



Clinical trial results:

Follow Up of the Phase III, Multicentre, Non Comparative, One Single Group, Open Study to Assess the Long Term Efficacy and Tolerability of Pamoate of Triptorelin 11.25 mg in Children with Precocious Puberty Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2008-000565-39 |
| Trial protocol | FR |
| Global end of trial date | 27 January 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 13 January 2017 |
| First version publication date | 13 January 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | 2-54-52014-159 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00909844 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Ipsen Pharma |
| Sponsor organisation address | 65 quai Georges Gorse, Boulogne Billancourt Cedex, France, 92650 |
| Public contact | Medical Director, Endocrinology, Ipsen Pharma, clinical.trials@ipsen.com |
| Scientific contact | Medical Director, Endocrinology, Ipsen Pharma, clinical.trials@ipsen.com |

Notes:

Paediatric regulatory details

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|--|-----|
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of triptorelin pamoate 11.25 mg with respect to the proportion of children who maintain a regression or stabilisation of sexual maturity until the end of the study.

Protection of trial subjects:

The clinical study was conducted in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, under the ethical principles laid down in the Declaration of Helsinki. In addition, this clinical study adhered to all local regulatory requirements.

Background therapy:

The present study (2-54-52014-159) is a follow up study which allows patients included in the phase III 2-54-52014-143 study to be treated with triptorelin pamoate 11.25 mg prolonged release 3 month formulation until puberty. This follow up study was to start on the day of the last visit (Month 6) of study 2-54-52014-143 and therefore patients entering study 2-54-52014-159 had already received triptorelin pamoate 11.25 mg (2 injections) in study 2-54-52014-143.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 23 April 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 35 |
| Worldwide total number of subjects | 35 |
| EEA total number of subjects | 35 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 35 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was designed as a multicentre study and included 10 investigational sites in France. This follow up study was to start on the day of the last visit (Month 6) of the phase III 2-54-52014-143 study and was to end when the Investigator judged that the patient had completed his/her treatment, i.e. at around 11 years in girls and 13 in boys.

Pre-assignment

Screening details:

A maximum of 35 patients could be included in this study (i.e. the number of patients who had completed the phase III 2-54-52014-143 study). A total of 35 patients were screened and enrolled in this current study (2-54-52014-159).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------------------------|
| Arm title | Triptorelin Pamoate 11.25 mg |
|-----------|------------------------------|

Arm description:

11.25 mg triptorelin pamoate (prolonged release formulation) was administered via intramuscular (i.m.) injection once every 3 months from Baseline until end of the study treatment.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | triptorelin |
| Investigational medicinal product code | triptorelin |
| Other name | Decapeptyl P.R. |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

The study treatment was triptorelin pamoate 11.25 mg prolonged release formulation over 3 months, delivering a dose of 11.25 mg of triptorelin. Treatment consisted of a single i.m. injection of this 3 month formulation every 3 months until the end of the treatment.

| Number of subjects in period 1 | Triptorelin Pamoate 11.25 mg |
|--------------------------------|------------------------------|
| Started | 35 |
| Completed | 31 |
| Not completed | 4 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Triptorelin Pamoate 11.25 mg |
|-----------------------|------------------------------|

Reporting group description:

11.25 mg triptorelin pamoate (prolonged release formulation) was administered via intramuscular (i.m.) injection once every 3 months from Baseline until end of the study treatment.

| Reporting group values | Triptorelin Pamoate 11.25 mg | Total | |
|--|---------------------------------|---------|--|
| Number of subjects | 35 | 35 | |
| Age categorical Units: Subjects | | | |
| Age Continuous | | | |
| Baseline characteristics are presented for Intention-To-Treat Population (ITT) population, consisting of all enrolled patients who received at least one injection of study treatment in this follow up study. The reported baseline measure data were not re-collected at the start of the current study and are derived from data collected at Baseline of study 2-54-52014-143. | | | |
| Units: years arithmetic mean standard deviation | 8.73 ± 1.07 | - | |
| Gender Categorical Units: Subjects | | | |
| Female Male | 34 1 | 34 1 | |
| Weight at Pretreatment Units: kilogram (kg) arithmetic mean standard deviation | 32.4 ± 6.9 | - | |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Triptorelin Pamoate 11.25 mg |
| Reporting group description: 11.25 mg triptorelin pamoate (prolonged release formulation) was administered via intramuscular (i.m.) injection once every 3 months from Baseline until end of the study treatment. | |

Primary: Proportion of children with a stabilisation or regression of Tanner pubertal stage at the end of the study (Final Visit), compared to Pretreatment (Month -6) and Baseline (Month 0)

| | |
|-----------------|---|
| End point title | Proportion of children with a stabilisation or regression of Tanner pubertal stage at the end of the study (Final Visit), compared to Pretreatment (Month -6) and Baseline (Month 0) ^[1] |
|-----------------|---|

End point description:

The primary efficacy analysis was assessment of efficacy of triptorelin pamoate 11.25 mg with respect to the proportion of children who maintain a regression or stabilisation of sexual maturity (based on Tanner breast [girls] or genital [boys] pubertal stage) until the end of the study. Study treatment was to last until the end of the therapeutic period; visits for Months 36 and 48 were therefore optional since a child may already have finished the study at a prior visit. The Final Visit only occurred if the child did not end the study by a complete visit such as at Months 24, 36 or 48. Results are only presented for the proportion of girls with regression or stabilisation of Tanner breast pubertal stage (n=34). Only one boy was included in the study so results are not presented for this patient. Please also note the additional post-hoc analysis for regression or stabilisation of Tanner breast pubertal stage which applied the variable Last Visit on Treatment instead of Final Visit.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Months 12, 24, 36, 48 and End of Study (if applicable)

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: Only descriptive analysis was planned and performed for the primary endpoint and no comparative analysis is presented.

| End point values | Triptorelin Pamoate 11.25 mg | | | |
|-------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Compared to Pretreatment (Month -6) | 61.8 (43.56 to 77.83) | | | |
| Compared to Baseline (Month 0) | 52.9 (35.13 to 70.22) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Luteinizing Hormone (LH) response to Gonadotropin-Releasing Hormone

(GnRH) tests

| | |
|-----------------|--|
| End point title | Luteinizing Hormone (LH) response to Gonadotropin-Releasing Hormone (GnRH) tests |
|-----------------|--|

End point description:

A suppressed LH response to the GnRH test was defined as a stimulated peak of LH ≤ 3 international units per litre (IU/L). Proportion of patients who had a suppressed LH response to the GnRH test is reported. Only data for Pretreatment (Month -6) and Baseline (Month 0) is reported since almost no hormonal data was collected after Baseline and as a result, there was insufficient patient data available for analysis at all post-Baseline timepoints.

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

End point timeframe:

Month -6 and Month 0

| | | | | |
|----------------------------------|------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Pretreatment (Month -6) | 0 (0 to 0) | | | |
| Baseline (Month 0) | 91.4 (76.9 to 98.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of oestradiol in girls or testosterone in boys both measured by radioimmunoassay (RIA)

| | |
|-----------------|---|
| End point title | Levels of oestradiol in girls or testosterone in boys both measured by radioimmunoassay (RIA) |
|-----------------|---|

End point description:

Mean levels of oestradiol in girls or testosterone in boys are reported (n = number of patients with data available for analysis). Only data for Pretreatment (Month -6) and Baseline (Month 0) is reported since almost no hormonal data was collected after Baseline and as a result, there was insufficient patient data available for analysis at all post-Baseline timepoints.

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

End point timeframe:

Month -6 and Month 0

| | | | | |
|--|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: picograms per millilitre (pg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Oestradiol at Pretreatment (Girls; n=34) | 18.6 (± 9.8) | | | |
| Oestradiol at Baseline (Girls; n=34)) | 8.7 (± 4.5) | | | |
| Testosterone at Pretreatment (Boy; n=1)) | 6.8 (± 0) | | | |
| Testosterone at Baseline (Boy; n=1)) | 0.56 (± 0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Follicle Stimulating Hormone (FSH) response to GnRH test

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|---|--|
| End point title | Follicle Stimulating Hormone (FSH) response to GnRH test |
| End point description: | |
| A suppressed FSH response to the GnRH test was defined as a stimulated peak of FSH ≤3 IU/L. Proportion of patients who had a suppressed FSH response to the GnRH test is reported. Only data for Pretreatment (Month -6) and Baseline (Month 0) is reported since almost no hormonal data was collected after Baseline and as a result, there was insufficient patient data available for analysis at all post-Baseline timepoints. | |
| End point type | Secondary |
| End point timeframe: | |
| Month -6 and Month 0 | |

| | | | | |
|----------------------------------|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Pretreatment (Month -6) | 0 (0 to 0) | | | |
| Baseline (Month 0) | 82.9 (66.4 to 93.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Body Mass Index (BMI) for chronological age variation

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|-----------------|---|
| End point title | Body Mass Index (BMI) for chronological age variation |
|-----------------|---|

End point description:

Mean changes of BMI from Pretreatment at Baseline, Month 12 and End of Study, and from Baseline at Month 12 and End of Study are reported (n = number of patients with data available for analysis). No results are reported for the later timepoints (Months 24, 36 and 48) due to too few patient data available.

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

End point timeframe:

Months -6, 0, 12 and End of Study

| End point values | Triptorelin Pamoate 11.25 mg | | | |
|---|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: kilograms per metre squared (kg/m ²) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Pretreatment at Baseline (n=35) | 0.4 (± 0.7) | | | |
| Change from Pretreatment at Month 12 (n=30) | 1.6 (± 1.3) | | | |
| Change from Pretreatment at End of Study (n=31) | 2.4 (± 1.6) | | | |
| Change from Baseline at Month 12 (n=30) | 1.1 (± 1) | | | |
| Change from Baseline at End of Study (n=31) | 1.9 (± 1.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: BMI standard deviation (SD) score for chronological age variation

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|-----------------|---|
| End point title | BMI standard deviation (SD) score for chronological age variation |
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End point description:

Mean changes of BMI SD score from Pretreatment at Baseline, Month 12 and End of Study, and from Baseline at Month 12 and End of Study are reported (n = number of patients with data available for analysis). SD score is a standard term used in growth studies and represents standard deviations calculated as the patient value minus the mean divided by the SD. SD scores vary depending on the age and sex of the child. No results are reported for the later timepoints (Months 24, 36 and 48) due to too few patient data available.

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

End point timeframe:

Months -6, 0, 12 and End of Study

| | | | | |
|--|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: SD score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Pretreatment at Baseline (n=35) | 0.06 (± 0.3) | | | |
| Change from Pretreatment at Month 12 (n=30) | 0.8 (± 0.8) | | | |
| Change from Pretreatment at End of Study (n=31) | 0.1 (± 0.5) | | | |
| Change from Baseline at Month 12 (n=30) | 0.09 (± 0.3) | | | |
| Change from Baseline at End of Study (n=31) | 0.01 (± 0.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological parameters variations: height SD score

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|---|--|
| End point title | Auxological parameters variations: height SD score |
| End point description: | |
| Mean changes of height SD score from Pretreatment at Baseline, Month 12 and End of Study, and from Baseline at Month 12 and End of Study are reported (n = number of patients with data available for analysis). SD score is a standard term used in growth studies and represents standard deviations calculated as the patient value minus the mean divided by the SD. SD scores vary depending on the age and sex of the child. No results are reported for the later timepoints (Months 24, 36 and 48) due to too few patient data available. | |
| End point type | Secondary |
| End point timeframe: | |
| Months -6, 0, 12 and End of Study | |

| | | | | |
|--|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: SD score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Pretreatment at Baseline (n=34) | 0.1 (± 0.1) | | | |
| Change from Pretreatment at Month 12 (n=30) | -0.1 (± 0.3) | | | |
| Change from Pretreatment at End of Study (n=31) | -0.4 (± 0.5) | | | |
| Change from Baseline at Month 12 (n=29) | -0.1 (± 0.2) | | | |
| Change from Baseline at End of Study (n=31) | -0.4 (± 0.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological parameters variations: growth velocity SD score

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|-----------------|---|
| End point title | Auxological parameters variations: growth velocity SD score |
|-----------------|---|

End point description:

Mean changes of growth velocity SD score from Pretreatment at Baseline, Month 12 and End of Study, and from Baseline at Month 12 and End of Study are reported (n = number of patients with data available for analysis). SD score is a standard term used in growth studies and represents standard deviations calculated as the patient value minus the mean divided by the SD. SD scores vary depending on the age and sex of the child. No results are reported for the later timepoints (Months 24, 36 and 48) due to too few patient data available.

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

End point timeframe:

Months -6, 0, 12 and End of Study

| End point values | Triptorelin Pamoate 11.25 mg | | | |
|---|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: SD score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Pretreatment at Baseline (n=26) | -1.9 (± 2.1) | | | |
| Change from Pretreatment at Month 12 (n=24) | -2.4 (± 2.1) | | | |
| Change from Pretreatment at End of Study (n=24) | -2.7 (± 2.5) | | | |
| Change from Baseline at Month 12 (n=23) | -1.1 (± 1.4) | | | |
| Change from Baseline at End of Study (n=24) | -1.1 (± 1.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological parameters variations: weight variation

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|-----------------|---|
| End point title | Auxological parameters variations: weight variation |
|-----------------|---|

End point description:

Mean changes of weight from Pretreatment at Baseline, Month 12 and End of Study, and from Baseline at Month 12 and End of Study are reported (n = number of patients with data available for analysis). No

results are reported for the later timepoints (Months 24, 36 and 48) due to too few patient data available.

| | |
|-----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Months -6, 0, 12 and End of Study | |

| | | | | |
|---|------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from Pretreatment at Baseline (n=35) | 2.5 (± 1.5) | | | |
| Change from Pretreatment at Month 12 (n=30) | 7.6 (± 3.5) | | | |
| Change from Pretreatment at End of Study (n=31) | 13.2 (± 6.2) | | | |
| Change from Baseline at Month 12 (n=29) | 5.1 (± 2.8) | | | |
| Change from Baseline at End of Study (n=31) | 10.7 (± 6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Predicted adult height SD score

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|--|---------------------------------|
| End point title | Predicted adult height SD score |
| End point description: | |
| Mean change of predicted adult height SD score from Pretreatment at Baseline is reported (n = 31 for number of patients with data available for analysis). Note that data for this endpoint was only available for girls. SD score is a standard term used in growth studies and represents standard deviations calculated as the patient value minus the mean divided by the SD. SD scores vary depending on the age and sex of the child. No results are reported for any post-Baseline timepoints (Months 12, 24, 36 and 48) due to too few patient data available. | |
| End point type | Secondary |
| End point timeframe: | |
| Month -6 and Month 0 | |

| | | | | |
|--------------------------------------|------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: centimetre (cm) | | | | |
| arithmetic mean (standard deviation) | 0.3 (± 0.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Bone age maturation

| | |
|-----------------|---------------------|
| End point title | Bone age maturation |
|-----------------|---------------------|

End point description:

Mean change in difference between bone age and chronological age from Pretreatment at Baseline is reported (n = 33 for number of patients with data available for analysis). No results are reported for any post-Baseline timepoints (Months 12, 24, 36 and 48) due to too few patient data available.

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

End point timeframe:

Month -6 and Month 0

| | | | | |
|--------------------------------------|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: years | | | | |
| arithmetic mean (standard deviation) | -0.2 (± 0.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of girls with an uterine length < 36 millimetres (mm)

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|-----------------|--|
| End point title | Proportion of girls with an uterine length < 36 millimetres (mm) |
|-----------------|--|

End point description:

Proportion (percentage) of girls who had an uterine length < 36 mm at Pretreatment and at Baseline are reported (n = number of patients with data available for analysis). No results are reported for any post-Baseline timepoints (Months 12, 24, 36 and 48) due to too few patient data available.

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

End point timeframe:

Month -6 and Month 0

| | | | | |
|----------------------------------|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Pretreatment | 42.4 (25.5 to 60.8) | | | |
| Baseline | 41.2 (24.7 to 59.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of children with a stabilisation or regression of Tanner pubic hair pubertal stage at the end of the study (Final Visit), compared to Pretreatment (Month -6) and Baseline (Month 0)

| | |
|-----------------|---|
| End point title | Proportion of children with a stabilisation or regression of Tanner pubic hair pubertal stage at the end of the study (Final Visit), compared to Pretreatment (Month -6) and Baseline (Month 0) |
|-----------------|---|

End point description:

Pubic hair was measured by the Tanner method on a scale of 1 to 6. A low grade (i.e. 1) corresponds to a pre-pubertal stage and a high grade (i.e. 5 or 6) to an adult stage. Proportion of patients who had stabilisation or regression (no change in grade or a reduced grade) of Tanner pubic hair pubertal stage is reported. Study treatment was to last until the end of the therapeutic period; visits for Months 36 and 48 were optional because if the girl was already 11 and the boy already 13, they would have finished the study at a prior visit. The Final Visit was to occur only if the child did not end the study by a complete visit such as at Months 24, 36 or 48. Please also note the additional post-hoc analysis for proportion of children with a stabilisation or regression of Tanner pubic hair pubertal stage which applied the variable Last Visit on Treatment instead of Final Visit.

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

End point timeframe:

Months 12, 24, 36, 48 and End of Study (if applicable)

| | | | | |
|-------------------------------------|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Compared to Pretreatment (Month -6) | 37.1 (21.5 to 55.1) | | | |
| Compared to Baseline (Month 0) | 31.4 (16.9 to 49.3) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Proportion of girls with a stabilisation or regression of Tanner breast pubertal stage at the end of the study (Last Visit on Treatment), compared to Pretreatment (Month -6) and Baseline (Month 0)

| | |
|-----------------|--|
| End point title | Proportion of girls with a stabilisation or regression of Tanner breast pubertal stage at the end of the study (Last Visit on Treatment), compared to Pretreatment (Month -6) and Baseline (Month 0) |
|-----------------|--|

End point description:

The primary efficacy analysis was the assessment of efficacy of triptorelin pamoate 11.25 mg with respect to the proportion of children who maintain a regression or stabilisation of sexual maturity (based on Tanner breast [girls] or genital [boys] pubertal stage) until the end of the study. Results reported for the primary endpoint applied the variable 'Final Visit' for comparison to Pretreatment and Baseline. Since it was determined that the majority of patients had a Final Visit >3 months after their last injection, a post-hoc analysis of the proportion of girls with regression or stabilisation of Tanner breast pubertal stage was performed which applied the derived variable 'Last Visit on Treatment' to compare to Pretreatment stage and to Baseline. This post-hoc analysis was judged to be appropriate since triptorelin pamoate 3-month formulation allows release of the active compound over 3 months and beyond this time, pubertal development is expected to progress.

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

End point timeframe:

Months 12, 24, 36, 48 and End of Study (if applicable)

| | | | | |
|-------------------------------------|------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| Compared to Pretreatment (Month -6) | 91.2 (76.32 to 98.14) | | | |
| Compared to Baseline (Month 0) | 91.2 (76.32 to 98.14) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Proportion of children with a stabilisation or regression of Tanner pubic hair pubertal stage at the end of the study (Last Visit on Treatment), compared to Pretreatment (Month -6)

| | |
|-----------------|--|
| End point title | Proportion of children with a stabilisation or regression of Tanner pubic hair pubertal stage at the end of the study (Last Visit on Treatment), compared to Pretreatment (Month -6) |
|-----------------|--|

End point description:

One secondary efficacy endpoint in this study was the proportion of children who had stabilisation or regression (no change in grade or a reduced grade) of Tanner pubic hair pubertal stage at the end of the study. Results reported for this secondary endpoint applied the variable 'Final Visit' for comparison to Pretreatment and Baseline. Since it was determined that the majority of patients had a Final Visit >3

months after their last injection, a post-hoc analysis of the proportion of children with regression or stabilisation of Tanner pubic hair pubertal stage was performed which applied the derived variable 'Last Visit on Treatment' for comparison to the Pretreatment stage. This post-hoc analysis was judged to be appropriate since triptorelin pamoate 3-month formulation allows release of the active compound over 3 months and beyond this time, pubertal development is expected to progress.

| | |
|--|----------|
| End point type | Post-hoc |
| End point timeframe: | |
| Months 12, 24, 36, 48 and End of Study (if applicable) | |

| | | | | |
|-------------------------------|------------------------------------|--|--|--|
| End point values | Triptorelin Pamoate 11.25 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: percentage of patients | | | | |
| number (not applicable) | 57.1 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 51 months (up to 48 months treatment + 3 months follow up)

Adverse event reporting additional description:

Adverse event (AE) data is reported as treatment-emergent AEs

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Triptorelin Pamoate 11.25 mg |
|-----------------------|------------------------------|

Reporting group description:

11.25 mg triptorelin pamoate (prolonged release formulation) was administered via intramuscular (i.m.) injection once every 3 months from Baseline until end of the study treatment.

| Serious adverse events | Triptorelin Pamoate 11.25 mg | | |
|--|---------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Triptorelin Pamoate 11.25 mg | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 35 (45.71%) | | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| occurrences (all) | 9 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|--|---------------------|--|--|
| Pelvic pain subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

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| Only Pretreatment and Baseline data is reported for the hormonal-related endpoints as almost no hormonal data was collected after Baseline. Too few patient data was available for many timepoints so only limited post-Baseline data is reported overall. |
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Notes: