



## Clinical trial results:

**A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of pasireotide LAR in patients with Cushing's disease**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.**

## Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2009-011128-70       |
| Trial protocol           | GB ES DE NL BE PL IT |
| Global end of trial date | 21 December 2016     |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 19 July 2018 |
| First version publication date | 19 July 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CSOM230G2304 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01374906 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma, AG   |
| Sponsor organisation address | CH-4002, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a> |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a> |

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                       | 21 December 2016 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 December 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of two pasireotide long-acting regimens (starting doses of 10 mg and 30 mg followed by up-titration if needed or continuation of the same dose) independently in patients with Cushing's disease after 7 months of treatment regardless of up titration at Month 4.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Argentina: 1          |
| Country: Number of subjects enrolled | Belgium: 7            |
| Country: Number of subjects enrolled | Brazil: 6             |
| Country: Number of subjects enrolled | Canada: 4             |
| Country: Number of subjects enrolled | China: 36             |
| Country: Number of subjects enrolled | France: 8             |
| Country: Number of subjects enrolled | Germany: 6            |
| Country: Number of subjects enrolled | United Kingdom: 1     |
| Country: Number of subjects enrolled | India: 3              |
| Country: Number of subjects enrolled | Italy: 19             |
| Country: Number of subjects enrolled | Japan: 11             |
| Country: Number of subjects enrolled | Netherlands: 2        |
| Country: Number of subjects enrolled | Peru: 9               |
| Country: Number of subjects enrolled | Poland: 8             |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | Spain: 3              |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Thailand: 1       |
| Country: Number of subjects enrolled | Turkey: 8         |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects   | 150               |
| EEA total number of subjects         | 54                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 147 |
| From 65 to 84 years                       | 3   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

At least 148 patients (Pts.) were planned & 150 were randomized & analyzed. Pts. were all treated with either pasireotide long-acting 10 mg or pasireotide long-acting 30 mg. 81 Pts. completed the Core phase & entered the Extension phase with 39 completing the Extension phase.

### Pre-assignment

Screening details:

Planned: at least 148 patients - Randomized & Analyzed: 150 patients; 74 patients in 10 mg arm and 76 patients in 30 mg arm.

### 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, Assessor |

### Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| <b>Arm title</b>             | 10 mg pasireotide LAR dose |

Arm description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | pasireotide LAR   |
| Investigational medicinal product code | SOM230            |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Pasireotide long-acting was administered as an intra-muscular depot intragluteal injection once every 28 days ( $\pm 2$  days). Pasireotide long-acting ampoules were supplied to the investigators at dose strengths of 10 mg, 10 mg + 20 mg and 40 mg kits.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | 30 mg pasireotide LAR dose |
|------------------|----------------------------|

Arm description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | pasireotide LAR   |
| Investigational medicinal product code | SOM230            |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Pasireotide long-acting was administered as an intra-muscular depot intragluteal injection once every 28 days ( $\pm 2$  days). Pasireotide long-acting ampoules were supplied to the investigators at dose strengths of 10 mg, 10 mg + 20 mg and 40 mg kits.

| <b>Number of subjects in period 1</b> | 10 mg pasireotide<br>LAR dose | 30 mg pasireotide<br>LAR dose |
|---------------------------------------|-------------------------------|-------------------------------|
| Started                               | 74                            | 76                            |
| Completed                             | 34                            | 28                            |
| Not completed                         | 40                            | 48                            |
| Abnormal laboratory value(s)          | -                             | 3                             |
| Adverse event, serious fatal          | -                             | 2                             |
| Consent withdrawn by subject          | 15                            | 9                             |
| Adverse event, non-fatal              | 10                            | 11                            |
| Unsatisfactory therapeutic effect     | 11                            | 19                            |
| Administrative problems               | 2                             | 2                             |
| Protocol deviation                    | 2                             | 2                             |

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | 10 mg pasireotide LAR dose |
|-----------------------|----------------------------|

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | 30 mg pasireotide LAR dose |
|-----------------------|----------------------------|

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.

| Reporting group values                             | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose | Total |
|--|----------------------------|----------------------------|-------|
| Number of subjects                                 | 74                         | 76                         | 150   |
| Age categorical<br>Units: Subjects                 |                            |                            |       |
| In utero   | 0                          | 0                          | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                          | 0                          | 0     |
| Newborns (0-27 days)                               | 0                          | 0                          | 0     |
| Infants and toddlers (28 days-23 months)           | 0                          | 0                          | 0     |
| Children (2-11 years)                              | 0                          | 0                          | 0     |
| Adolescents (12-17 years)                          | 0                          | 0                          | 0     |
| Adults (18-64 years)                               | 73                         | 74                         | 147   |
| From 65-84 years                                   | 1                          | 2                          | 3     |
| 85 years and over                                  | 0                          | 0                          | 0     |
| Age Continuous<br>Units: years                     |                            |                            |       |
| arithmetic mean                                    | 38.3                       | 38.6                       |       |
| standard deviation                                 | ± 12.52                    | ± 12.99                    | -     |
| Gender, Male/Female<br>Units: Subjects             |                            |                            |       |
| Female   | 58                         | 60                         | 118   |
| Male   | 16                         | 16                         | 32    |
| Race/Ethnicity<br>Units: Subjects                  |                            |                            |       |
| Caucasian  | 39                         | 44                         | 83    |
| Asian  | 27                         | 24                         | 51    |
| Black  | 2                          | 0                          | 2     |
| Other  | 6                          | 8                          | 14    |

## End points

### End points reporting groups

|   |                            |
|---|----------------------------|
| Reporting group title   | 10 mg pasireotide LAR dose |
| Reporting group description:<br>Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR. |                            |
| Reporting group title   | 30 mg pasireotide LAR dose |
| Reporting group description:<br>Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR. |                            |
| Subject analysis set title  | 5 mg pasireotide LAR dose  |
| Subject analysis set type   | Sub-group analysis         |
| Subject analysis set description:<br>These patients were dosed with 5 mg of Pasireotide LAR to assess Pharmacokinetics (PK).  |                            |
| Subject analysis set title  | 40 mg pasireotide LAR dose |
| Subject analysis set type   | Sub-group analysis         |
| Subject analysis set description:<br>These patients were dosed with 40 mg of Pasireotide LAR to assess Pharmacokinetics (PK).   |                            |
| Subject analysis set title  | 5 mg pasireotide LAR dose  |
| Subject analysis set type   | Sub-group analysis         |
| Subject analysis set description:<br>These patients were dosed with 5 mg of Pasireotide LAR to assess Pharmacokinetics (PK).  |                            |
| Subject analysis set title  | 40 mg pasireotide LAR dose |
| Subject analysis set type   | Sub-group analysis         |
| Subject analysis set description:<br>These patients were dosed with 40 mg of Pasireotide LAR to assess Pharmacokinetics (PK).   |                            |

### Primary: Percentage participants that attained a mUFC $\leq 1.0 \times \text{ULN}$ at Month 7 regardless of dose titration

|   |  |
|---|--|
| End point title   | Percentage participants that attained a mUFC $\leq 1.0 \times \text{ULN}$ at Month 7 regardless of dose titration <sup>[1]</sup> |
| End point description:<br>Percentage of participants that attained a mean urinary free cortisol (mUFC) $\leq 1.0 \times$ upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4. Patients who discontinued before month 4 evaluations classed as non-responders. For patients missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. |  |
| End point type  | Primary  |
| End point timeframe:<br>Month 7   |  |

#### 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: All analyses in this study were descriptive in nature. No comparisons were made between the two arms, and no p-values are reported. For the primary and key-secondary, success was based on estimating the response rate (and 95% CI) in each arm.

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  | 41.9 (30.51 to 53.94)      | 40.8 (29.65 to 52.67)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants that attained a mUFC $\leq 1.0 \times \text{ULN}$ at Month 7 and had not had a dose increase at Month 4

|                 |  |
|-----------------|--|
| End point title | Percentage of participants that attained a mUFC $\leq 1.0 \times \text{ULN}$ at Month 7 and had not had a dose increase at Month 4 |
|-----------------|--|

End point description:

Percentage of participants that attain a mUFC  $\leq 1.0 \times \text{ULN}$  at Month 7 and had not had a dose increase at Month 4. Patients who had a dose increase prior to Month 7 were counted as non-responders in this analysis. Patients who discontinued before month 4 evaluations classed as non-responders. For patients missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. A responder was defined as a patient who attains mUFC  $\leq 1.0 \times \text{ULN}$  and had not had a dose increase at Month 4.

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

End point timeframe:

Month 7

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  | 28.4 (18.50 to 40.05)      | 31.6 (21.39 to 43.25)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Actual change in mean urinary free cortisol (mUFC) from baseline

|                 |  |
|-----------------|--|
| End point title | Actual change in mean urinary free cortisol (mUFC) from baseline |
|-----------------|--|

End point description:

Actual change in mUFC (nmol/24h) from baseline by randomized groups.

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



End point timeframe:

baseline, Month 7 (M7), Month 12 (M12), Month 24 (M24) , Month 36 (M36)

| End point values                     | 10 mg<br>pasireotide LAR<br>dose | 30 mg<br>pasireotide LAR<br>dose |  |  |
|--------------------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type                   | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed          | 74                               | 76                               |  |  |
| Units: nmol/24h                      |                                  |                                  |  |  |
| arithmetic mean (standard deviation) |                                  |                                  |  |  |
| M7 (n = 57, 67)                      | -192.4 (±<br>271.59)             | -234.3 (±<br>362.86)             |  |  |
| M12 (n = 50, 54)                     | -195.1 (±<br>282.46)             | -247.6 (±<br>387.05)             |  |  |
| M24 (n = 33, 25)                     | -236.2 (±<br>292.91)             | -265.2 (±<br>313.47)             |  |  |
| M36 (n = 14, 4)                      | -398.4 (±<br>136.09)             | -164.6 (±<br>66.76)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change in mean urinary free cortisol (mUFC) from baseline

|  |  |
|--|--|
| End point title  | Percentage change in mean urinary free cortisol (mUFC) from baseline |
| End point description:   |  |
| Percentage change in mUFC (nmol/24h) from baseline by randomized groups. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| M7, M12, M24, M36  |  |

| End point values                     | 10 mg<br>pasireotide LAR<br>dose | 30 mg<br>pasireotide LAR<br>dose |  |  |
|--------------------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type                   | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed          | 74                               | 76                               |  |  |
| Units: percentage change             |                                  |                                  |  |  |
| arithmetic mean (standard deviation) |                                  |                                  |  |  |
| M7 (n= 57, 67)                       | -29.3 (±<br>102.76)              | -33.2 (±<br>61.37)               |  |  |
| M12 (n= 50, 54)                      | -30.3 (±<br>79.73)               | -31.1 (±<br>78.41)               |  |  |
| M24 (n= 33, 25)                      | -50.9 (±<br>76.48)               | -51.2 (±<br>35.41)               |  |  |
| M36 (n = 14, 4)                      | -71.6 (±<br>20.44)               | -48.8 (±<br>11.36)               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients who attain mUFC $\leq 1.0 \times \text{ULN}$

|                 |   |
|-----------------|---|
| End point title | Percentage of patients who attain mUFC $\leq 1.0 \times \text{ULN}$ |
|-----------------|---|

End point description:

Controlled responder: mUFC  $\leq 1.0 \times \text{ULN}$  by randomized groups.

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

End point timeframe:

M7, M12, M24, M36, M48, M60

| End point values                        | 10 mg<br>pasireotide LAR<br>dose | 30 mg<br>pasireotide LAR<br>dose |  |  |
|---|----------------------------------|----------------------------------|--|--|
| Subject group type                      | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed             | 74                               | 76                               |  |  |
| Units: percentage of participants       |                                  |                                  |  |  |
| number (confidence interval 95%)        |                                  |                                  |  |  |
| M7 - Controlled responder (n = 74, 76)  | 39.2 (28.04 to 51.23)            | 40.8 (29.65 to 52.67)            |  |  |
| M12 - Controlled responder (n = 74, 76) | 35.1 (24.39 to 47.11)            | 25.0 (15.77 to 36.26)            |  |  |
| M24 - Controlled responder (n = 63, 61) | 39.7 (27.57 to 52.80)            | 21.3 (11.86 to 33.68)            |  |  |
| M36 - Controlled responder (n = 50, 50) | 22.0 (11.53 to 35.96)            | 4.0 (0.49 to 13.71)              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients who attain mUFC $\leq 1.0 \times \text{ULN}$ or have at least 50 % reduction from baseline in mUFC

|                 |   |
|-----------------|---|
| End point title | Percentage of patients who attain mUFC $\leq 1.0 \times \text{ULN}$ or have at least 50 % reduction from baseline in mUFC |
|-----------------|---|

End point description:

Controlled responder: mUFC  $\leq 1.0 \times \text{ULN}$ . Partially controlled responder: at least 50% reduction in mUFC from Baseline, and mUFC  $> 1.0 \times \text{ULN}$ .

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

End point timeframe:

M7, M12, M24, M36, M48, M60

| <b>End point values</b>           | 10 mg<br>pasireotide LAR<br>dose | 30 mg<br>pasireotide LAR<br>dose |  |  |
|-----------------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed       | 74                               | 76                               |  |  |
| Units: percentage of participants |                                  |                                  |  |  |
| number (confidence interval 95%)  |                                  |                                  |  |  |
| M7 (n = 74, 76)                   | 44.6 (33.02 to 56.61)            | 53.9 (42.13 to 65.45)            |  |  |
| M12 (n= 74, 76)                   | 45.9 (34.29 to 57.93)            | 42.1 (30.86 to 53.98)            |  |  |
| M24 (n= 63, 61)                   | 46.0 (33.39 to 59.06)            | 27.9 (17.15 to 40.83)            |  |  |
| M36 (n = 50, 50)                  | 28.0 (16.23 to 42.49)            | 6.0 (1.25 to 16.55)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients who are controlled responders (mUFC ≤ 1.0 xULN) on at least 4 of the 7 mUFC assessments by Month 7 & on at least 7 of the 12 mUFC assessments by Month 12.

|                 |   |
|-----------------|---|
| End point title | Percentage of patients who are controlled responders (mUFC ≤ 1.0 xULN) on at least 4 of the 7 mUFC assessments by Month 7 & on at least 7 of the 12 mUFC assessments by Month 12. |
|-----------------|---|

End point description:

Percentage of patients with mUFC ≤ 1.0 x ULN at a minimum of 4 months up to and including Month 7, and at a minimum of 7 months up to and including Month 12 by randomized groups.

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

End point timeframe:

Month 7, Month 12

| <b>End point values</b>           | 10 mg<br>pasireotide LAR<br>dose | 30 mg<br>pasireotide LAR<br>dose |  |  |
|-----------------------------------|----------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                  | Reporting group                  |  |  |
| Number of subjects analysed       | 74                               | 76                               |  |  |
| Units: percentage of participants |                                  |                                  |  |  |
| number (confidence interval 95%)  |                                  |                                  |  |  |
| Month 7                           | 25.7 (16.22 to 37.16)            | 31.6 (21.39 to 43.25)            |  |  |
| Month 12                          | 25.7 (16.22 to 37.16)            | 25.0 (15.77 to 36.26)            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients with uncontrolled response at Month 7 & Month 12 within the subset of patients who had uncontrolled response at a) Months 1 and 2; b) Months 1, 2, and 3

|                 |   |
|-----------------|---|
| End point title | Percentage of patients with uncontrolled response at Month 7 & Month 12 within the subset of patients who had uncontrolled response at a) Months 1 and 2; b) Months 1, 2, and 3 |
|-----------------|---|

End point description:

Percentage of patients with mUFC > 1.0 xULN at Month 7 and Month 12 within the subset of patients who were uncontrolled at a) Months 1 & 2, b) Months 1, 2, & 3 by randomized groups.

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

End point timeframe:

Month 7, Month12

| End point values                                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|---|----------------------------|----------------------------|--|--|
| Subject group type                                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed                       | 74                         | 76                         |  |  |
| Units: percentage of participants                 |                            |                            |  |  |
| number (not applicable)                           |                            |                            |  |  |
| Uncontrolled Resp @ M7: subset: M1 & 2 (33, 33)   | 60.6                       | 60.6                       |  |  |
| Uncontrolled Resp @ M7: subset: M1,2 & 3 (31, 29) | 61.3                       | 65.5                       |  |  |
| Uncontrolled Resp @ M12: subset: M1 & 2 (33, 33)  | 69.7                       | 69.7                       |  |  |
| Uncontrolled Resp @ M12: subset: M1 & 2 (31, 29)  | 74.2                       | 72.4                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first achievement of attaining a mUFC $\leq 1.0 \times \text{ULN}$ or at least a 50% reduction in mUFC from baseline

|                 |  |
|-----------------|--|
| End point title | Time to first achievement of attaining a mUFC $\leq 1.0 \times \text{ULN}$ or at least a 50% reduction in mUFC from baseline |
|-----------------|--|

End point description:

Time to first achievement of attaining a mUFC  $\leq 1.0 \times \text{ULN}$  or at least a 50% reduction in mUFC from baseline by randomized groups.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Month 7, Month 12    |           |

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: Percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  |                            |                            |  |  |
| Month 7                           | 86.2 (76.1 to 93.5)        | 83.4 (72.6 to 91.8)        |  |  |
| Month 12                          | 90.1 (80.7 to 96.2)        | 94.5 (81.0 to 99.4)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of controlled or partially controlled response

|   |   |
|---|---|
| End point title   | Duration of controlled or partially controlled response |
| End point description:  |   |
| Duration of controlled or partially controlled response is defined as the period starting from the date of patient's first normalization (mUFC ≤ 1.0 x ULN) or at least 50% reduction from baseline up to the date when the patient's mUFC > 1.0 x ULN and the reduction from baseline falls to less than 50% for the first time. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Month 6, 12, 18   |   |

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: Percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  |                            |                            |  |  |
| Month 6                           | 78.0 (66.5 to 87.7)        | 72.9 (61.2 to 83.4)        |  |  |
| Month 12                          | 84.0 (73.1 to 92.2)        | 82.8 (71.5 to 91.5)        |  |  |
| Month 18                          | 84.0 (73.1 to 92.2)        | 87.1 (74.6 to 95.3)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline on plasma adrenocorticotrophic hormone (ACTH) over time

|  |   |
|--|---|
| End point title  | Percentage change from baseline on plasma adrenocorticotrophic hormone (ACTH) over time |
| End point description:<br>Percentage change in ACTH (pmol/L) from Baseline by randomized groups. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Months 7, 12, 24 & 36  |   |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 74                         | 76                         |  |  |
| Units: Percentage change             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| M7 (n = 54, 62)                      | 2.7 (± 57.14)              | -13.5 (± 46.75)            |  |  |
| M12 (n = 44, 52)                     | -10.2 (± 57.57)            | -14.5 (± 38.72)            |  |  |
| M24 (n = 31, 23)                     | -12.1 (± 43.51)            | 2.5 (± 68.69)              |  |  |
| M36 (n = 13, 5)                      | -15.4 (± 36.90)            | -0.6 (± 48.13)             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline on serum cortisol over time

|  |   |
|--|---|
| End point title  | Percentage change from baseline on serum cortisol over time |
| End point description:<br>Percentage change in serum cortisol (nmol/L) from Baseline by randomized groups. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Months 7, 12, 24 & 36  |   |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 74                         | 76                         |  |  |
| Units: Percentage change             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| M7 (n = 55, 66)                      | -8.2 (± 37.83)             | -5.1 (± 40.20)             |  |  |
| M12 (n = 46, 54)                     | -12.1 (± 29.69)            | -0.4 (± 35.91)             |  |  |
| M24 (n = 32, 25)                     | -15.6 (± 30.67)            | -7.4 (± 38.37)             |  |  |
| M36 (n = 14, 5)                      | 0.6 (± 55.67)              | -23.2 (± 31.19)            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Actual change from baseline in clinical signs over time: Blood Pressure

|                        |   |
|------------------------|---|
| End point title        | Actual change from baseline in clinical signs over time: Blood Pressure |
| End point description: | Change in blood pressure measurements from Baseline.                    |
| End point type         | Secondary   |
| End point timeframe:   | Month 7   |

| End point values                      | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|---------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                    | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed           | 57                         | 67                         |  |  |
| Units: mmHg                           |                            |                            |  |  |
| arithmetic mean (standard deviation)  |                            |                            |  |  |
| Supine systolic blood pressure (SBP)  | -6.8 (± 15.64)             | -4.6 (± 14.51)             |  |  |
| Supine diastolic blood (DBP) pressure | -4.8 (± 12.06)             | -3.0 (± 12.12)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in clinical signs over time

|                        |   |
|------------------------|---|
| End point title        | Percentage change from baseline in clinical signs over time   |
| End point description: | Percentage change in parameter measurements: blood pressure, body mass index, waist circumference, fasting serum lipid profile, weight, bone density and body composition (examined by DXA scan) from |

Baseline

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Month 7              |           |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 57                         | 67                         |  |  |
| Units: Percentage change             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| SBP (n = 57, 67)                     | -4.3 (± 11.46)             | -3.0 (± 10.18)             |  |  |
| DBP (n = 57, 67)                     | -4.7 (± 14.19)             | -2.6 (± 13.78)             |  |  |
| BMI (n = 57, 67)                     | -2.6 (± 5.26)              | -6.1 (± 6.94)              |  |  |
| Weight (n = 57, 67)                  | -2.6 (± 5.26)              | -6.1 (± 6.91)              |  |  |
| Waist circumference (n = 53, 63)     | -1.4 (± 8.60)              | -6.6 (± 10.06)             |  |  |
| HDL (n = 55, 64)                     | -6.7 (± 15.18)             | 0.3 (± 20.91)              |  |  |
| Total cholesterol (n = 56, 64)       | -7.2 (± 16.86)             | -6.6 (± 16.40)             |  |  |
| Triglycerides (n = 56, 64)           | 4.2 (± 39.54)              | -0.9 (± 39.61)             |  |  |
| Body composition (n = 41, 48)        | -2.4 (± 6.68)              | -3.6 (± 10.47)             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients having a favorable shift from baseline in clinical signs

|                 |   |
|-----------------|---|
| End point title | Percentage of patients having a favorable shift from baseline in clinical signs |
|-----------------|---|

End point description:

This includes patients with improvements, no change or worsening in symptoms from baseline. Clinical signs over time include: facial rubor, fat pads, hirsutism, striae, (via photographs by a second local physician who was blinded to the treatment dose and time point of the photograph) and muscle strength.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Month 7              |           |

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: Percentage of participants |                            |                            |  |  |
| number (not applicable)           |                            |                            |  |  |



|                                     |      |      |  |  |
|-------------------------------------|------|------|--|--|
| Facial rubor (n = 52, 56)           | 32.7 | 53.6 |  |  |
| Hirsutism (females only) (n= 42,46) | 22.2 | 32.6 |  |  |
| Striae (n = 52, 55)                 | 23.1 | 23.6 |  |  |
| Bruising (n = 52, 56)               | 25.0 | 14.3 |  |  |
| Supraclavicular fat pad (n= 52,56)  | 40.4 | 28.6 |  |  |
| Dorsal fat pad (n = 52, 55)         | 28.8 | 40.0 |  |  |
| Muscle strength (n = 56, 66)        | 8.9  | 4.5  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants that attained a mean urinary free cortisol (mUFC) $\leq 1.0 \times$ upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4.

|                 |   |
|-----------------|---|
| End point title | Percentage of participants that attained a mean urinary free cortisol (mUFC) $\leq 1.0 \times$ upper limit of normal (ULN) at Month 7 regardless of dose up-titration at Month 4. |
|-----------------|---|

End point description:

All of the participants who discontinued prior to month 4 evaluations were classed as non-responders. For participants missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. Analysis split by screening strata of mUFC Stratum 1: mUFC  $1.5 \times$  to  $< 2.0 \times$  ULN Stratum 2: mUFC  $2.0 \times$  to  $\leq 5.0 \times$  ULN

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

End point timeframe:

Month 7

| End point values  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|---|----------------------------|----------------------------|--|--|
| Subject group type  | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed                                     | 74                         | 76                         |  |  |
| Units: percentage of participants                               |                            |                            |  |  |
| number (confidence interval 95%)                                |                            |                            |  |  |
| stratum: $1.5 \times$ ULN to $< 2.0 \times$ ULN (n=25,25)       | 52.0 (31.31 to 72.20)      | 52.0 (31.31 to 72.20)      |  |  |
| stratum: $2.0 \times$ ULN to $\leq 5.0 \times$ ULN (n = 49, 51) | 36.7 (23.42 to 51.71)      | 35.3 (22.43 to 49.93)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients that attain a reduction of at least 50% in mUFC from baseline

|                 |  |
|-----------------|--|
| End point title | Percentage of patients that attain a reduction of at least 50% in mUFC from baseline |
|-----------------|--|

End point description:

All of the participants who discontinued prior to month 4 evaluations were classed as non-responders. For participants missing month 7 mUFC assessments, the last available mUFC assessment at or after month 4 was carried forward as the month 7 mUFC assessment value. Analysis split by screening strata of mUFC Stratum 1:

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

End point timeframe:

Months 7, 12, 24 & 36

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  |                            |                            |  |  |
| M7                                | 35.1 (24.39 to 47.11)      | 43.4 (32.08 to 55.29)      |  |  |
| M12                               | 35.1 (24.39 to 47.11)      | 38.2 (27.25 to 50.02)      |  |  |
| M24 (n = 24, 14)                  | 83.3 (62.62 to 95.26)      | 57.1 (28.86 to 82.34)      |  |  |
| M36 (n = 8, 3)                    | 100 (63.06 to 100.00)      | 33.33 (0.84 to 90.57)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first achievement of at least a 50% reduction in mUFC from baseline

|                 |   |
|-----------------|---|
| End point title | Time to first achievement of at least a 50% reduction in mUFC from baseline |
|-----------------|---|

End point description:

Time to first achievement of a 50% reduction in mUFC from baseline

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

End point timeframe:

every month in the core phase and every 3 months in the extension phase) up to and including the cut-off date for the Month 12 CSR (10-Nov-2015)

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: Percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  |                            |                            |  |  |

|     |                     |                     |  |  |
|-----|---------------------|---------------------|--|--|
| M7  | 80.5 (69.7 to 89.3) | 73.4 (62.4 to 83.4) |  |  |
| M12 | 84.4 (74.0 to 92.3) | 80.7 (69.4 to 89.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of at least 50% reduction in mUFC from baseline

|  |  |
|--|--|
| End point title  | Duration of at least 50% reduction in mUFC from baseline |
| End point description:<br>Duration of 50% reduction from baseline is defined as the period starting from the date of patient's first 50% reduction from baseline |  |
| End point type   | Secondary  |
| End point timeframe:<br>Months 6, 12 & 18  |  |

| End point values                  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed       | 74                         | 76                         |  |  |
| Units: Percentage of participants |                            |                            |  |  |
| number (confidence interval 95%)  |                            |                            |  |  |
| M6                                | 78.4 (66.6 to 88.3)        | 77.8 (66.0 to 87.7)        |  |  |
| M12                               | 84.9 (73.7 to 93.1)        | 83.7 (72.6 to 92.1)        |  |  |
| M18                               | 84.9 (73.7 to 93.1)        | 83.7 (72.6 to 92.1)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic (PK) parameter: Ctrough

|   |   |
|---|---|
| End point title   | Pharmacokinetic (PK) parameter: Ctrough |
| End point description:<br>Pasireotide trough levels (Ctrough) was one of the parameters used for PK assessments. Ctrough is the pre-dose PK concentration with an elapsed time from previous injection of 28+/-2 days. All patients randomized to the study had at least one PK observation and were therefore included in the pharmacokinetic analysis set (PAS). PK observations with missing concentrations, missing dose, missing elapsed time or an elapsed time from previous injection outside of 28 ±2 days window were excluded. |   |
| End point type  | Secondary                               |
| End point timeframe:<br>Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337  |   |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose | 5 mg pasireotide LAR dose | 40 mg pasireotide LAR dose |
|--------------------------------------|----------------------------|----------------------------|---------------------------|----------------------------|
| Subject group type                   | Reporting group            | Reporting group            | Subject analysis set      | Subject analysis set       |
| Number of subjects analysed          | 65                         | 64                         | 5                         | 44                         |
| Units: ng/mL                         |                            |                            |                           |                            |
| arithmetic mean (standard deviation) |                            |                            |                           |                            |
| Day 29 (n = 65, 64, 0, 0)            | 2.03 (± 1.25)              | 7.63 (± 4.58)              | 9.99 (± 9.99)             | 9.9 (± 9.99)               |
| Day 57 (n = 57, 61, 1, 0)            | 2.35 (± 1.15)              | 7.82 (± 4.22)              | 0.83 (± 9.99)             | 9.99 (± 9.99)              |
| Day 85 (n = 59, 51, 2, 0)            | 2.39 (± 1.32)              | 8.56 (± 4.26)              | 1.03 (± 0.63)             | 9.99 (± 9.99)              |
| Day 113 (n = 51, 49, 3, 0)           | 2.40 (± 1.11)              | 8.31 (± 3.87)              | 1.29 (± 0.24)             | 9.99 (± 9.99)              |
| Day 141 (n = 25, 50, 2, 20)          | 2.47 (± 0.94)              | 7.88 (± 4.00)              | 1.04 (± 0.68)             | 10.7 (± 4.91)              |
| Day 169 (n = 29, 51, 2, 22)          | 2.47 (± 0.95)              | 8.46 (± 3.51)              | 2.01 (± 0.22)             | 12.0 (± 5.08)              |
| Day 197 (n = 35, 44, 2, 21)          | 2.88 (± 1.29)              | 9.13 (± 4.25)              | 0.72 (± 0.39)             | 11.9 (± 5.87)              |
| Day 225 (n = 22, 28, 3, 34)          | 2.68 (± 0.98)              | 8.57 (± 4.70)              | 1.19 (± 0.43)             | 11.3 (± 5.18)              |
| Day 253 (n = 17, 27, 5, 33)          | 2.87 (± 1.57)              | 9.00 (± 4.93)              | 1.77 (± 0.88)             | 12.1 (± 5.21)              |
| Day 281 (n = 13, 16, 3, 44)          | 3.36 (± 1.48)              | 8.18 (± 4.23)              | 1.24 (± 0.52)             | 11.4 (± 5.85)              |
| Day 309 (n = 23, 19, 1, 43)          | 2.50 (± 0.99)              | 9.34 (± 5.61)              | 0.66 (± 9.99)             | 12.0 (± 4.58)              |
| Day 337 (n = 21, 15, 3, 41)          | 3.07 (± 1.62)              | 8.90 (± 4.37)              | 1.91 (± 1.79)             | 12.6 (± 6.21)              |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic (PK) parameter: Cmax

|   |                                      |
|---|--------------------------------------|
| End point title   | Pharmacokinetic (PK) parameter: Cmax |
| End point description:  |                                      |
| Pasireotide peak levels (Cmax) was one of the parameters used for PK assessments. Cmax is the post-dose PK concentration with an elapsed time from the previous injection of 21+/-2 days. All patients randomized to the study had at least one PK observation and were therefore included in the pharmacokinetic analysis set (PAS). Cmax PK observations ("Day 20" and "Day 104") with an elapsed time from the previous injection outside of 21+/-2 days window were excluded. |                                      |
| End point type  | Secondary                            |
| End point timeframe:  |                                      |
| Days 22, 106, 190   |                                      |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose | 5 mg pasireotide LAR dose | 40 mg pasireotide LAR dose |
|--------------------------------------|----------------------------|----------------------------|---------------------------|----------------------------|
| Subject group type                   | Reporting group            | Reporting group            | Subject analysis set      | Subject analysis set       |
| Number of subjects analysed          | 67                         | 69                         | 3                         | 22                         |
| Units: ng/mL                         |                            |                            |                           |                            |
| arithmetic mean (standard deviation) |                            |                            |                           |                            |
| Day 22 (M 0.75) (n= 67, 69, 0, 0)    | 3.0 (± 1.50)               | 8.2 (± 3.99)               | 9.99 (± 9.99)             | 9.99 (± 9.99)              |
| Day 106 (M 3.75) (n = 54, 51, 3, 0)  | 3.3 (± 1.92)               | 9.4 (± 3.72)               | 1.7 (± 0.42)              | 9.99 (± 9.99)              |

|                                     |                   |                    |                   |                    |
|-------------------------------------|-------------------|--------------------|-------------------|--------------------|
| Day 190 (M6.75) (n = 32, 40, 2, 22) | 4.0 ( $\pm$ 1.73) | 10.0 ( $\pm$ 3.91) | 1.4 ( $\pm$ 0.78) | 12.1 ( $\pm$ 5.21) |
|-------------------------------------|-------------------|--------------------|-------------------|--------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Actual change in standardized score of Cushing's disease HRQoL (CushingQOL) score from baseline

|                 |   |
|-----------------|---|
| End point title | Actual change in standardized score of Cushing's disease HRQoL (CushingQOL) score from baseline |
|-----------------|---|

End point description:

CushingQol is a disease-specific patient-reported outcome instrument. It is a single-domain 12 item Cushing's disease quality of life instrument. The Cushing's syndrome quality of life (CushingQoL) questionnaire is a single domain questionnaire which includes 12 self-report items scored using a five point Likert scale anchored at (1=always/very much and 5=never/not at all). The patient is asked to report what they think or feel about their Cushing's syndrome and how much the illness has interfered in usual activities over the past 4 weeks. The total score is standardized on a 0-100 scale with lower scores indicating a greater impact on quality of life.

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

End point timeframe:

Months 7, 12, 24 & 36

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 74                         | 76                         |  |  |
| Units: scores on a scale             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| M7 (n = 56, 64)                      | 5.7 ( $\pm$ 15.97)         | 7.8 ( $\pm$ 11.63)         |  |  |
| M12 (n = 47, 53)                     | 6.4 ( $\pm$ 17.56)         | 6.8 ( $\pm$ 14.42)         |  |  |
| M24 (n = 32, 25)                     | 5.9 ( $\pm$ 15.56)         | 8.7 ( $\pm$ 12.80)         |  |  |
| M36 (n = 13, 4)                      | 1.4 ( $\pm$ 9.10)          | 14.6 ( $\pm$ 5.10)         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Actual change in SF-12v2 score from Baseline - Mental component summary

|                 |   |
|-----------------|---|
| End point title | Actual change in SF-12v2 score from Baseline - Mental component summary |
|-----------------|---|

End point description:

SF-12v2 General Health Survey is a general patient reported outcome instrument over time. It is scored to provide eight health domain scores (Bodily Pain (BP), General Health (GH), Physical Functioning (PF), Role-Physical (RP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH)).

These eight domain scores can be combined to form two summary scores reflecting overall physical and mental health: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The analyses reported here focus on PCS and MCS scores. The domain scores use a norm-based score, which standardizes the scores with respect to the mean and standard deviation of a nationally representative sample of United States (US) adults.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Months 7, 12 & 24    |           |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 74                         | 76                         |  |  |
| Units: scores on a scale             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| M7 (n = 33, 37)                      | 4.1 (± 8.81)               | 4.3 (± 8.05)               |  |  |
| M12 (n = 28, 33)                     | 2.3 (± 9.97)               | 3.3 (± 8.26)               |  |  |
| M24 (n = 9, 5)                       | 3.3 (± 10.43)              | 6.4 (± 2.53)               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Actual change in SF-12v2 score from Baseline - Physical component summary

|                 |   |
|-----------------|---|
| End point title | Actual change in SF-12v2 score from Baseline - Physical component summary |
|-----------------|---|

End point description:

SF-12v2 General Health Survey is a general patient reported outcome instrument over time. It is scored to provide eight health domain scores (Bodily Pain (BP), General Health (GH), Physical Functioning (PF), Role-Physical (RP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH)). These eight domain scores can be combined to form two summary scores reflecting overall physical and mental health: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The analyses reported here focus on PCS and MCS scores. The domain scores use a norm-based score, which standardizes the scores with respect to the mean and standard deviation of a nationally representative sample of United States (US) adults.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Months 7, 12 & 24    |           |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 74                         | 76                         |  |  |
| Units: scores on a scale             |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |

|                  |              |               |  |  |
|------------------|--------------|---------------|--|--|
| M7 (n = 33, 37)  | 1.9 (± 8.50) | -0.8 (± 7.46) |  |  |
| M12 (n = 28, 33) | 4.9 (± 5.56) | -0.5 (± 6.73) |  |  |
| M24 (n = 9, 5)   | 5.3 (± 4.32) | -1.1 (± 5.54) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Actual change from baseline in clinical signs over time: Body Mass Index (BMI)

|   |  |
|---|--|
| End point title   | Actual change from baseline in clinical signs over time: Body Mass Index (BMI) |
| End point description:<br>Change in BMI measurements from Baseline. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Month 7                                     |  |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 57                         | 67                         |  |  |
| Units: kg/m <sup>2</sup>             |                            |                            |  |  |
| arithmetic mean (standard deviation) | -0.7 (± 1.60)              | -1.8 (± 2.05)              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Actual change from baseline in clinical signs over time: Weight

|  |   |
|--|---|
| End point title  | Actual change from baseline in clinical signs over time: Weight |
| End point description:<br>Actual change from baseline in clinical signs over time: Weight. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Month 7  |   |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 57                         | 67                         |  |  |
| Units: kg                            |                            |                            |  |  |
| arithmetic mean (standard deviation) | -1.8 (± 4.16)              | -4.6 (± 5.08)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Actual change from baseline in clinical signs over time: Body Composition: Region

|  |   |
|--|---|
| End point title  | Actual change from baseline in clinical signs over time: Body Composition: Region |
| End point description:<br>Change in body composition: region measurements from Baseline. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Month 7  |   |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 41                         | 48                         |  |  |
| Units: percentage fat                |                            |                            |  |  |
| arithmetic mean (standard deviation) | -1.0 (± 2.64)              | -1.8 (± 3.97)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Actual change from baseline in clinical signs over time: Waist circumference

|   |  |
|---|--|
| End point title   | Actual change from baseline in clinical signs over time: Waist circumference |
| End point description:<br>Change in waist circumference measurements from Baseline. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Month 7   |  |



| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 53                         | 63                         |  |  |
| Units: cm                            |                            |                            |  |  |
| arithmetic mean (standard deviation) | -1.6 (± 8.47)              | -7.1 (± 11.78)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Actual Change From Baseline in Clinical Signs Over Time: cholesterol & triglycerides

|  |  |
|--|--|
| End point title  | Actual Change From Baseline in Clinical Signs Over Time: cholesterol & triglycerides |
| End point description:<br>Change in parameter measurements: cholesterol & triglycerides from Baseline. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Month 7  |  |

| End point values                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose |  |  |
|--------------------------------------|----------------------------|----------------------------|--|--|
| Subject group type                   | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed          | 56                         | 64                         |  |  |
| Units: mmol/L                        |                            |                            |  |  |
| arithmetic mean (standard deviation) |                            |                            |  |  |
| Total cholesterol (n = 56, 64)       | -0.5 (± 1.07)              | -0.4 (± 1.00)              |  |  |
| HDL cholesterol (n = 55, 64)         | -0.1 (± 0.28)              | 0 (± 0.32)                 |  |  |
| Triglycerides (n = 56, 64)           | 0 (± 0.53)                 | -0.2 (± 0.64)              |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | 10 mg pasireotide LAR dose |
|-----------------------|----------------------------|

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 10 mg of Pasireotide LAR.

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | 30 mg pasireotide LAR dose |
|-----------------------|----------------------------|

Reporting group description:

Randomization was stratified based on Screening mUFC to ensure balanced distribution of disease severity in the two dose arms. These patients were dosed with 30 mg of Pasireotide LAR.

|                       |              |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All Patients

| Serious adverse events  | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose | All Patients      |
|---|----------------------------|----------------------------|-------------------|
| Total subjects affected by serious adverse events                   |                            |                            |                   |
| subjects affected / exposed   | 22 / 74 (29.73%)           | 19 / 76 (25.00%)           | 41 / 150 (27.33%) |
| number of deaths (all causes)                                       | 0                          | 2                          | 2                 |
| number of deaths resulting from adverse events                      | 0                          | 0                          | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |                            |                   |
| Endometrial cancer  |                            |                            |                   |
| subjects affected / exposed   | 1 / 74 (1.35%)             | 1 / 76 (1.32%)             | 2 / 150 (1.33%)   |
| occurrences causally related to treatment / all                     | 0 / 1                      | 0 / 1                      | 0 / 2             |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                      | 0 / 0             |
| Vascular disorders  |                            |                            |                   |
| Deep vein thrombosis  |                            |                            |                   |
| subjects affected / exposed   | 0 / 74 (0.00%)             | 1 / 76 (1.32%)             | 1 / 150 (0.67%)   |
| occurrences causally related to treatment / all                     | 0 / 0                      | 1 / 1                      | 1 / 1             |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                      | 0 / 0             |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| Hypertensive crisis                                  |                |                |                 |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Pregnancy, puerperium and perinatal conditions       |                |                |                 |
| Abortion spontaneous                                 |                |                |                 |
| subjects affected / exposed                          | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                |                |                 |
| Injection site pain                                  |                |                |                 |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Malaise  |                |                |                 |
| subjects affected / exposed                          | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Reproductive system and breast disorders             |                |                |                 |
| Endometrial hyperplasia                              |                |                |                 |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Ovarian cyst   |                |                |                 |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                |                |                 |
| Dysphonia  |                |                |                 |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Dyspnoea   |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary artery thrombosis                     |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1           |
| Pulmonary embolism                              |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 2 / 76 (2.63%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Investigations                                  |                |                |                 |
| Blood cortisol decreased                        |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 76 (1.32%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2          | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Blood cortisol increased                        |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gamma-glutamyltransferase increased             |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                |                 |
| Femoral neck fracture                           |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Road traffic accident                           |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Stress fracture                                 |                |                |                 |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 76 (0.00%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac disorders                               |                |                |                 |
| Angina pectoris                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Angina unstable                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac arrest                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiac failure                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiopulmonary failure                         |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1           |
| Coronary artery occlusion                       |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sinus bradycardia                               |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Anaemia   |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |
| Anogenital dysplasia                            |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastric ulcer                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Haemorrhoids                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Large intestine polyp                           |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Oedematous pancreatitis                         |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Cholecystitis acute                             |                |                |                 |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 76 (0.00%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cholelithiasis                                  |                |                |                 |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 3 / 76 (3.95%) | 5 / 150 (3.33%) |
| occurrences causally related to treatment / all | 2 / 2          | 2 / 3          | 4 / 5           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Renal and urinary disorders                     |                |                |                 |
| Acute kidney injury                             |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nephrolithiasis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Endocrine disorders                             |                |                |                 |
| Adrenal insufficiency                           |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hyperadrenocorticism                            |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pituitary-dependent Cushing's syndrome          |                |                |                 |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 1 / 76 (1.32%) | 3 / 150 (2.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Arthritis                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Osteoarthritis                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Osteoporosis                                    |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Spondylolisthesis                               |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                |                |                 |
| Cellulitis                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Diverticulitis                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis  |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Septic shock                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 76 (1.32%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Subcutaneous abscess                            |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                |                |                 |



|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Diabetes mellitus                               |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 76 (0.00%) | 1 / 150 (0.67%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hyperglycaemia                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 76 (1.32%) | 2 / 150 (1.33%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | 10 mg pasireotide LAR dose | 30 mg pasireotide LAR dose | All Patients       |
|---|----------------------------|----------------------------|--------------------|
| Total subjects affected by non-serious adverse events |                            |                            |                    |
| subjects affected / exposed                           | 73 / 74 (98.65%)           | 76 / 76 (100.00%)          | 149 / 150 (99.33%) |
| Vascular disorders                                    |                            |                            |                    |
| Hypertension  |                            |                            |                    |
| subjects affected / exposed                           | 11 / 74 (14.86%)           | 13 / 76 (17.11%)           | 24 / 150 (16.00%)  |
| occurrences (all)                                     | 14                         | 14                         | 28                 |
| Hypotension   |                            |                            |                    |
| subjects affected / exposed                           | 4 / 74 (5.41%)             | 5 / 76 (6.58%)             | 9 / 150 (6.00%)    |
| occurrences (all)                                     | 5                          | 5                          | 10                 |
| General disorders and administration site conditions  |                            |                            |                    |
| Asthenia  |                            |                            |                    |
| subjects affected / exposed                           | 10 / 74 (13.51%)           | 5 / 76 (6.58%)             | 15 / 150 (10.00%)  |
| occurrences (all)                                     | 11                         | 9                          | 20                 |
| Fatigue   |                            |                            |                    |
| subjects affected / exposed                           | 13 / 74 (17.57%)           | 15 / 76 (19.74%)           | 28 / 150 (18.67%)  |
| occurrences (all)                                     | 15                         | 18                         | 33                 |
| Oedema peripheral                                     |                            |                            |                    |
| subjects affected / exposed                           | 9 / 74 (12.16%)            | 12 / 76 (15.79%)           | 21 / 150 (14.00%)  |
| occurrences (all)                                     | 15                         | 13                         | 28                 |
| Pyrexia   |                            |                            |                    |
| subjects affected / exposed                           | 5 / 74 (6.76%)             | 2 / 76 (2.63%)             | 7 / 150 (4.67%)    |
| occurrences (all)                                     | 6                          | 2                          | 8                  |
| Respiratory, thoracic and mediastinal disorders       |                            |                            |                    |

|  |                      |                     |                        |
|--|----------------------|---------------------|------------------------|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 74 (2.70%)<br>2  | 4 / 76 (5.26%)<br>4 | 6 / 150 (4.00%)<br>6   |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 74 (10.81%)<br>8 | 5 / 76 (6.58%)<br>5 | 13 / 150 (8.67%)<br>13 |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 6 / 74 (8.11%)<br>10 | 5 / 76 (6.58%)<br>6 | 11 / 150 (7.33%)<br>16 |
| Blood cortisol decreased<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 74 (5.41%)<br>4  | 2 / 76 (2.63%)<br>5 | 6 / 150 (4.00%)<br>9   |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 74 (1.35%)<br>1  | 6 / 76 (7.89%)<br>6 | 7 / 150 (4.67%)<br>7   |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                              | 6 / 74 (8.11%)<br>7  | 7 / 76 (9.21%)<br>7 | 13 / 150 (8.67%)<br>14 |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)                  | 7 / 74 (9.46%)<br>10 | 6 / 76 (7.89%)<br>6 | 13 / 150 (8.67%)<br>16 |
| Glycosylated haemoglobin increased<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 74 (5.41%)<br>5  | 4 / 76 (5.26%)<br>4 | 8 / 150 (5.33%)<br>9   |
| Lipase increased<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 74 (2.70%)<br>2  | 4 / 76 (5.26%)<br>5 | 6 / 150 (4.00%)<br>7   |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 74 (5.41%)<br>4  | 3 / 76 (3.95%)<br>3 | 7 / 150 (4.67%)<br>7   |
| Injury, poisoning and procedural complications<br>Contusion  |                      |                     |                        |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 4 / 74 (5.41%)<br>4 | 1 / 76 (1.32%)<br>1 | 5 / 150 (3.33%)<br>5 |
| Cardiac disorders                                |                     |                     |                      |
| Palpitations                                     |                     |                     |                      |
| subjects affected / exposed                      | 4 / 74 (5.41%)      | 3 / 76 (3.95%)      | 7 / 150 (4.67%)      |
| occurrences (all)                                | 4                   | 3                   | 7                    |
| Sinus bradycardia                                |                     |                     |                      |
| subjects affected / exposed                      | 4 / 74 (5.41%)      | 5 / 76 (6.58%)      | 9 / 150 (6.00%)      |
| occurrences (all)                                | 8                   | 8                   | 16                   |
| Nervous system disorders                         |                     |                     |                      |
| Dizziness  |                     |                     |                      |
| subjects affected / exposed                      | 10 / 74 (13.51%)    | 8 / 76 (10.53%)     | 18 / 150 (12.00%)    |
| occurrences (all)                                | 19                  | 9                   | 28                   |
| Headache   |                     |                     |                      |
| subjects affected / exposed                      | 18 / 74 (24.32%)    | 10 / 76 (13.16%)    | 28 / 150 (18.67%)    |
| occurrences (all)                                | 25                  | 14                  | 39                   |
| Paraesthesia                                     |                     |                     |                      |
| subjects affected / exposed                      | 1 / 74 (1.35%)      | 4 / 76 (5.26%)      | 5 / 150 (3.33%)      |
| occurrences (all)                                | 1                   | 5                   | 6                    |
| Blood and lymphatic system disorders             |                     |                     |                      |
| Anaemia  |                     |                     |                      |
| subjects affected / exposed                      | 4 / 74 (5.41%)      | 5 / 76 (6.58%)      | 9 / 150 (6.00%)      |
| occurrences (all)                                | 7                   | 13                  | 20                   |
| Ear and labyrinth disorders                      |                     |                     |                      |
| Vertigo  |                     |                     |                      |
| subjects affected / exposed                      | 5 / 74 (6.76%)      | 0 / 76 (0.00%)      | 5 / 150 (3.33%)      |
| occurrences (all)                                | 6                   | 0                   | 6                    |
| Gastrointestinal disorders                       |                     |                     |                      |
| Abdominal discomfort                             |                     |                     |                      |
| subjects affected / exposed                      | 4 / 74 (5.41%)      | 2 / 76 (2.63%)      | 6 / 150 (4.00%)      |
| occurrences (all)                                | 5                   | 2                   | 7                    |
| Abdominal distension                             |                     |                     |                      |
| subjects affected / exposed                      | 4 / 74 (5.41%)      | 5 / 76 (6.58%)      | 9 / 150 (6.00%)      |
| occurrences (all)                                | 4                   | 6                   | 10                   |
| Abdominal pain                                   |                     |                     |                      |
| subjects affected / exposed                      | 11 / 74 (14.86%)    | 13 / 76 (17.11%)    | 24 / 150 (16.00%)    |
| occurrences (all)                                | 15                  | 15                  | 30                   |

|   |                        |                        |                          |
|---|------------------------|------------------------|--------------------------|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)        | 3 / 74 (4.05%)<br>4    | 8 / 76 (10.53%)<br>9   | 11 / 150 (7.33%)<br>13   |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                | 5 / 74 (6.76%)<br>5    | 5 / 76 (6.58%)<br>5    | 10 / 150 (6.67%)<br>10   |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                   | 26 / 74 (35.14%)<br>49 | 35 / 76 (46.05%)<br>67 | 61 / 150 (40.67%)<br>116 |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 74 (5.41%)<br>6    | 1 / 76 (1.32%)<br>1    | 5 / 150 (3.33%)<br>7     |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 74 (4.05%)<br>4    | 5 / 76 (6.58%)<br>5    | 8 / 150 (5.33%)<br>9     |
| Frequent bowel movements<br>subjects affected / exposed<br>occurrences (all)    | 4 / 74 (5.41%)<br>4    | 0 / 76 (0.00%)<br>0    | 4 / 150 (2.67%)<br>4     |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                      | 17 / 74 (22.97%)<br>33 | 16 / 76 (21.05%)<br>21 | 33 / 150 (22.00%)<br>54  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                    | 7 / 74 (9.46%)<br>11   | 2 / 76 (2.63%)<br>2    | 9 / 150 (6.00%)<br>13    |
| Hepatobiliary disorders   |                        |                        |                          |
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)              | 15 / 74 (20.27%)<br>18 | 33 / 76 (43.42%)<br>42 | 48 / 150 (32.00%)<br>60  |
| Cholestasis<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 74 (5.41%)<br>4    | 2 / 76 (2.63%)<br>2    | 6 / 150 (4.00%)<br>6     |
| Gallbladder cholesterolosis<br>subjects affected / exposed<br>occurrences (all) | 2 / 74 (2.70%)<br>2    | 4 / 76 (5.26%)<br>4    | 6 / 150 (4.00%)<br>6     |
| Hepatic function abnormal   |                        |                        |                          |

|   |                       |                     |                        |
|---|-----------------------|---------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                          | 2 / 74 (2.70%)<br>1   | 4 / 76 (5.26%)<br>4 | 6 / 150 (4.00%)<br>5   |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 74 (1.35%)<br>1   | 6 / 76 (7.89%)<br>6 | 7 / 150 (4.67%)<br>7   |
| Skin and subcutaneous tissue disorders                                    |                       |                     |                        |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)              | 2 / 74 (2.70%)<br>2   | 5 / 76 (6.58%)<br>5 | 7 / 150 (4.67%)<br>7   |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)              | 2 / 74 (2.70%)<br>2   | 5 / 76 (6.58%)<br>5 | 7 / 150 (4.67%)<br>7   |
| Erythema<br>subjects affected / exposed<br>occurrences (all)              | 2 / 74 (2.70%)<br>2   | 4 / 76 (5.26%)<br>5 | 6 / 150 (4.00%)<br>7   |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)              | 5 / 74 (6.76%)<br>7   | 6 / 76 (7.89%)<br>7 | 11 / 150 (7.33%)<br>14 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 74 (5.41%)<br>7   | 2 / 76 (2.63%)<br>2 | 6 / 150 (4.00%)<br>9   |
| Skin exfoliation<br>subjects affected / exposed<br>occurrences (all)      | 3 / 74 (4.05%)<br>4   | 4 / 76 (5.26%)<br>4 | 7 / 150 (4.67%)<br>8   |
| Endocrine disorders   |                       |                     |                        |
| Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all) | 4 / 74 (5.41%)<br>30  | 6 / 76 (7.89%)<br>7 | 10 / 150 (6.67%)<br>37 |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)        | 1 / 74 (1.35%)<br>1   | 4 / 76 (5.26%)<br>4 | 5 / 150 (3.33%)<br>5   |
| Musculoskeletal and connective tissue disorders                           |                       |                     |                        |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)            | 9 / 74 (12.16%)<br>14 | 4 / 76 (5.26%)<br>4 | 13 / 150 (8.67%)<br>18 |
| Back pain   |                       |                     |                        |

|                                    |                  |                  |                   |
|------------------------------------|------------------|------------------|-------------------|
| subjects affected / exposed        | 8 / 74 (10.81%)  | 8 / 76 (10.53%)  | 16 / 150 (10.67%) |
| occurrences (all)                  | 12               | 8                | 20                |
| Muscle spasms                      |                  |                  |                   |
| subjects affected / exposed        | 1 / 74 (1.35%)   | 5 / 76 (6.58%)   | 6 / 150 (4.00%)   |
| occurrences (all)                  | 1                | 6                | 7                 |
| Musculoskeletal chest pain         |                  |                  |                   |
| subjects affected / exposed        | 0 / 74 (0.00%)   | 4 / 76 (5.26%)   | 4 / 150 (2.67%)   |
| occurrences (all)                  | 0                | 4                | 4                 |
| Myalgia                            |                  |                  |                   |
| subjects affected / exposed        | 4 / 74 (5.41%)   | 4 / 76 (5.26%)   | 8 / 150 (5.33%)   |
| occurrences (all)                  | 4                | 4                | 8                 |
| Pain in extremity                  |                  |                  |                   |
| subjects affected / exposed        | 6 / 74 (8.11%)   | 6 / 76 (7.89%)   | 12 / 150 (8.00%)  |
| occurrences (all)                  | 7                | 9                | 16                |
| Infections and infestations        |                  |                  |                   |
| Bronchitis                         |                  |                  |                   |
| subjects affected / exposed        | 5 / 74 (6.76%)   | 2 / 76 (2.63%)   | 7 / 150 (4.67%)   |
| occurrences (all)                  | 5                | 4                | 9                 |
| Gastroenteritis                    |                  |                  |                   |
| subjects affected / exposed        | 7 / 74 (9.46%)   | 2 / 76 (2.63%)   | 9 / 150 (6.00%)   |
| occurrences (all)                  | 9                | 2                | 11                |
| Influenza                          |                  |                  |                   |
| subjects affected / exposed        | 12 / 74 (16.22%) | 6 / 76 (7.89%)   | 18 / 150 (12.00%) |
| occurrences (all)                  | 14               | 8                | 22                |
| Nasopharyngitis                    |                  |                  |                   |
| subjects affected / exposed        | 18 / 74 (24.32%) | 13 / 76 (17.11%) | 31 / 150 (20.67%) |
| occurrences (all)                  | 26               | 26               | 52                |
| Upper respiratory tract infection  |                  |                  |                   |
| subjects affected / exposed        | 5 / 74 (6.76%)   | 6 / 76 (7.89%)   | 11 / 150 (7.33%)  |
| occurrences (all)                  | 6                | 7                | 13                |
| Urinary tract infection            |                  |                  |                   |
| subjects affected / exposed        | 10 / 74 (13.51%) | 9 / 76 (11.84%)  | 19 / 150 (12.67%) |
| occurrences (all)                  | 13               | 16               | 29                |
| Metabolism and nutrition disorders |                  |                  |                   |
| Decreased appetite                 |                  |                  |                   |

|                             |                  |                  |                   |
|-----------------------------|------------------|------------------|-------------------|
| subjects affected / exposed | 3 / 74 (4.05%)   | 12 / 76 (15.79%) | 15 / 150 (10.00%) |
| occurrences (all)           | 3                | 13               | 16                |
| Diabetes mellitus           |                  |                  |                   |
| subjects affected / exposed | 15 / 74 (20.27%) | 20 / 76 (26.32%) | 35 / 150 (23.33%) |
| occurrences (all)           | 15               | 22               | 37                |
| Hypercholesterolaemia       |                  |                  |                   |
| subjects affected / exposed | 3 / 74 (4.05%)   | 6 / 76 (7.89%)   | 9 / 150 (6.00%)   |
| occurrences (all)           | 3                | 6                | 9                 |
| Hyperglycaemia              |                  |                  |                   |
| subjects affected / exposed | 36 / 74 (48.65%) | 35 / 76 (46.05%) | 71 / 150 (47.33%) |
| occurrences (all)           | 58               | 53               | 111               |
| Hyperlipidaemia             |                  |                  |                   |
| subjects affected / exposed | 1 / 74 (1.35%)   | 4 / 76 (5.26%)   | 5 / 150 (3.33%)   |
| occurrences (all)           | 1                | 4                | 5                 |
| Hyperuricaemia              |                  |                  |                   |
| subjects affected / exposed | 5 / 74 (6.76%)   | 5 / 76 (6.58%)   | 10 / 150 (6.67%)  |
| occurrences (all)           | 5                | 5                | 10                |
| Hypoglycaemia               |                  |                  |                   |
| subjects affected / exposed | 10 / 74 (13.51%) | 12 / 76 (15.79%) | 22 / 150 (14.67%) |
| occurrences (all)           | 26               | 58               | 84                |
| Type 2 diabetes mellitus    |                  |                  |                   |
| subjects affected / exposed | 3 / 74 (4.05%)   | 4 / 76 (5.26%)   | 7 / 150 (4.67%)   |
| occurrences (all)           | 3                | 5                | 8                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 15 September 2011 | In the original protocol, the investigators were unblinded to the dose and mUFC value after the patient completed Month 7. This amendment extended the blind of the Investigator until the Month 12 analyses have been performed to prevent bias associated with unblinding of Investigators, and to protect the integrity of the study; the time from the start of each individual 24-hour urine collection by the patient until storage was reduced from 14 days to 6 days to take into account the stability period of urinary creatinine at normal refrigeration temperatures; to ensure the blind was maintained, explicit language was added to prevent sites from assessing any cortisol-related parameters; the exclusion criterion relating to patients with HbA1c >8% was modified to exclude such patients regardless of the use of anti-diabetic medication; exclusion criteria were modified to include hypomagnesemia as a risk factor for torsade de pointes; new process for eligibility confirmation within the IRT system was established; requirement to record salivary cortisol and mUFC on eCRFs for screen failures was removed. Data record was done via central laboratory data transfer; mifepristone washout was added and 24h creatine clearance was removed; inconsistent language was corrected throughout the protocol; editorial and typographical errors were corrected throughout the study. |
| 13 December 2011  | Additional hepatic-related safety measures as a result of an internal hepatic medical review of pasireotide studies were included; the Beck's Depression Inventory II was removed from the secondary efficacy assessments as it was no longer deemed feasible; the washout period for octreotide LAR, lanreotide SR and lanreotide autogel was clarified to be 14 weeks; in order to prevent unblinding of investigators to dose levels, the instructions for use of the pasireotide long-acting 5 mg ampoule were updated; clarification was provided through edited text and inconsistent language was corrected throughout the protocol   |
| 08 October 2012   | Investigators were given the option to allow patients to remain on the current dose at Months 4, 7 and/or 9 visits in case of tolerability issues that in his/her clinical judgment would guide against a potential dose up-titration; language on glucose monitoring and treatment was expanded to reinforce glycemic goals of treatment per current ADA and European Association for the Study of Diabetes guidelines and to emphasize the need to initiate anti-hyperglycemic treatment accordingly; continued measuring quality of life change and Global impression of change over time into the extension phase allowed. In addition, a new SF-12v2 General Health Survey was introduced; pregnancy guidelines were updated; clarification was provided through edited text and inconsistent language was corrected throughout the protocol  |
| 13 May 2013       | Investigators, site staff, Novartis study team and related vendors gained access to mUFC and other cortisol-related assessments throughout the study while maintaining the blinding to the randomized treatment group until the Month 12 analysis. In addition, central MRI readings were also made available to investigators, site staff, Novartis study team and related vendors throughout the study; removal of clinical benefit question pertaining to dose up-titration at Months 7, 9, 12 and during the extension phase; language related to CRH test stimulation was updated; option to roll over patients post extension phase into a long term safety study was clarified; clarification was provided through edited text, and inconsistent language was corrected throughout the protocol   |
| 29 August 2013    | Instructions for use were updated for 30 mg dose using 60 mg kit and include procedure for preparation of the 30 mg dose using the 60 mg vial; patients who had completed Month 24 prior to the Month 12 database lock were allowed to continue beyond Month 24, and until the long-term safety study is opened to patients enrolled in the study; additional pregnancy assessments (urine pregnancy test) were added in the study as a safety precaution  |



|              |  |
|--------------|--|
| 07 June 2016 | <p>The purpose of this amendment was to clarify that DXA and MRI scans, required once every six months during treatment, were not required at the End of Study Treatment Visit if previous scan(s) were performed within the last six months.</p> <p>The clinical rationale for this action was that clinically relevant changes in parameters measured by these techniques were not expected to occur or be detected within a six month period.</p> |
|--------------|--|

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

|   |
|---|
| <p>All analyses in this study were descriptive in nature. No comparisons were made between the two arms, and no p-values are reported. For the primary and key-secondary, success was based on estimating the response rate (and 95% CI) in each arm.</p> |
|---|

Notes: