# Clinical trial results:
# A Phase 3, Randomized, Multi-Center, Open-Label Study to Evaluate the Efficacy and Safety of Leuprolide Acetate 11.25 and 30 mg Formulations in Children with Central Precocious Puberty

## Summary

| | |
|---|---|
| EudraCT number | 2014-004493-42 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 12 March 2010 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 April 2016 |
| First version publication date | 22 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | L-CP07-167 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00635817 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | AbbVie |
| Sponsor organisation address | 1 North Waukegan Road, North Chicago, IL, United States, 60064 |
| Public contact | Global Medical Information, AbbVie, 001 800-633-9110, |
| Scientific contact | Peter Bacher, AbbVie, peter.bacher@abbvie.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 12 March 2010 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2010 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to determine if 11.25 and 30 mg formulations of leuprolide are effective in treating children with Central Precocious Puberty (CPP).

Protection of trial subjects:

Prior to performing any trial-related procedures, the parent must review, understand, and sign an informed consent form and any privacy statement/authorization form required by the region. Each subject must review, understand and sign the Assent form when appropriate (as specified either by the Institutional Review Board and/or State, Regional and/or Local Regulations).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 June 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 | United States: 84 |
| Worldwide total number of subjects | 84 |
| EEA total number of subjects | 0 |

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) | 1 |
| Children (2-11 years) | 83 |
| 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:

Eighteen sites in the United States and 4 sites in Puerto Rico enrolled subjects into the study. The first subject was randomized 17 June 2008 and the last subject was randomized 12 Aug 2009.

### Pre-assignment

Screening details:

Subjects were randomized in a 1:1 ratio to 1 of the 2 treatment arms. To ensure balanced randomization, the study drug assignment was stratified on the basis of whether subjects were treatment-naive or had been treated with gonadotropin-releasing hormone agonist (GnRHa) previously.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Leuprolide Acetate 11.25 mg - Treatment Naive |

Arm description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Leuprolide acetate 3 month depot 11.25 mg |
| Investigational medicinal product code | |
| Other name | ABT-818, Lupron, leuprorelin acetate |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Two intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months (mo) apart.

| | |
|---|---|
| **Arm title** | Leuprolide Acetate 11.25 mg - Previous Treatment |

Arm description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Leuprolide acetate 3 month depot 11.25 mg |
| Investigational medicinal product code | |
| Other name | ABT-818, Lupron, leuprorelin acetate |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Two intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months (mo) apart.

| | |
|---|---|
| **Arm title** | Leuprolide Acetate 30 mg - Treatment Naive |

Arm description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Leuprolide acetate 3 month depot 30 mg |
| Investigational medicinal product code | |
| Other name | ABT-818, Lupron, leuprorelin acetate |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Two intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months (mo) apart.

| | |
|---|---|
| **Arm title** | Leuprolide Acetate 30 mg - Previous Treatment |

Arm description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Leuprolide acetate 3 month depot 30 mg |
| Investigational medicinal product code | |
| Other name | ABT-818, Lupron, leuprorelin acetate |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Two intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months (mo) apart.

| **Number of subjects in period 1** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive |
|---|---|---|---|
| Started | 21 | 21 | 21 |
| Completed | 15 | 19 | 19 |
| Not completed | 6 | 2 | 2 |
| Not specified | 6 | 2 | 2 |

| **Number of subjects in period 1** | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|
| Started | 21 |
| Completed | 21 |
| Not completed | 0 |
| Not specified | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Leuprolide Acetate 11.25 mg - Treatment Naive |
| Reporting group description: | |
| Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 11.25 mg - Previous Treatment |
| Reporting group description: | |
| Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 30 mg - Treatment Naive |
| Reporting group description: | |
| Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 30 mg - Previous Treatment |
| Reporting group description: | |
| Subjects who received at least 1 dose of study drug. | |

| Reporting group values | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive |
|---|---|---|---|
| Number of subjects | 21 | 21 | 21 |
| Age Categorical<br>Units: Participants | | | |
| <=18 years | 21 | 21 | 21 |
| Between 18 and 65 years | 0 | 0 | 0 |
| >=65 years | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 7.4 | 8.1 | 7.3 |
| standard deviation | ± 1.47 | ± 1.83 | ± 1.74 |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 19 | 20 | 19 |
| Male | 2 | 1 | 2 |

| Reporting group values | Leuprolide Acetate 30 mg - Previous Treatment | Total | |
|---|---|---|---|
| Number of subjects | 21 | 84 | |
| Age Categorical<br>Units: Participants | | | |
| <=18 years | 21 | 84 | |
| Between 18 and 65 years | 0 | 0 | |
| >=65 years | 0 | 0 | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 8.4 | | |
| standard deviation | ± 1.75 | - | |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 18 | 76 | |
| Male | 3 | 8 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Leuprolide Acetate 11.25 mg - Treatment Naive |
| Reporting group description: Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 11.25 mg - Previous Treatment |
| Reporting group description: Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 30 mg - Treatment Naive |
| Reporting group description: Subjects who received at least 1 dose of study drug. | |
| Reporting group title | Leuprolide Acetate 30 mg - Previous Treatment |
| Reporting group description: Subjects who received at least 1 dose of study drug. | |
| Subject analysis set title | Leuprolide Acetate 11.25 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects from both treatment groups who received 11.25 mg leuprolide acetate, both treatment naive and previously treated, were combined. | |
| Subject analysis set title | Leuprolide Acetate 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects from both treatment groups who received 30 mg leuprolide acetate, both treatment naive and previously treated, were combined. | |

### Primary: Percentage of Participants With Suppression of Peak Stimulated Luteinizing Hormone (<4 mIU/mL) From Month 2 Through Month 6

| | |
|---|---|
| End point title | Percentage of Participants With Suppression of Peak Stimulated Luteinizing Hormone (<4 mIU/mL) From Month 2 Through Month 6[1] |
| End point description: Percentage of participants with suppression of peak stimulated luteinizing hormone that was measured after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test at Month (Mo) 2, 3, and 6. The analysis was performed according to a life table method. Subjects who withdrew without peak-stimulated luteinizing hormone >=4 mIU/mL were censored at their last measurement of peak-stimulated luteinizing hormone. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement of peak stimulated luteinizing hormone at Mo 2 or afterward defined as the intent-to-treat population. | |
| End point type | Primary |
| End point timeframe: Month 2 through 6 | |

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: Descriptive data were summarized for this end point per protocol.

| End point values | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 21 | 21 | 21 |
| Units: Percentage of Participants | | | | |

| | | | | |
|---|---|---|---|---|
| number (confidence interval 95%) | 76.2 (58 to 94.4) | 80.7 (63.6 to 97.7) | 90.5 (77.9 to 100) | 100 (100 to 100) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Suppression of Basal Estradiol <20 pg/mL by Visit

| | |
|---|---|
| End point title | Percentage of Participants with Suppression of Basal Estradiol <20 pg/mL by Visit |

End point description:

Percentage of participants with suppression of estradiol, out of the number of girls with at least 1 estradiol measurement at each visit (n/N%). Only girls are analyzed in this outcome measure. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population. N=the number of patients with available data at each time point.

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

End point timeframe:

Month 1, 2, 3 and 6

| End point values | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 19 | 20 | 19 | 18 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Mo 1 (Arm A N=17, B N=18, C N=19, D N=16) | 100 (80.5 to 100) | 100 (81.5 to 100) | 100 (82.4 to 100) | 100 (79.4 to 100) |
| Mo 2 (Arm A N=19, B N=14, C N=19, D N=14) | 94.7 (74 to 99.9) | 100 (76.8 to 100) | 100 (82.4 to 100) | 100 (76.8 to 100) |
| Mo 3 (Arm A N=15, B N=18, C N=17, D N=18) | 100 (78.2 to 100) | 100 (81.5 to 100) | 100 (80.5 to 100) | 100 (81.5 to 100) |
| Mo 6 (Arm A N=12, B N=16, C N=15, D N=17) | 100 (73.5 to 100) | 93.8 (69.8 to 99.8) | 100 (78.2 to 100) | 100 (80.5 to 100) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Suppression of Testosterone in <30 ng/dL by Visit

| | |
|---|---|
| End point title | Percentage of Participants With Suppression of Testosterone in <30 ng/dL by Visit |

End point description:

Percentage of participants with suppression of testosterone, out of the number of boys with at least 1 testosterone measurement at each visit (n/N%). Only boys are analyzed in this outcome measure. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population. N=the number of patients with available data at each time point.

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

End point timeframe:

Month 1, 2, 3 and 6

| **End point values** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2 | 1 | 2 | 3 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Mo 1 (Arm A N=2, B N=1, C N=2, D N=3) | 50 (1.3 to 98.7) | 100 (2.5 to 100) | 100 (15.8 to 100) | 100 (29.2 to 100) |
| Mo 2 (Arm A N=2, B N=1, C N=2, D N=3) | 50 (1.3 to 98.7) | 100 (2.5 to 100) | 100 (15.8 to 100) | 100 (29.2 to 100) |
| Mo 3 (Arm A N=2, B N=1, C N=2, D N=3) | 50 (1.3 to 98.7) | 100 (2.5 to 100) | 100 (15.8 to 100) | 100 (29.2 to 100) |
| Mo 6 (Arm A N=1, B N=1, C N=2, D N=3) | 100 (2.5 to 100) | 100 (2.5 to 100) | 100 (15.8 to 100) | 100 (29.2 to 100) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Peak-stimulated Luteinizing Hormone Concentration by Visit

| End point title | Peak-stimulated Luteinizing Hormone Concentration by Visit |
|---|---|

End point description:

Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population. N=the number of patients with available data at each time point.

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

End point timeframe:

Baseline, Month 1, 2, 3 and 6

| End point values | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 21 | 21 | 21 |
| Units: mIU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Arm A N=21, B N=21, C N=21, D N=21) | 45.9 (± 42.38) | 1.8 (± 1.78) | 23.5 (± 16.76) | 1.7 (± 1.09) |
| Mo 1 (Arm A N=21, B N=21, C N=21, D N=21) | 4.4 (± 7.29) | 1.7 (± 1.36) | 1.9 (± 1.74) | 1.4 (± 0.76) |
| Mo 2 (Arm A N=21, B N=20, C N=21, D N=20) | 4.5 (± 7.2) | 2 (± 1.48) | 2 (± 2.25) | 1.5 (± 0.73) |
| Mo 3 (Arm A N=16, B N=20, C N=20, D N=21) | 2.3 (± 1.23) | 1.8 (± 1.1) | 1.4 (± 0.78) | 1.5 (± 0.61) |
| Mo 6 (Arm A N=15, B N=18, C N=18, D N=21) | 2 (± 0.85) | 2.5 (± 2.43) | 1.6 (± 0.95) | 1.5 (± 0.89) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Suppression of the Physical Signs of Puberty (Breast Development) at Month 6

| End point title | Percentage of Participants With Suppression of the Physical Signs of Puberty (Breast Development) at Month 6 |
|---|---|

End point description:

Percentage of participants with suppression of breast development, out of the number of girls with pubertal staging of breast development (n/N%). Only girls are analyzed in this outcome measure. Breast development was rated from Stage 1 (early development) through Stage 5 (full development) according to a Tanner Staging pictogram. Girls entering the study with fully developed breasts (Stage 5) were excluded from this analysis. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population.

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

End point timeframe:

Month 6

| End point values | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 18 | 17 | 17 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 92.9 (66.1 to 99.8) | 88.9 (65.3 to 98.6) | 82.4 (56.6 to 96.2) | 82.4 (56.6 to 96.2) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Suppression of the Physical Signs of Puberty (Testicular Volume and Genital Development) at Month 6

| End point title | Percentage of Participants With Suppression of the Physical Signs of Puberty (Testicular Volume and Genital Development) at Month 6 |
|---|---|

End point description:

Percentage of participants with suppression of genital development and testicular volume, out of the number of boys with pubertal staging of genital development or testicular volume (n/N%). Only boys are analyzed in this outcome measure. External genital development (testes and penis) was rated from Stage 1 (early development) through Stage 5 (full development) according to a Tanner Staging pictogram. Boys entering the study with fully developed genitals (Stage 5) were excluded from this analysis. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population.

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

End point timeframe:

Month 6

| **End point values** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 1 | 2 | 3 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 100 (2.5 to 100) | 0 (0 to 97.5) | 50 (1.3 to 98.7) | 33.3 (0.8 to 90.6) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Incremental Growth Rate (cm/Year) at Month 6

| End point title | Change From Baseline in Incremental Growth Rate (cm/Year) at Month 6 |
|---|---|

End point description:

The growth rate at baseline was the growth rate during the last year before the start of treatment and was calculated with the measurement closest to Day -336 (before Day -30) and the measurement up to Day 1. Growth rate at Month 6 was defined as the ratio of the change in height from Day 1 to the

change in chronological age, with an approximate 6-month interval between the 2 height measurements. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population. N=the number of patients with available data at each time point.

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

End point timeframe:

Baseline and Month 6

| **End point values** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 | 21 | 21 | 21 |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Arm A N=20, B N=21, C N=21, D N=21) | 7.25 (± 5.3) | 6.58 (± 2.39) | 7.83 (± 5.96) | 6.05 (± 1.55) |
| Mo 6 (Arm A N=14, B N=19, C N=19, D N=21) | -2.51 (± 5.29) | -0.98 (± 2.24) | -2.34 (± 4.22) | -0.91 (± 2.45) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Ratio of Change From Baseline in Bone Age/Change From Baseline in Chronological Age at Month 6

| End point title | Ratio of Change From Baseline in Bone Age/Change From Baseline in Chronological Age at Month 6 |
|---|---|

End point description:

The ratio at Month 6 was calculated as (bone age at Month 6 - bone age at baseline)/(chronological age at Month 6 - chronological age at baseline). Observed data were used with no imputation for missing data. Baseline bone-age radiograph was performed at or within 3 months of the Screening Visit. Participants must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population.

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

End point timeframe:

Baseline to Month 6

| **End point values** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 18 | 18 | 21 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 0.59 (± 0.59) | 0.5 (± 0.57) | 1 (± 0.74) | 1.07 (± 1.6) |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Percentage of Participants With Suppression of Peak Stimulated Luteinizing Hormone (<4 mIU/mL) From Month 2 Through Month 6 (Simple Percentage With Binomial Exact Confidence Intervals)

| End point title | Percentage of Participants With Suppression of Peak Stimulated Luteinizing Hormone (<4 mIU/mL) From Month 2 Through Month 6 (Simple Percentage With Binomial Exact Confidence Intervals) |
|---|---|

End point description:

Percentage of participants with suppression of peak stimulated luteinizing hormone that was measured after a GnRHa stimulation test at Mo 2, 3, and 6. A simple percentage and binomial exact confidence intervals were used in this analysis. Participants who withdrew with luteinizing hormone that remained suppressed were counted as a success. This analysis was performed after the clinical study report was completed and is included to match the FDA package insert. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement of peak stimulated luteinizing hormone at Mo 2 or afterward defined as the intent-to-treat population.

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

End point timeframe:

Month 2 through 6

| **End point values** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 11.25 mg - Previous Treatment | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 21 | 21 | 21 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 76.2 (52.8 to 91.8) | 81 (58.1 to 94.6) | 90.5 (69.6 to 98.8) | 100 (83.9 to 100) |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Percentage of Participants With a Decrease From Baseline in the Ratio of Bone Age to Chronological Age at Month 6 Compared to Baseline

| End point title | Percentage of Participants With a Decrease From Baseline in the Ratio of Bone Age to Chronological Age at Month 6 Compared to Baseline |
|---|---|

End point description:

The ratio at baseline or Month 6 was calculated as bone age at baseline or Month 6/chronological age at

baseline or Month 6. The percentage of participants with a decrease in the ratio was calculated as a simple percentage for each dose group. Observed data were used with no imputation for missing data. The baseline time frame was increased from the secondary outcome in this analysis to include all participants with a bone age radiograph at screening. This analysis was performed after the clinical study report was completed & is included to match the FDA package insert. The baseline time frame was increased from the secondary outcome to this analysis to include all participants with a bone age radiograph at screening.

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

End point timeframe:

Baseline to Month 6

| **End point values** | Leuprolide Acetate 11.25 mg | Leuprolide Acetate 30 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 33 | 40 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 87.9 | 75 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were defined as any event with an onset data after the first dose of study drug and with an onset date no more than 30 days after the last day of study drug treatment which is 84 days after the last injection date.

Adverse event reporting additional description:

Safety analyses were performed with available data from all subjects who received at least 1 injection of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 12.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Leuprolide Acetate 11.25 mg - Treatment Naive |

Reporting group description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Reporting group title | Leuprolide Acetate 30 mg - Treatment Naive |

Reporting group description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Reporting group title | Leuprolide Acetate 30 mg - Previous Treatment |

Reporting group description:

Subjects who received at least 1 dose of study drug.

| | |
|---|---|
| Reporting group title | Leuprolide Acetate 11.25 mg - Previous Treatment |

Reporting group description:

Subjects who received at least 1 dose of study drug.

| Serious adverse events | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Leuprolide Acetate 11.25 mg - Previous Treatment | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Leuprolide Acetate 11.25 mg - Treatment Naive | Leuprolide Acetate 30 mg - Treatment Naive | Leuprolide Acetate 30 mg - Previous Treatment |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 15 / 21 (71.43%) | 17 / 21 (80.95%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 21 (9.52%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 2 | 1 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 21 (9.52%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 6 / 21 (28.57%) | 6 / 21 (28.57%) |
| occurrences (all) | 2 | 7 | 12 |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 4 / 21 (19.05%) | 7 / 21 (33.33%) |
| occurrences (all) | 5 | 4 | 9 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 21 (9.52%) | 6 / 21 (28.57%) |
| occurrences (all) | 2 | 2 | 9 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 21 (19.05%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 4 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 21 (9.52%) | 5 / 21 (23.81%) |
| occurrences (all) | 1 | 3 | 8 |
| Nasal congestion | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 4 / 21 (19.05%) | 1 / 21 (4.76%) |
| occurrences (all) | 4 | 4 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhea | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 21 (0.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 1 | 0 | 6 |
| Psychiatric disorders | | | |
| Mood altered | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 21 (9.52%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Endocrine disorders | | | |
| Goiter | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 21 (9.52%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 21 (4.76%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 1 | 4 |
| Infections and infestations | | | |
| Ear Infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 21 (4.76%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 21 (4.76%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 2 | 2 |
| Otitis media | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 3 / 21 (14.29%) | 2 / 21 (9.52%) |
| occurrences (all) | 2 | 3 | 2 |

| **Non-serious adverse events** | Leuprolide Acetate 11.25 mg - Previous Treatment | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 21 (85.71%) | | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | | |
| occurrences (all) | 2 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin laceration<br>subjects affected / exposed<br>occurrences (all) | <br>2 / 21 (9.52%)<br>2<br><br><br>0 / 21 (0.00%)<br>0 | | |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 21 (0.00%)<br>0<br><br><br>4 / 21 (19.05%)<br>4 | | |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 21 (4.76%)<br>1 | | |
| General disorders and administration site conditions<br>Injection site pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | <br><br>4 / 21 (19.05%)<br>6<br><br><br>2 / 21 (9.52%)<br>2 | | |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 21 (4.76%)<br>2 | | |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 21 (4.76%)<br>1 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasal congestion | <br><br>4 / 21 (19.05%)<br>4<br><br> | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinorrhea<br>subjects affected / exposed<br>occurrences (all) | 1 / 21 (4.76%)<br>2<br><br>2 / 21 (9.52%)<br>3<br><br>3 / 21 (14.29%)<br>3<br><br>0 / 21 (0.00%)<br>0 | | |
| Psychiatric disorders<br>Mood altered<br>subjects affected / exposed<br>occurrences (all) | 1 / 21 (4.76%)<br>1 | | |
| Endocrine disorders<br>Goiter<br>subjects affected / exposed<br>occurrences (all) | 0 / 21 (0.00%)<br>0 | | |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 2 / 21 (9.52%)<br>2 | | |
| Infections and infestations<br>Ear Infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Otitis media<br>subjects affected / exposed<br>occurrences (all) | 2 / 21 (9.52%)<br>2<br><br>2 / 21 (9.52%)<br>2<br><br>4 / 21 (19.05%)<br>5<br><br>0 / 21 (0.00%)<br>0 | | |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 21 (14.29%)<br>3 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 February 2008 | The primary purpose of this amendment was to include a lower dose of leuprolide acetate (11.25 mg) in addition to the 30 mg dose, both administered with a 3-month dosing interval; to increase the number of study subjects to approximately 80, approximately 40 naïve to GnRHa therapy (a minimum of 30) and a minimum of 40 subjects previously treated with GnRHa; to change the study design to a randomized open-label study utilizing an Interactive Voice-Response System/Interactive Web-Response System to randomize subjects. The option for entry into a separate open-label extension study for qualifying subjects who were adequately suppressed through Month 6 of this study, was included. The Posttreatment Follow-up Period was extended to 12 weeks (occurred 12 weeks following the subject's Month 6 visit) to better coincide with routine office visit schedule for standard of care treatment. Telephone calls were added to assess the occurrence of any potential hormonal flare responses to the 11.25 and 30 mg leuprolide acetate depot doses. Clarifications to the adverse event assessment section were made. Windows for retrospective diagnostic imaging (diagnostic brain imaging by magnetic resonance imaging (MRI)/computed tomography (CT) scan; screening pelvic, adrenal, and testicular ultrasounds) and laboratory test results (beta human chorionic gonadotropin [β-hCG] in male subjects, adrenal blood tests, GnRHa stimulation testing) were increased. Growth rate and bone age versus chronological age were changed from additional endpoints to secondary endpoints, and peak-stimulated luteinizing hormone concentration was added as a secondary endpoint. 14. Prior and concomitant use of insulin-like growth factor-1 (IGF-1) and use of estrogen preparations within 2 months of Day 1 were added as exclusionary criteria. |
| 06 April 2009 | As a result of the transition of the Lupron program from TAP Pharmaceuticals to Abbott, the primary purpose of Amendment 2 was to document changes regarding Sponsor name and contact information and to provide a new fax number and a revised timeline for reporting serious adverse events to Abbott. Major changes included the following:<br>-include convulsions as a rarely reported event<br>-document that the commercially-available generic leuprolide acetate daily injection (Leuprolide Acetate Injection) will be used to conduct the GnRHa Stimulation test<br>-clarify that a copy of the hand-wrist radiograph will be maintained at the study site in the subject's study file and include reference to (and a sample of) the Hand/Wrist Radiograph Transmittal Form that is submitted with the radiograph to Lifespan<br>-clarify that screening baseline sex steroids are required even if a stimulation test in the treatment-naïve population was performed within the past 30 days<br>-clarify that at the Month 6 and Early Discontinuation Visits, the blood collections for basal gonadotropin and sex steroids are relative to the Day 1 depot Injection<br>-clarify that the congenital adrenal hyperplasia (CAH) panel was not required if an alternative cause of precocious puberty had been ruled-out, that testosterone levels were only performed on males, and that an adrenocorticotropic hormone (ACTH) stimulation test was required prior to randomization if the initial Screening CAH panel results were inconclusive<br>-incorporate a longer study duration as a result of the enrollment period having been extended a few months<br>-update criteria for withdrawal (accelerated progression of pubertal symptoms, excluding pubic hair, any time after the Month 2 study visit)<br>-clarify premature discontinuation from trial, permitted/prohibited medications, adverse event and serious adverse event procedures |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported