 103 (3.88%) 4 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed occurrences (all) | 11 / 101 (10.89%) 15 | 16 / 103 (15.53%) 18 | |
| Asthenia | | | |
| subjects affected / exposed occurrences (all) | 8 / 101 (7.92%) 8 | 6 / 103 (5.83%) 6 | |
| Injection site pain | | | |
| subjects affected / exposed occurrences (all) | 8 / 101 (7.92%) 30 | 4 / 103 (3.88%) 10 | |
| Oedema peripheral | | | |
| subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 5 | 7 / 103 (6.80%) 12 | |
| Pyrexia | | | |
| subjects affected / exposed occurrences (all) | 4 / 101 (3.96%) 6 | 6 / 103 (5.83%) 7 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed occurrences (all) | 35 / 101 (34.65%) 57 | 37 / 103 (35.92%) 75 | |
| Abdominal pain | | | |
| subjects affected / exposed occurrences (all) | 23 / 101 (22.77%) 32 | 18 / 103 (17.48%) 34 | |
| Vomiting | | | |
| subjects affected / exposed occurrences (all) | 17 / 101 (16.83%) 21 | 10 / 103 (9.71%) 28 | |
| Nausea | | | |
| subjects affected / exposed occurrences (all) | 15 / 101 (14.85%) 28 | 13 / 103 (12.62%) 22 | |
| Flatulence | | | |
| subjects affected / exposed occurrences (all) | 12 / 101 (11.88%) 13 | 9 / 103 (8.74%) 12 | |
| Constipation | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 11 / 101 (10.89%) 13 | 14 / 103 (13.59%) 16 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 7 / 101 (6.93%) 7 | 9 / 103 (8.74%) 15 | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 8 | 3 / 103 (2.91%) 4 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 101 (2.97%) 3 | 8 / 103 (7.77%) 11 | |
| Haemorrhoids subjects affected / exposed occurrences (all) | 0 / 101 (0.00%) 0 | 7 / 103 (6.80%) 7 | |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 15 / 101 (14.85%) 16 | 7 / 103 (6.80%) 7 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 6 / 101 (5.94%) 7 | 1 / 103 (0.97%) 2 | |
| Cough subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 5 | 3 / 103 (2.91%) 8 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 5 | 3 / 103 (2.91%) 4 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 7 / 101 (6.93%) 8 | 3 / 103 (2.91%) 3 | |
| Alopecia subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 5 | 4 / 103 (3.88%) 4 | |
| Pruritus | | | |

| | | | |
|--------------------------------------------------|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 101 (4.95%) 5 | 5 / 103 (4.85%) 17 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 11 / 101 (10.89%) | 11 / 103 (10.68%) | |
| occurrences (all) | 12 | 11 | |
| Arthralgia | | | |
| subjects affected / exposed | 10 / 101 (9.90%) | 10 / 103 (9.71%) | |
| occurrences (all) | 15 | 11 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | 3 / 103 (2.91%) | |
| occurrences (all) | 8 | 6 | |
| Muscle spasms | | | |
| subjects affected / exposed | 5 / 101 (4.95%) | 4 / 103 (3.88%) | |
| occurrences (all) | 5 | 4 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 101 (8.91%) | 17 / 103 (16.50%) | |
| occurrences (all) | 10 | 23 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | 11 / 103 (10.68%) | |
| occurrences (all) | 13 | 13 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 101 (2.97%) | 6 / 103 (5.83%) | |
| occurrences (all) | 5 | 6 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 101 (9.90%) | 9 / 103 (8.74%) | |
| occurrences (all) | 11 | 11 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 9 / 101 (8.91%) | 4 / 103 (3.88%) | |
| occurrences (all) | 9 | 5 | |
| Dehydration | | | |
| subjects affected / exposed | 5 / 101 (4.95%) | 1 / 103 (0.97%) | |
| occurrences (all) | 7 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 January 2007 | Protocol Amendment 1 <ul style="list-style-type: none">• Inclusion criteria modification addition of subject with gastrinomas and tumours of unknown origin; extension of the window for the tumour biopsy.• Clarification on safety assessment (removal of local tolerance and disease progression from adverse event, role of the DSMC).• Clarification on procedures (blood sampling conditions and study drug injection).• Clarification on statistical definitions and testing.• Removal of plans for an interim analysis on the study and addition of a SSR. |
| 30 July 2007 | Protocol Amendment 2 <ul style="list-style-type: none">• Modification of the inclusion criteria (tumour biopsy and CT-scan window• Specification about the randomisation list to be provided to the independent statistician in charge of reporting for DSMC. |
| 30 April 2008 | Protocol Amendment 3 <ul style="list-style-type: none">• Introduction of the plan for an extension study to enable subjects to continue to receive lanreotide Autogel after completion of 96 weeks of treatment and to allow any subject that progressed while on placebo, to enter into the extension study. A request would be made by the Investigator for a potential code break due to centrally assessed disease progression confirmed by RECIST to verify subject's entry into the extension study. |
| 04 April 2009 | Protocol Amendment 4 <ul style="list-style-type: none">• Change of saline solution in the United States of America.• Change of Sponsor name and address and of coordinating office name. |
| 05 March 2010 | Protocol Amendment 5 <ul style="list-style-type: none">• Addition of hepatic tumour load evaluation on subject CT/MRI scan at baseline visit.• Removal of restriction regarding centres recruiting more than 20 subjects.• Addition of sensitivity analyses to investigate the robustness of the results of the primary efficacy analysis. |
| 11 February 2011 | Protocol Amendment 6 <ul style="list-style-type: none">• Changes in response to US FDA to use the log rank test instead of the Cox PH model originally planned for the primary analysis of PFS, to follow up subjects for OS and to analyse OS as a secondary endpoint.• Planned update to CRF and ICF to collect OS data.• Change to the number of SSRs to one in response to advice from the FDA that this should be sufficient. |
| 28 February 2012 | Protocol Amendment 7 <ul style="list-style-type: none">• To replace Ipsen Pharma S.A. with new laboratories, performing the PK evaluation and anti lanreotide antibody testing, due to site closure. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported