

**Clinical trial results:**

A randomized placebo-controlled study in patients with a Gallium-68 DOTATATE PET/CT positive, clinically non-functioning pituitary macroadenoma (NFMA) of the effect of Lanreotide autosolution on Tumor (adenoma) size

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-001234-22 |
| Trial protocol | NL |
| Global end of trial date | 26 May 2021 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 07 February 2025 |
| First version publication date | 07 February 2025 |
| Summary attachment (see zip file) | Trial publication in The Lancet Regional Health - Europe (Boertien et al 2024 - Lanreotide versus placebo for tumour reductionpdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------------|
| Sponsor protocol code | NL52821.018.15 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Nederlands Trial Register: NTR5275, National Trial Register (new): NL5136 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Academic Medical Center |
| Sponsor organisation address | Meibergdreef 9, Amsterdam, Netherlands, 1105 AZ |
| Public contact | Eric Fliers, principal investigator, Academic Medical Center (currently part of Amsterdam UMC), 0031 205666071, e.fliers@amsterdamumc.nl |
| Scientific contact | Eric Fliers, principal investigator, Academic Medical Center (currently part of Amsterdam UMC), 0031 205666071, e.fliers@amsterdamumc.nl |

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 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 May 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 May 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of lanreotide autosolution during 72 weeks, as compared to placebo, on tumour size in patients with a non-functioning pituitary macroadenoma and positive pituitary somatostatin receptor imaging using Gallium-68 DOTATATE PET/CT.

Note that our planned number of subjects was 66, as the percentage of positive Gallium-68 DOTATATE uptake was unknown and only those with positive uptake would be randomized for treatment. The final number of enrolled patients was 49 in order to be able to randomize 44 subjects between lanreotide and placebo.

Protection of trial subjects:

The study was approved by the ethics committee and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All trial subjects were informed in full on the trial details, and received information in writing before providing informed consent. Privacy rules regarding collection and storing of medical and personal data were adhered to. Insurance was in place in case of damage caused by participation in the study. Trial subjects could withdraw from the study at any time and for any reason. All adverse events were recorded and followed up, and if necessary, subjects were withdrawn for medical reasons.

Background therapy:

Subjects who had undergone previous adenoma surgery were eligible for inclusion, as long as the tumour remnant was >1cm in size.

Evidence for comparator:

The comparator in our study is placebo.

| | |
|---|------------------|
| Actual start date of recruitment | 03 November 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: 49 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 49 |

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) | 31 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between 3 November 2015 and 10 December 2019. The study was conducted in an outpatient setting and eligible patients were referred by endocrinologists at academic and non-academic hospitals in the Netherlands for inclusion at one of the participating centres.

Pre-assignment

Screening details:

After inclusion and informed consent, all participants underwent the study 68Ga-DOTATATE PET-CT. Only those participants with positive tracer uptake within the adenoma were randomised for study treatment.

Pre-assignment period milestones

| | |
|--|-------------------------------|
| Number of subjects started | 49 |
| Intermediate milestone: Number of subjects | 68Ga-DOTATATE PET-CT scan: 49 |
| Number of subjects completed | 44 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-------------------------------|
| Reason: Number of subjects | Physician decision: 1 |
| Reason: Number of subjects | negative 68Ga-DOTATATE PET: 4 |

Period 1

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

Blinding implementation details:

The randomisation list was stored in a secure trial file at the Pharmacy and was only disclosed after database lock. As the prefilled lanreotide syringes differed in appearance from the placebo, injections were administered by trained, independent nurses who were unmasked to treatment allocation, a method also used in previous trials. To maintain blinding during transport, prepared study medication was placed in an opaque bag within a sealed cardboard box.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Lanreotide |

Arm description:

Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Somatuline Autosolution |
| Investigational medicinal product code | PR1 |
| Other name | lanreotide acetate, Somatuline Autogel |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use, Solution for injection |

Dosage and administration details:

Pre-filled syringes with dosage of 120mg (volume 0.4mL), administered every 28 days as a deep subcutaneous injection into the superior, external quadrant of the buttock.

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

Arm description:

Treatment with placebo, consisting of saline 0.9%

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | saline 0.9% |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Solution for injection , Subcutaneous use |

Dosage and administration details:

Solution of saline (sodium chloride 0.9%), delivered in plastic bottle with syringe and needle. Trained nurses drew up 0.4 mL (matching the Somatuline Autosolution volume) to prepare the injection for administration. Injections were administered every 28 days as a deep subcutaneous injection into the superior, external quadrant of the buttock.

| Number of subjects in period 1^[1] | Lanreotide | Placebo |
|---|------------|---------|
| Started | 22 | 22 |
| 24 week visit | 19 | 22 |
| 48 week visit | 16 | 20 |
| Completed | 13 | 19 |
| Not completed | 9 | 3 |
| Adverse event, non-fatal | 4 | - |
| Lack of efficacy | 3 | 3 |
| Protocol deviation | 2 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: After inclusion and informed consent, all 49 participants underwent the study 68Ga-DOTATATE PET-CT. Only those participants with positive tracer uptake within the adenoma were randomised for study treatment and formed the overall trial (and are thus reported in the baseline period), this number is 44 as prespecified in the power calculation.

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | Lanreotide |
| Reporting group description: | |
| Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Treatment with placebo, consisting of saline 0.9% | |

| Reporting group values | Lanreotide | Placebo | Total |
|--|--------------|--------------|-------|
| Number of subjects | 22 | 22 | 44 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 15 | 11 | 26 |
| From 65-84 years | 7 | 11 | 18 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.8 | 63.5 | |
| standard deviation | ± 8.2 | ± 8.5 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 6 | 16 |
| Male | 12 | 16 | 28 |
| Any pituitary hormone deficiency | | | |
| Units: Subjects | | | |
| No | 7 | 11 | 18 |
| Yes | 15 | 11 | 26 |
| Previous NFPMA resection | | | |
| At any time before study participation. NFPMA = non-functioning pituitary macroadenoma | | | |
| Units: Subjects | | | |
| No | 7 | 13 | 20 |
| Yes | 15 | 9 | 24 |
| Centre of inclusion | | | |
| Units: Subjects | | | |
| Amsterdam UMC location AMC | 15 | 16 | 31 |
| Amsterdam UMC location VUmc | 1 | 3 | 4 |
| Leiden University Medical Centre (LUMC) | 6 | 3 | 9 |
| Baseline NFPMA cranio-caudal diameter | | | |
| NFPMA=non-functioning pituitary macroadenoma | | | |
| Units: millimetre(s) | | | |
| median | 16.2 | 16.3 | |
| inter-quartile range (Q1-Q3) | 13.4 to 20.6 | 14.8 to 19.3 | - |
| Baseline NFPMA tumour volume | | | |
| NFPMA = non-functioning pituitary macroadenoma | | | |
| Units: cubic millimeter | | | |
| median | 2782 | 2722 | |

| | | | |
|--|--------------|--------------|---|
| inter-quartile range (Q1-Q3) | 1868 to 4067 | 1937 to 3967 | - |
| 68Ga-DOTATATE PET NFPMA SUVmean | | | |
| The mean standard uptake value measured within the adenoma. SUV is a unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value. | | | |
| Units: unit(s) | | | |
| median | 6.1 | 5.0 | |
| inter-quartile range (Q1-Q3) | 3.2 to 8.1 | 2.7 to 6.7 | - |
| 68Ga-DOTATATE PET NFPMA SUVmax | | | |
| The maximum standard uptake value measured within the adenoma. SUV is a unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value. | | | |
| Units: unit(s) | | | |
| median | 7.9 | 6.4 | |
| inter-quartile range (Q1-Q3) | 5.0 to 11.0 | 3.5 to 9.1 | - |

Subject analysis sets

| | |
|----------------------------|---------------------------|
| Subject analysis set title | All included participants |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Clinical characteristics of all participants with 68Ga-DOTATATE PET-positive and PET-negative adenoma. Only PET-positive participants were randomised to study treatment. Note: there is no centrally assessed baseline or end tumour size (cranio-caudal diameter and tumour volume) data for this subject analysis set.

| | |
|----------------------------|--|
| Subject analysis set title | Per-protocol population - lanreotide group |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the lanreotide group who completed the study (n=13).

| | |
|----------------------------|---|
| Subject analysis set title | Per-protocol population - placebo group |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the placebo group who completed the study (n=19).

| Reporting group values | All included participants | Per-protocol population - lanreotide group | Per-protocol population - placebo group |
|------------------------|---------------------------|--|---|
| Number of subjects | 49 | 13 | 19 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 31 | | |
| From 65-84 years | 18 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.3 | | |
| standard deviation | ± 10.2 | ± | ± |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 18 | | |
| Male | 31 | | |

| | | | |
|--|------------|--|--|
| Any pituitary hormone deficiency | | | |
| Units: Subjects | | | |
| No | 20 | | |
| Yes | 29 | | |
| Previous NFPMA resection | | | |
| At any time before study participation. NFPMA = non-functioning pituitary macroadenoma | | | |
| Units: Subjects | | | |
| No | 23 | | |
| Yes | 26 | | |
| Centre of inclusion | | | |
| Units: Subjects | | | |
| Amsterdam UMC location AMC | 34 | | |
| Amsterdam UMC location VUmc | 5 | | |
| Leiden University Medical Centre (LUMC) | 10 | | |
| Baseline NFPMA cranio-caudal diameter | | | |
| NFPMA=non-functioning pituitary macroadenoma | | | |
| Units: millimetre(s) | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | | | |
| Baseline NFPMA tumour volume | | | |
| NFPMA = non-functioning pituitary macroadenoma | | | |
| Units: cubic millimeter | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | | | |
| 68Ga-DOTATATE PET NFPMA SUVmean | | | |
| The mean standard uptake value measured within the adenoma. SUV is an unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value. | | | |
| Units: unit(s) | | | |
| median | 5.4 | | |
| inter-quartile range (Q1-Q3) | 2.9 to 7.2 | | |
| 68Ga-DOTATATE PET NFPMA SUVmax | | | |
| The maximum standard uptake value measured within the adenoma. SUV is a unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value. | | | |
| Units: unit(s) | | | |
| median | 7.0 | | |
| inter-quartile range (Q1-Q3) | 3.5 to 9.6 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Lanreotide |
| Reporting group description: Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration. | |
| Reporting group title | Placebo |
| Reporting group description: Treatment with placebo, consisting of saline 0.9% | |
| Subject analysis set title | All included participants |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Clinical characteristics of all participants with 68Ga-DOTATATE PET-positive and PET-negative adenoma. Only PET-positive participants were randomised to study treatment. Note: there is no centrally assessed baseline or end tumour size (cranio-caudal diameter and tumour volume) data for this subject analysis set. | |
| Subject analysis set title | Per-protocol population - lanreotide group |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the lanreotide group who completed the study (n=13). | |
| Subject analysis set title | Per-protocol population - placebo group |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the placebo group who completed the study (n=19). | |

Primary: Change in cranio-caudal diameter

| | |
|--|----------------------------------|
| End point title | Change in cranio-caudal diameter |
| End point description: | |
| End point type | Primary |
| End point timeframe: Primary outcome was the change in cranio-caudal tumour diameter from baseline to week-72 or treatment discontinuation. | |

| End point values | Lanreotide | Placebo | Per-protocol population - lanreotide group | Per-protocol population - placebo group |
|--------------------------------------|-----------------|-----------------|--|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 13 | 19 |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | 1.2 (± 2.5) | 1.3 (± 1.5) | 1.3 (± 3.0) | 1.2 (± 1.6) |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Primary outcome main, additional & sensitivity ana/Table S3. Change in tumour size from baseline to end-of-trea/Fig S1. Primary&secondary tumour size outcomes in ITT & PP/Table 2 |
|-----------------------------------|--|

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Primary outcome main analysis (ITT population) |
|-----------------------------------|--|

Statistical analysis description:

For the main analysis of the primary outcome change in cranio-caudal diameter, all data up to treatment discontinuation was included (ie, 'while-on-treatment' strategy). An analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

| | |
|---|----------------------------|
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.93 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 1.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6 |

Notes:

[1] - The statistical significance level for analyses was set at $p = 0.05$ (two-sided). There was no need for multiplicity adjustments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Primary outcome in per-protocol population |
|-----------------------------------|--|

Statistical analysis description:

For the analysis of the primary outcome change in cranio-caudal diameter in the per-protocol population an analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

| | |
|---|--|
| Comparison groups | Per-protocol population - placebo group v Per-protocol population - lanreotide group |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 1.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

| | |
|---|--|
| Statistical analysis title | Primary outcome multiple imputation missing data |
| Statistical analysis description: | |
| A supplementary efficacy analysis applied univariate multiple imputation to impute missing week-72 MRI data, assuming missingness at random (MAR). Data were imputed separately in each treatment group using a regression model, and 27 imputed datasets were generated (corresponding to 27% of missing week-72 data). Each dataset was assessed with the earlier specified ANCOVA model and results were pooled using Rubin's rules. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.66 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.25 |
| upper limit | 1.97 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.82 |

| | |
|--|---|
| Statistical analysis title | Pattern-mixture model (sensitivity), $\delta = +0.317\text{mm}$ |
| Statistical analysis description: | |
| Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ , delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets. | |
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.16 |
| upper limit | 2.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.83 |

| | |
|--|---|
| Statistical analysis title | Pattern-mixture model (sensitivity), $\delta = +0.634\text{mm}$ |
| Statistical analysis description: | |
| Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ , delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets. | |
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.09 |
| upper limit | 2.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.83 |

| | |
|--|---|
| Statistical analysis title | Pattern-mixture model (sensitivity), $\delta = +0.950\text{mm}$ |
| Statistical analysis description: | |
| Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ , delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets. | |
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.45 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | 2.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.84 |

| | |
|--|---|
| Statistical analysis title | Pattern-mixture model (sensitivity), $\delta = +1.267\text{mm}$ |
| Statistical analysis description: | |
| Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ , delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets. | |
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.39 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 2.41 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.85 |

| | |
|--|---|
| Statistical analysis title | Pattern-mixture model (sensitivity), $\delta = +2.534\text{mm}$ |
| Statistical analysis description: | |
| Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ , delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets. | |
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.22 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 2.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.91 |

| | |
|--|---|
| Statistical analysis title | Tipping point analysis, $\delta = -5.385\text{mm}$ for lanreotide |
| Statistical analysis description: | |
| A tipping-point analysis explored which δ -shift was needed to overturn the conclusion of the main analysis (ie, in which alternative post-dropout scenario would treatment effect be statistically significant). This involved subtracting increasing percentages of the mean change from the MAR imputed data in the lanreotide group until the resulting treatment effect following ANCOVA was statistically significant. The required δ of -5.385mm was considered clinically highly implausible. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.002 |
| upper limit | 3.78 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.96 |

| | |
|---|----------------------------|
| Statistical analysis title | Linear mixed effects model |
| Statistical analysis description: | |
| Linear mixed effects model to account for repeated MRI measurements obtained at varying time-points. Post-baseline cranio-caudal diameter was modelled with treatment group, measurement time, groupby time interaction, baseline cranio-caudal diameter, and baseline diameterbytime interaction as fixed effects, a by-subject random intercept, and a first-order autoregressive residual autocorrelation structure. Treatment effect was estimated as the contrast between adjusted group means at final time | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.82 ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 1.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.58 |

Notes:

[2] - The final model was modified post-hoc to include the additional fixed effects of baseline cranio-caudal diameter and baseline diameterbytime interaction to correctly adjust for baseline size; the outcome/response vector was adjusted to only contain post-baseline measurements. As an additional post-hoc optimisation, a residual correlation matrix was specified to address possible residual serial autocorrelation not sufficiently accounted for by the random intercept.

[3] - Treatment effect estimated as the contrast between treatment groups at final measurement time (corresponding to week-72) using R emmeans package, based on leastsquare means with Satterthwaite method for approximation of degrees of freedom

| | |
|--|--|
| Statistical analysis title | Mixed model for repeated measurements (MMRM) |
| Statistical analysis description: | |
| Data were fitted post-hoc with a MMRM to relax the LME assumption of linear time trends, with time as categorical variable and an unstructured covariance matrix to model within-patient residual errors. This required 'simplification' of post-baseline time data to a factor with only 4 levels: time1=measurement obtained before week-24 visit, time2=week-24 visit, time3=measurement obtained between week-24 and week-72 visit, and time4=week-72 (end) visit. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Post-hoc |
| Analysis type | superiority ^[4] |
| P-value | = 0.92 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 1.44 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.75 |

Notes:

[4] - The model included the fixed effects of group, time, groupbytime interaction, baseline size, and baseline sizebytime interaction; and an unstructured covariance matrix to model within-patient residual errors.

[5] - Treatment effect estimated as the contrast between treatment groups at end visit (corresponding to week-72) using R emmeans package, based on leastsquare means with Satterthwaite method for approximation of degrees of freedom

Secondary: Change in tumour volume

| | |
|--|-------------------------|
| End point title | Change in tumour volume |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| The change in tumour volume from baseline to week-72 or treatment discontinuation. | |

| End point values | Lanreotide | Placebo | Per-protocol population - lanreotide group | Per-protocol population - placebo group |
|---------------------------------------|-----------------|-----------------|--|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 13 | 19 |
| Units: cubic millimeter | | | | |
| median (inter-quartile range (Q1-Q3)) | 424 (61 to 811) | 181 (19 to 738) | 590 (91 to 828) | 260 (26 to 1049) |

Statistical analyses

| Statistical analysis title | Tumour volume main analysis (ITT population) |
|--|--|
| Statistical analysis description: | |
| For the main analysis of the secondary outcome change in tumour volume, all data up to treatment discontinuation was included (ie, 'while-on-treatment' strategy). An analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.94 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -422 |
| upper limit | 486 |

Notes:

[6] - Tumour volume values were natural log-transformed before analysis due to non-normal distribution with moderate positive skewness, the back-transformed estimated mean difference and 95% CI are reported.

| Statistical analysis title | Tumour volume per-protocol population |
|--|--|
| Statistical analysis description: | |
| For the analysis of the secondary outcome change in tumour volume in the per-protocol population an analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate. | |
| Comparison groups | Per-protocol population - lanreotide group v Per-protocol population - placebo group |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.94 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 24 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -657 |
| upper limit | 706 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 333 |

Notes:

[7] - Tumour volume values in the per-protocol population were sufficiently normally distributed and thus not (natural log) transformed for analysis.

Secondary: Time to tumour volume progression

| | |
|-----------------|-----------------------------------|
| End point title | Time to tumour volume progression |
|-----------------|-----------------------------------|

End point description:

Tumour progression was defined as clinically significant increase in tumour volume of $\geq 20\%$.

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

End point timeframe:

Time to progression was defined as the interval in weeks between start of study treatment and the first subsequent MRI scan showing a clinically significant increase in tumour volume, counting events in each group.

| End point values | Lanreotide | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: events | 9 | 5 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Kaplan-Meier estimates of time to tumour progression/ Fig 2. |
|-----------------------------------|--|

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Time to progression in tumour volume |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Time to progression compared between groups with stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline. Hazard ratio derived from a Cox proportional-hazards model with terms for study treatment and tumour growth at baseline; with no statistically significant interaction between these terms. There were 9 events in placebo group (median time to progression 72 wks, 95% CI not reached), and 5 events in placebo group (median time not reached).

| | |
|---|----------------------|
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.11 [8] |
| Method | Stratified log-rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 2.37 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 7.15 |

Notes:

[8] - Stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline.

Secondary: Change in SF-36 component score physical functioning

| | |
|-----------------|--|
| End point title | Change in SF-36 component score physical functioning |
|-----------------|--|

End point description:

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

End point timeframe:

The change in quality of life based on SF-36 component score physical functioning (PF) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -0.4 (± 16.1) | -5.5 (± 16.1) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Spider plots of mean SF-36 component scores /Fig S3. SF-36 Change in SF-36 component scores/Table S4. Change in quality |
|-----------------------------------|--|

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Change in SF-36 physical functioning |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

| | |
|---|-----------------------|
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.47 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 3.8 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.7 |
| upper limit | 14.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.2 |

Secondary: Change in SF-36 component score limitations physical health

| | |
|-----------------|---|
| End point title | Change in SF-36 component score limitations physical health |
|-----------------|---|

End point description:

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

End point timeframe:

The change in quality of life based on SF-36 component score role limitations due to physical health problems (RP) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -12.0 (± 26.9) | -4.8 (± 36.5) | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Change in SF-36 limitations physical |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

| | |
|---|-----------------------|
| Comparison groups | Placebo v Lanreotide |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.34 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.2 |
| upper limit | 9.9 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.4 |

Secondary: Change in SF-36 component score bodily pain

| | |
|--|---|
| End point title | Change in SF-36 component score bodily pain |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| The change in quality of life based on SF-36 component score bodily pain (BP) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale. | |

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -8.5 (± 26.1) | -2.9 (± 13.7) | | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | Change in SF-36 bodily pain |
| Statistical analysis description: | |
| Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19 |
| upper limit | 5.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.1 |

Secondary: Change in SF-36 component score general health

| | |
|-----------------|--|
| End point title | Change in SF-36 component score general health |
|-----------------|--|

End point description:

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

End point timeframe:

The change in quality of life based on SF-36 component score general health perceptions (GH) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -1.6 (\pm 13.7) | -1.1 (\pm 12.0) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Change in SF-36 general health |
|----------------------------|--------------------------------|

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

| | |
|---|----------------------------|
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.78 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.3 |
| upper limit | 7.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.1 |

Secondary: Change in SF-36 component score vitality

| | |
|-----------------|--|
| End point title | Change in SF-36 component score vitality |
|-----------------|--|

End point description:

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

End point timeframe:

The change in quality of life based on SF-36 component score vitality (VT) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -5.4 (\pm 17.3) | -0.9 (\pm 12.7) | | |

Statistical analyses

| Statistical analysis title | Change in SF-36 vitality |
|---|----------------------------|
| Statistical analysis description: | |
| Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -6.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.8 |
| upper limit | 2.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.6 |

Secondary: Change in SF-36 component score social functioning

| | |
|---|--|
| End point title | Change in SF-36 component score social functioning |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| The change in quality of life based on SF-36 component score social functioning (SF) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale. | |

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -5.6 (\pm 22.0) | -4.5 (\pm 14.2) | | |

Statistical analyses

| Statistical analysis title | Change in SF-36 social functioning |
|-----------------------------------|------------------------------------|
|-----------------------------------|------------------------------------|

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

| | |
|---|----------------------------|
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.61 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.7 |
| upper limit | 8.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.8 |

Secondary: Change in SF-36 component score limitations emotional

| | |
|-----------------|---|
| End point title | Change in SF-36 component score limitations emotional |
|-----------------|---|

End point description:

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

End point timeframe:

The change in quality of life based on SF-36 component score role limitations due to emotional problems (RE) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -8.7 (± 30.9) | -6.1 (± 24.4) | | |

Statistical analyses

| Statistical analysis title | Change in SF-36 limitations emotional |
|--|---------------------------------------|
| Statistical analysis description: | |
| Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.47 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -6.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.4 |
| upper limit | 10.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.5 |

Secondary: Change in SF-36 component score general mental health

| | |
|--|---|
| End point title | Change in SF-36 component score general mental health |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| The change in quality of life based on SF-36 component score general mental health (MH) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale. | |

| End point values | Lanreotide | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: unit(s) | | | | |
| arithmetic mean (standard deviation) | -4.9 (± 13.4) | 0.2 (± 6.8) | | |

Statistical analyses

| Statistical analysis title | Change in SF-36 general mental health |
|---|---------------------------------------|
| Statistical analysis description: | |
| Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation. | |
| Comparison groups | Lanreotide v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.12 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -5.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.9 |
| upper limit | 1.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.3 |

Other pre-specified: Tumour volume percentage change

| | |
|--|---------------------------------|
| End point title | Tumour volume percentage change |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Percentage change in tumour volume from baseline measurement to week 72 or treatment discontinuation. No between-group analysis performed on this end point. | |

| End point values | Lanreotide | Placebo | | |
|---------------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: percent | | | | |
| median (inter-quartile range (Q1-Q3)) | 17.2 (1.5 to 29.7) | 7.8 (0.7 to 16.2) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to tumour volume or cranio-caudal diameter progression

| | |
|-----------------|---|
| End point title | Time to tumour volume or cranio-caudal diameter progression |
|-----------------|---|

End point description:

Tumour progression was defined as clinically significant increase of either in tumour volume ($\geq 20\%$) or cranio-caudal diameter (≥ 2 mm) on any subsequent MRI scan past baseline.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Time to progression was defined as the interval in weeks between start of study treatment and the first subsequent MRI scan showing a clinically significant increase in tumour volume or cranio-caudal diameter, counting events in each group.

| End point values | Lanreotide | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: events | 11 | 9 | | |

| | |
|----------------------------|---|
| Attachments (see zip file) | Kaplan-Meier estimates of time to tumour progression/ Fig S2. |
|----------------------------|---|

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Time to tumour progression |
|----------------------------|----------------------------|

Statistical analysis description:

Time to progression compared between groups with stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline. Hazard ratio derived from a Cox proportional-hazards model with terms for study treatment and tumour growth at baseline; with no statistically significant interaction between these terms. There were 11 events in lanreotide group (median time to progression 72 wks, 95% CI 50.6-83.4), and 9 events in placebo group (median time not reached).

| | |
|-------------------|----------------------|
| Comparison groups | Lanreotide v Placebo |
|-------------------|----------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 44 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.25 ^[9] |
| Method | Stratified log-rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 4.15 |

Notes:

[9] - Stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any undesirable event, finding, or change from baseline (eg, worsening of known dyspepsia) occurring between study enrolment and up to 30 days after treatment completion or discontinuation was considered an adverse event.

Adverse event reporting additional description:

AEs were assessed systematically at each study visit (via i.a. a fasting blood sample, measurement of vitals, and a semi-structured interview focused on AEs/side effects). Non-systematically assessed AEs (through self-reporting at any time during study participation) are not reported here, but have been published.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Lanreotide |
|-----------------------|------------|

Reporting group description:

Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.

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

Reporting group description:

Treatment with placebo, consisting of saline 0.9%

| Serious adverse events | Lanreotide | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 22 (27.27%) | 3 / 22 (13.64%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Hospital admission for observation after bike accident | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Hospital admission for planned adenoma resection | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 22 (9.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospital admission for planned ileocecal resection due to | | | |

| | | | |
|---|---|----------------|--|
| complicated Crohn's disease | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hospital admission for analysis of chest pain and/or dyspnoea | Additional description: Critical conditions such as pulmonary embolism or myocardial ischemia were ruled out. | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Lanreotide | Placebo | |
|---|---|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 22 (100.00%) | 21 / 22 (95.45%) | |
| Investigations | | | |
| Insulin-like growth factor decreased | Additional description: Age-adjusted IGF-1 SDS below -2.0 | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 22 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Weight decreased | Additional description: Unintentional weight loss | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Thyroxine free decreased | Additional description: Free thyroxine below lower limit of normal | | |
| subjects affected / exposed | 6 / 22 (27.27%) | 1 / 22 (4.55%) | |
| occurrences (all) | 6 | 1 | |
| Liver function test increased | Additional description: Comprising alanine aminotransferase or gamma-glutamyltransferase >2 times the upper limit of normal or alkaline phosphatase >20 U/L above the upper limit of normal | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 2 / 22 (9.09%) | |
| occurrences (all) | 4 | 2 | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 22 (9.09%) | |
| occurrences (all) | 0 | 2 | |
| Cardiac disorders | | | |
| Bradycardia | Additional description: defined as <60 beats per minute | | |

| | | | |
|---|--|----------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 22 (18.18%) 4 | 0 / 22 (0.00%) 0 | |
| Nervous system disorders | | | |
| Dizziness | Additional description: Dizziness or light-headedness | | |
| subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 3 / 22 (13.64%) 3 | |
| Headache | | | |
| subjects affected / exposed occurrences (all) | 7 / 22 (31.82%) 7 | 4 / 22 (18.18%) 4 | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed occurrences (all) | 12 / 22 (54.55%) 12 | 0 / 22 (0.00%) 0 | |
| Fatigue | | | |
| subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 5 | 3 / 22 (13.64%) 3 | |
| Eye disorders | | | |
| Visual impairment | Additional description: Visual complaints or disturbances | | |
| subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 3 / 22 (13.64%) 3 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | Additional description: Complaints of abdominal pain, discomfort, cramps | | |
| subjects affected / exposed occurrences (all) | 10 / 22 (45.45%) 10 | 2 / 22 (9.09%) 2 | |
| Frequent bowel movements | Additional description: Increased stool frequency or diarrhoea | | |
| subjects affected / exposed occurrences (all) | 16 / 22 (72.73%) 16 | 4 / 22 (18.18%) 4 | |
| Nausea | Additional description: nausea or dyspepsia | | |
| subjects affected / exposed occurrences (all) | 8 / 22 (36.36%) 8 | 1 / 22 (4.55%) 1 | |
| Decreased appetite | | | |
| subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 1 / 22 (4.55%) 1 | |
| Flatulence | | | |
| subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 1 / 22 (4.55%) 1 | |

| | | | |
|---|---|-----------------|--|
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | Additional description: Any complaint of increased hair loss or decreased hair growth | | |
| subjects affected / exposed | 5 / 22 (22.73%) | 0 / 22 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Endocrine disorders | | | |
| Impaired fasting glucose | Additional description: Defined as fasting glucose level of 5.7–6.9 mmol/L | | |
| subjects affected / exposed | 10 / 22 (45.45%) | 3 / 22 (13.64%) | |
| occurrences (all) | 10 | 3 | |
| Hyperglycaemia | Additional description: Defined as glucose level ≥ 7 mmol/L | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) | |
| occurrences (all) | 1 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 13 October 2016 | <ul style="list-style-type: none">- Leiden University Medical Centre added as participating centre to achieve target recruitment goal- Ability to perform the 68Ga-DOTATATE PET/CT at Amsterdam UMC location AMC- Possibility for participants to have study injections administered at home by trained nurses of a specialised homecare company (Eurocept Homecare). |
| 31 August 2017 | <ul style="list-style-type: none">- Clearer definition of exclusion criterion concerning dopamine receptor agonist use: "Use of dopamine receptor agonists" was modified to "Use of dopamine receptor agonist in the past 6 months". Inclusions up to this amendment were not affected by the modification. |
| 30 November 2018 | <ul style="list-style-type: none">- Increased sample size to 22 participants per treatment group to account for an observed overall dropout rate of ~25%.- More detailed statistical analysis section. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/39070749>

<http://www.ncbi.nlm.nih.gov/pubmed/32792446>

<http://www.ncbi.nlm.nih.gov/pubmed/34191241>