# Clinical trial results:
# A Phase 3, Multicenter, Open-Label, Two-Part Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Leuprolide Acetate 45 mg 6-Month Depot Formulation in Children With Central Precocious Puberty (CPP)

## Summary

| | |
|---|---|
| EudraCT number | 2022-004131-61 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 29 November 2023 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 May 2024 |
| First version publication date | 17 May 2024 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | M16-904 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03695237 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co.KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@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? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 29 November 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and efficacy of LA 45 mg 6-month depot formulation for the treatment of CPP in children who are either naive to treatment with a GnRHa or who have been previously treated with a GnRHa.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 October 2018 |
| 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 | Puerto Rico: 2 |
| Country: Number of subjects enrolled | United States: 43 |
| Worldwide total number of subjects | 45 |
| 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) | 0 |
| Children (2-11 years) | 45 |
| 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:

Participants were enrolled at 16 sites in the United States including Puerto Rico.
The study enrolled pediatric participants with central precocious puberty (CPP) who were either naïve to treatment with a gonadotropin-releasing hormone receptor agonist (GnRHa) or who had been previously treated with a GnRHa.

### Pre-assignment

Screening details:

The study was conducted in 2 parts. In Part 1, leuprolide acetate (LA) 45 mg 6-month depot formulation was evaluated from Baseline to Week 48. Following completion of Part 1 assessments, participants continued in Part 2 (extension period) to evaluate long-term treatment of LA 45 mg 6-month depot formulation (up to 24 months).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Leuprolide Acetate - Previously Treated |

Arm description:

Participants who had been previously treated with a GnRHa for at least 6 months prior to enrollment received leuprolide acetate (LA) 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Leuprolide Acetate |
| Investigational medicinal product code | ABT-818 |
| Other name | Lupron Depot-PED® |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Administered intramuscularly as an injection

| | |
|---|---|
| **Arm title** | Leuprolide Acetate - Treament Naïve |

Arm description:

Participants without previous GnRHa treatment prior to enrollment (treatment naïve) received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Leuprolide Acetate |
| Investigational medicinal product code | ABT-818 |
| Other name | Lupron Depot-PED® |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Administered intramuscularly as an injection

| **Number of subjects in period 1** | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve |
|---|---|---|
| Started | 18 | 27 |
| Completed | 8 | 20 |
| Not completed | 10 | 7 |
| Consent withdrawn by subject | 1 | 3 |
| Lost to follow-up | 1 | 2 |
| Other, Not Specified | 8 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Leuprolide Acetate - Previously Treated |
| Reporting group description: | |
| Participants who had been previously treated with a GnRHa for at least 6 months prior to enrollment received leuprolide acetate (LA) 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2. | |
| Reporting group title | Leuprolide Acetate - Treament Naïve |
| Reporting group description: | |
| Participants without previous GnRHa treatment prior to enrollment (treatment naïve) received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2. | |

| Reporting group values | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve | Total |
|---|---|---|---|
| Number of subjects | 18 | 27 | 45 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 8.1 | 7.7 | |
| standard deviation | ± 1.73 | ± 0.83 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 17 | 24 | 41 |
| Male | 1 | 3 | 4 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 9 | 11 |
| Not Hispanic or Latino | 16 | 18 | 34 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 1 | 0 | 1 |
| Black or African American | 4 | 3 | 7 |
| White | 12 | 18 | 30 |
| More than one race | 0 | 6 | 6 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Leuprolide Acetate - Previously Treated |

Reporting group description:

Participants who had been previously treated with a GnRHa for at least 6 months prior to enrollment received leuprolide acetate (LA) 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Reporting group title | Leuprolide Acetate - Treament Naïve |

Reporting group description:

Participants without previous GnRHa treatment prior to enrollment (treatment naïve) received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Subject analysis set title | Part 1: Leuprolide Acetate - Overall |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1.

| | |
|---|---|
| Subject analysis set title | Parts 1 and 2: Leuprolide Acetate - Previously Treated |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants who had been previously treated with a GnRHa for at least 6 months prior to enrollment received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Subject analysis set title | Parts 1 and 2: Leuprolide Acetate - Treament Naïve |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants without previous GnRHa treatment prior to enrollment (treatment naïve) received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Subject analysis set title | Parts 1 and 2: Leuprolide Acetate - Overall |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Subject analysis set title | Part 2: Leuprolide Acetate - Overall |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

### Primary: Percentage of Participants With Suppression of Peak Gonadotropin-releasing Hormone Agonist (GnRHa)-Stimulated Luteinizing Hormone (LH) to Less Than 4 mIU/mL at Week 24

| | |
|---|---|
| End point title | Percentage of Participants With Suppression of Peak Gonadotropin-releasing Hormone Agonist (GnRHa)-Stimulated Luteinizing Hormone (LH) to Less Than 4 mIU/mL at Week 24[1] |

End point description:

Suppression of GnRHa-stimulated luteinizing hormone (LH) was measured using a peak GnRHa stimulation test, performed using subcutaneous injection with an aqueous formulation of leuprolide acetate at 20 µg/kg.
Peak stimulated LH was calculated by taking the maximum LH concentrations measured from blood samples taken at 30 or 60 min following the GnRHa stimulation test.
Suppression of GnRHa-stimulated luteinizing hormone is defined as peak stimulated LH less than 4 mIU/mL.

The Full Analysis Set (FAS) consists of all participants who received at least 1 dose of study drug.

Participants with missing GnRHa-stimulated LH results at Week 24 were counted as not achieving suppression.

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

End point timeframe:

Week 24 (prior to the Week 24 dose); samples for LH measurement were taken 30 and 60 minutes after the stimulation test injection.

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: Statistical analyses per protocol are presented in the data table.

| **End point values** | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve | Part 1: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 18 | 27 | 45 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 94.4 (72.7 to 99.9) | 81.5 (61.9 to 93.7) | 86.7 (73.2 to 95.0) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Percentage of Participants With Suppression of Peak GnRHa-stimulated LH to Less Than 4 mIU/mL at Weeks 12, 20, 44, and 48

| End point title | Part 1: Percentage of Participants With Suppression of Peak GnRHa-stimulated LH to Less Than 4 mIU/mL at Weeks 12, 20, 44, and 48 |
|---|---|

End point description:

Suppression of GnRHa-stimulated luteinizing hormone (LH) was measured using a peak GnRHa stimulation test, performed using subcutaneous injection with an aqueous formulation of leuprolide acetate at 20 µg/kg.
Peak stimulated LH was calculated by taking the maximum LH concentrations measured from blood samples taken at 30 or 60 min following the GnRHa stimulation test.
Suppression of GnRHa-stimulated luteinizing hormone is defined as peak stimulated LH less than 4 mIU/mL.

The Full Analysis Set (FAS) consists of all participants who received at least 1 dose of study drug. Participants with missing GnRHa-stimulated LH results at a specific visit were counted as not achieving suppression for that visit.

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

End point timeframe:

Weeks 12, 20, 44, and 48 (prior to Week 48 dose); samples for LH measurement were taken 30 and 60 minutes after the stimulation test injection.

| End point values | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve | Part 1: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 18 | 27 | 45 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 12 | 83.3 (58.6 to 96.4) | 88.9 (70.8 to 97.7) | 86.7 (73.2 to 95.0) | |
| Week 20 | 94.4 (72.7 to 99.9) | 85.2 (66.3 to 95.8) | 88.9 (76.0 to 96.3) | |
| Week 44 | 88.9 (65.3 to 98.6) | 88.9 (70.8 to 97.7) | 88.9 (76.0 to 96.3) | |
| Week 48 | 83.3 (58.6 to 96.4) | 92.6 (75.7 to 99.1) | 88.9 (76.0 to 96.3) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Percentage of Female Participants With Suppression of Basal Estradiol to < 20 pg/mL at Weeks 12, 20, 24, 44, and 48

| End point title | Part 1: Percentage of Female Participants With Suppression of Basal Estradiol to < 20 pg/mL at Weeks 12, 20, 24, 44, and 48 |
|---|---|

End point description:

Estradiol concentrations were measured from blood samples taken at each study visit prior to stimulation testing (and prior to study drug administration at Weeks 24 and 48).

Full analysis set; n=female participants with available data at each time point.

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

End point timeframe:

Weeks 12, 20, 24, 44, and 48

| End point values | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve | Part 1: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 17 | 24 | 41 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 12; n=16, 22, 38 | 100.0 (79.4 to 100.0) | 95.5 (77.2 to 99.9) | 97.4 (86.2 to 99.9) | |
| Week 20; n=16, 23, 39 | 100.0 (79.4 to 100.0) | 95.7 (78.1 to 99.9) | 97.4 (86.5 to 99.9) | |
| Week 24; n=17, 21, 38 | 100.0 (80.5 to 100.0) | 95.2 (76.2 to 99.9) | 97.4 (86.2 to 99.9) | |
| Week 44; n=17, 21, 38 | 100.0 (80.5 to 100.0) | 100.0 (85.2 to 100.0) | 100.0 (91.2 to 100.0) | |
| Week 48; n=16, 24, 40 | 100.0 (79.4 to 100.0) | 100.0 (85.8 to 100.0) | 100.0 (91.2 to 100.0) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Percentage of Male Participants With Suppression of Basal Testosterone to < 30 ng/dL at Weeks 12, 20, 24, 44, and 48

| End point title | Part 1: Percentage of Male Participants With Suppression of Basal Testosterone to < 30 ng/dL at Weeks 12, 20, 24, 44, and 48 |
|---|---|

End point description:

Testosterone concentrations were measured from blood samples taken at each study visit prior to stimulation testing (and prior to study drug administration for Weeks 24 and 48).

Full analysis set; n=male participants with available data at each time point

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

End point timeframe:

Weeks 12, 20, 24, 44, and 48

| End point values | Leuprolide Acetate - Previously Treated | Leuprolide Acetate - Treament Naïve | Part 1: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 1 | 3 | 4 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 12; n=1, 2, 3 | 100.0 (2.5 to 100.0) | 100.0 (15.8 to 100.0) | 100.0 (29.2 to 100.0) | |
| Week 20; n=1, 2, 3 | 100.0 (2.5 to 100.0) | 100.0 (15.8 to 100.0) | 100.0 (29.2 to 100.0) | |
| Week 24; n=1, 3, 4 | 100.0 (2.5 to 100.0) | 100.0 (29.2 to 100.0) | 100.0 (39.8 to 100.0) | |
| Week 44; n=1, 3, 4 | 100.0 (2.5 to 100.0) | 100.0 (29.2 to 100.0) | 100.0 (39.8 to 100.0) | |
| Week 48; n=1, 3, 4 | 100.0 (2.5 to 100.0) | 100.0 (29.2 to 100.0) | 100.0 (39.8 to 100.0) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts 1 and 2: Percentage of Participants With Suppression of the Physical Signs of Puberty

| End point title | Parts 1 and 2: Percentage of Participants With Suppression of |
|---|---|

| | |
|---|---|
| | the Physical Signs of Puberty |

End point description:

Breast development in females and testicular volume or genital development in males was assessed using modified Tanner staging, on a scale from Stage 1 (prepubertal) to Stage 5 (adult characteristics).
Females: Suppression is defined as regression or no progression of breast development according to modified Tanner staging.
Males: Suppression is defined as regression or no progression in testicular volume and genital staging according to modified Tanner staging.

Full analysis set; n=results for males and females (with an assessment at each time point) are reported separately.

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

End point timeframe:

Part 1: Weeks 24 and 48; Part 2: Weeks 72, 96, 120, and 144

| **End point values** | Parts 1 and 2: Leuprolide Acetate - Previously Treated | Parts 1 and 2: Leuprolide Acetate - Treament Naïve | Parts 1 and 2: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 18 | 27 | 45 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Females: Week 24; n=17, 24, 41 | 94.1 | 91.7 | 92.7 | |
| Females: Week 48; n=17, 24, 41 | 88.2 | 91.7 | 90.2 | |
| Females: Week 72; n=16, 23, 39 | 93.8 | 95.7 | 94.9 | |
| Females: Week 96; n=14, 21, 35 | 100 | 90.5 | 94.3 | |
| Females: Week 120; n=12, 19, 31 | 91.7 | 89.5 | 90.3 | |
| Females: Week 144; n=6, 16, 22 | 83.3 | 87.5 | 86.4 | |
| Males: Week 24; n=1, 3, 4 | 0 | 66.7 | 50.0 | |
| Males: Week 48; n=1, 3, 4 | 100 | 66.7 | 75.0 | |
| Males: Week 72; n=1, 3, 4 | 0 | 66.7 | 50.0 | |
| Males: Week 96; n=1, 3, 4 | 100 | 66.7 | 75.0 | |
| Males: Week 120; n=1, 3, 4 | 0 | 66.7 | 50.0 | |
| Males: Week 144; n=1, 1, 2 | 0 | 100 | 50.0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Parts 1 and 2: Change From Baseline in Incremental Growth Rate

| | |
|---|---|
| End point title | Parts 1 and 2: Change From Baseline in Incremental Growth Rate |

End point description:

Growth rate (height in centimeter/year) was calculated both prior to treatment in the study and during the study. For Baseline calculation a historical measurement of height at least 6 months prior to Screening and the Screening value was used.

Full analysis set; n=participants with available data at Baseline (43 participants) and each time point.

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

End point timeframe:

Part 1: Baseline and Weeks 4, 12, 20, 24, 44, and 48; Part 2: Weeks 72, 96, 120, and 144

| **End point values** | Parts 1 and 2: Leuprolide Acetate - Previously Treated | Parts 1 and 2: Leuprolide Acetate - Treament Naïve | Parts 1 and 2: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 17 | 26 | 43 | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4; n=17, 26, 43 | -0.6 (± 9.99) | -0.9 (± 10.52) | -0.8 (± 10.19) | |
| Week 12; n=16, 25, 41 | -0.6 (± 4.09) | -2.9 (± 5.42) | -2.0 (± 5.02) | |
| Week 20; n=16, 24, 40 | -0.5 (± 2.61) | -3.8 (± 4.69) | -2.5 (± 4.28) | |
| Week 24; n=17, 26, 43 | -0.5 (± 2.81) | -3.7 (± 4.28) | -2.4 (± 4.03) | |
| Week 44; n=17, 25, 42 | -0.4 (± 2.48) | -4.1 (± 3.77) | -2.6 (± 3.76) | |
| Week 48; n=16, 26, 42 | -0.3 (± 2.67) | -3.5 (± 4.71) | -2.3 (± 4.32) | |
| Week 72; n=16, 25, 41 | -0.5 (± 2.09) | -4.3 (± 3.53) | -2.8 (± 3.55) | |
| Week 96; n=15, 23, 38 | -0.6 (± 2.29) | -4.9 (± 3.43) | -3.2 (± 3.68) | |
| Week 120; n=13, 21, 34 | -1.2 (± 1.96) | -5.6 (± 3.27) | -3.9 (± 3.54) | |
| Week 144; 7, 16, 23 | -1.0 (± 1.63) | -5.3 (± 2.76) | -4.0 (± 3.19) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Parts 1 and 2: Ratio of Change From Baseline in Bone Age to Change From Baseline in Chronological Age

| End point title | Parts 1 and 2: Ratio of Change From Baseline in Bone Age to Change From Baseline in Chronological Age |
|---|---|

End point description:

Bone age was assessed from radiographs of the hand and wrist by a central imaging vendor using the BoneXpert automated system.

A ratio less than 1 indicates less advancement of bone age compared to chronological age.

Full analysis set; n=non missing observations.

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

End point timeframe:

Part 1: Baseline and Weeks 24 and 48; Part 2: Weeks 72, 96, 120, and 144

| End point values | Parts 1 and 2: Leuprolide Acetate - Previously Treated | Parts 1 and 2: Leuprolide Acetate - Treament Naïve | Parts 1 and 2: Leuprolide Acetate - Overall | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 18 | 27 | 45 | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 24; n=18, 27, 45 | 0.5 (± 0.80) | 0.7 (± 0.56) | 0.6 (± 0.66) | |
| Week 48; n=18, 27, 45 | 0.2 (± 1.36) | 0.6 (± 0.41) | 0.5 (± 0.93) | |
| Week 72; n=17, 26, 43 | 0.6 (± 0.31) | 0.6 (± 0.38) | 0.6 (± 0.35) | |
| Week 96; n=15, 24, 39 | 0.6 (± 0.32) | 0.7 (± 0.28) | 0.6 (± 0.29) | |
| Week 120; n=13, 22, 35 | 0.5 (± 0.28) | 0.6 (± 0.34) | 0.6 (± 0.32) | |
| Week 144; n=7, 17, 24 | 0.6 (± 0.26) | 0.6 (± 0.24) | 0.6 (± 0.24) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Participants With Maintenance of Suppression of GnRHa-stimulated LH (< 4 mIU/mL)

| End point title | Part 2: Percentage of Participants With Maintenance of Suppression of GnRHa-stimulated LH (< 4 mIU/mL) |
|---|---|

End point description:

Suppression of GnRHa-stimulated luteinizing hormone (LH) was measured using a peak GnRHa stimulation test, performed using subcutaneous injection with an aqueous formulation of leuprolide acetate at 20 µg/kg.
Peak stimulated LH was calculated by taking the maximum LH concentrations measured from blood samples taken at 30 or 60 min following the GnRHa stimulation test.
Suppression of GnRHa-stimulated luteinizing hormone is defined as peak stimulated LH less than 4 mIU/mL.

Full analysis set; n=observed cases.

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

End point timeframe:

Weeks 72, 96, 120, and 144

| End point values | Part 2: Leuprolide Acetate - Overall | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 43 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 72; n=17, 26, 43 | 93.0 (80.9 to 98.5) | | | |
| Week 96; n=15, 23, 38 | 94.7 (82.3 to 99.4) | | | |
| Week 120; n=13, 22, 35 | 100.0 (90.0 to 100.0) | | | |

| | | | | |
|---|---|---|---|---|
| Week 144; n=7, 16, 23 | 100.0 (85.2 to 100.0) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Female Participants With Maintenance of Suppression of Basal Estradiol to < 20 pg/mL

| End point title | Part 2: Percentage of Female Participants With Maintenance of Suppression of Basal Estradiol to < 20 pg/mL |
|---|---|

End point description:

Estradiol concentrations were measured from blood samples taken at each study visit prior to stimulation testing.

Full analysis set; n=participants with non-missing observations.

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

End point timeframe:

Weeks 72, 96, 120, and 144

| End point values | Part 2: Leuprolide Acetate - Overall | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 39 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 72; n=16, 23, 39 | 100.0 (91.0 to 100.0) | | | |
| Week 96; n=14, 20, 34 | 100.0 (89.7 to 100.0) | | | |
| Week 120; n=11, 19, 30 | 100.0 (88.4 to 100.0) | | | |
| Week 144; n=6, 15, 21 | 100.0 (83.9 to 100.0) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Male Participants With Maintenance of Suppression of Testosterone to < 30 ng/dL

| End point title | Part 2: Percentage of Male Participants With Maintenance of Suppression of Testosterone to < 30 ng/dL |
|---|---|

End point description:

Male participants with maintenance of suppression of testosterone to < 30 ng/dL are assessed.

Full analysis set; n=participants with non-missing observations.

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

End point timeframe:

Weeks 72, 96, 120, and 144

| **End point values** | Part 2: Leuprolide Acetate - Overall | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 4 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Week 72; n=1, 3, 4 | 100.0 (39.8 to 100.0) | | | |
| Week 96; n=1, 3, 4 | 100.0 (39.8 to 100.0) | | | |
| Week 120; n=1, 3, 4 | 100.0 (39.8 to 100.0) | | | |
| Week 144; n=1, 1, 2 | 100.0 (15.8 to 100.0) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From screening through end of study; median 949.5 and 1092.0 days for previously-treated and treatment naïve participants, respectively.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Leuprolide Acetate - Treament Naïve |

Reporting group description:

Participants without previous GnRHa treatment prior to enrollment (treatment naïve) received leuprolide acetate 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| | |
|---|---|
| Reporting group title | Leuprolide Acetate - Previously Treated |

Reporting group description:

Participants who had been previously treated with a GnRHa for at least 6 months prior to enrollment received leuprolide acetate (LA) 45 mg every 6 months administered as an intramuscular injection for up to 48 weeks in Part 1 and for up to an additional 96 weeks in Part 2.

| Serious adverse events | Leuprolide Acetate - Treament Naïve | Leuprolide Acetate - Previously Treated | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Psychiatric disorders | | | |
| AFFECTIVE DISORDER | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Leuprolide Acetate - Treament Naïve | Leuprolide Acetate - Previously Treated | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 27 (100.00%) | 18 / 18 (100.00%) | |
| Vascular disorders | | | |
| HOT FLUSH | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| INJECTION SITE BRUISING | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 18 (11.11%) | |
| occurrences (all) | 0 | 2 | |
| INJECTED LIMB MOBILITY DECREASED | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| GAIT DISTURBANCE | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 3 | 1 | |
| FEELING HOT | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| FATIGUE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 3 / 18 (16.67%) | |
| occurrences (all) | 0 | 3 | |
| CRYING | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 1 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| INJECTION SITE DISCOMFORT | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| INJECTION SITE ERYTHEMA | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 3 / 18 (16.67%) | |
| occurrences (all) | 4 | 3 | |
| INJECTION SITE PRURITUS | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| INJECTION SITE REACTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 27 (33.33%) | 4 / 18 (22.22%) | |
| occurrences (all) | 18 | 6 | |
| INJECTION SITE SWELLING | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | |
| occurrences (all) | 2 | 5 | |
| INJECTION SITE WARMTH | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 18 (16.67%) | |
| occurrences (all) | 3 | 3 | |
| MALAISE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| MEDICAL DEVICE PAIN | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| PAIN | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 5 / 18 (27.78%) | |
| occurrences (all) | 7 | 9 | |
| PYREXIA | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 6 / 18 (33.33%) | |
| occurrences (all) | 6 | 6 | |
| SWELLING | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 3 | |
| TENDERNESS | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | |
| occurrences (all) | 3 | 2 | |
| INJECTION SITE PAIN | | | |
| subjects affected / exposed | 26 / 27 (96.30%) | 16 / 18 (88.89%) | |
| occurrences (all) | 94 | 39 | |
| Immune system disorders | | | |
| MULTIPLE ALLERGIES | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |
| SEASONAL ALLERGY | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| VULVOVAGINAL PRURITUS | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| VULVOVAGINAL DISCOMFORT | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| VAGINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| VAGINAL DISCHARGE | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| NIPPLE PAIN | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| BREAST TENDERNESS | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |
| BREAST PAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| NASAL CONGESTION | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 2 / 18 (11.11%) | |
| occurrences (all) | 3 | 2 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| COUGH | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | 3 / 18 (16.67%) | |
| occurrences (all) | 7 | 5 | |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| OROPHARYNGEAL PAIN | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 27 (11.11%) | 5 / 18 (27.78%) | |
| occurrences (all) | 3 | 6 | |
| WHEEZING | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| SNEEZING | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| SINUS CONGESTION | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| RHINORRHOEA | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | |
| occurrences (all) | 3 | 4 | |
| Psychiatric disorders | | | |
| AFFECTIVE DISORDER | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| AGGRESSION | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| TEARFULNESS | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| ANGER | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 0 / 18 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| ANXIETY | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| ATTENTION DEFICIT HYPERACTIVITY DISORDER | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| DEPRESSED MOOD | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| EMOTIONAL DISORDER | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 1 / 18 (5.56%) | |
| occurrences (all) | 7 | 1 | |
| HALLUCINATION, AUDITORY | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| INITIAL INSOMNIA | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| IRRITABILITY | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |
| MOOD ALTERED | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 1 / 18 (5.56%) | |
| occurrences (all) | 7 | 3 | |
| MOOD SWINGS | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Investigations | | | |
| WEIGHT INCREASED | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 18 (11.11%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 18 (11.11%) | |
| occurrences (all) | 0 | 2 | |
| FALL | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| FOOT FRACTURE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| FRACTURED COCCYX | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| HAND FRACTURE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| HUMAN BITE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| LIGAMENT SPRAIN | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 3 / 18 (16.67%) | |
| occurrences (all) | 3 | 3 | |
| MUSCLE STRAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| NAIL INJURY | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 3 / 18 (16.67%) | |
| occurrences (all) | 0 | 3 | |
| Nervous system disorders | | | |
| CLUSTER HEADACHE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 3 | |
| DIZZINESS | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| HEADACHE | | | |
| subjects affected / exposed | 9 / 27 (33.33%) | 9 / 18 (50.00%) | |
| occurrences (all) | 20 | 14 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| IRON DEFICIENCY ANAEMIA | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| LYMPHADENOPATHY | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| EAR PAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | |
| occurrences (all) | 1 | 2 | |
| Eye disorders | | | |
| EYE PAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| PHOTOPSIA | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 1 | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 18 (11.11%) | |
| occurrences (all) | 0 | 2 | |
| NAUSEA | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | |
| occurrences (all) | 3 | 2 | |
| LIP BLISTER | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| HAEMATOCHEZIA | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| DIARRHOEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 27 (11.11%) | 1 / 18 (5.56%) | |
| occurrences (all) | 3 | 2 | |
| ORAL PAIN | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | 1 / 18 (5.56%) | |
| occurrences (all) | 6 | 1 | |
| VOMITING | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 18 (16.67%) | |
| occurrences (all) | 5 | 3 | |
| TOOTHACHE | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| TOOTH IMPACTED | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| SKIN ODOUR ABNORMAL | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| RASH | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | |
| occurrences (all) | 3 | 3 | |
| PRURITUS | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 0 / 18 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| HYPERHIDROSIS | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| ERYTHEMA | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 3 | 1 | |

| | | | |
|---|---|---|---|
| ACNE | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| ECZEMA | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | |
| occurrences (all) | 1 | 3 | |
| JOINT RANGE OF MOTION DECREASED | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| KNEE DEFORMITY | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| MYALGIA | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 1 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 1 | |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 7 / 27 (25.93%) | 5 / 18 (27.78%) | |
| occurrences (all) | 8 | 5 | |
| COVID-19 | | | |
| subjects affected / exposed | 9 / 27 (33.33%) | 3 / 18 (16.67%) | |
| occurrences (all) | 10 | 3 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 3 / 18 (16.67%) | |
| occurrences (all) | 2 | 3 | |

| | | | |
|---|---|---|---|
| GASTROENTERITIS VIRAL | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| INFLUENZA | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 4 / 18 (22.22%) | |
| occurrences (all) | 3 | 5 | |
| LICE INFESTATION | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 4 / 18 (22.22%) | |
| occurrences (all) | 7 | 6 | |
| OTITIS EXTERNA | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |
| PHARYNGITIS STREPTOCOCCAL | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 2 / 18 (11.11%) | |
| occurrences (all) | 6 | 2 | |
| SINUSITIS | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 1 / 18 (5.56%) | |
| occurrences (all) | 4 | 1 | |
| TINEA VERSICOLOUR | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | |
| occurrences (all) | 1 | 1 | |
| VIRAL UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Metabolism and nutrition disorders | | | |
| ABNORMAL WEIGHT GAIN | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | |
| occurrences (all) | 2 | 1 | |
| IRON DEFICIENCY | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | |
| occurrences (all) | 0 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 June 2018 | Major changes included: primary and secondary endpoints defined at prespecified timepoints aligned with the duration of the pharmacological effect of LA 45 mg 6 month; other efficacy endpoints added to provide a more comprehensive evaluation of LA 45 mg 6 month at each scheduled assessment; biochemical assessments for hormonal flare/AOC phenomenon added; adverse events of special interest (AESIs) including neuropsychiatric events, seizure/convulsion, injection site reaction, and hypersensitivity reaction added to align with current LupronDepot US package insert; pubertal response to GnRHa stimulation test added at Screening for naïve subjects to align with the LH level for biochemical diagnosis of CPP used in clinical practice; timing of withdrawal criteria for inadequate suppression changed from Week 8 to Week 24 to avoid early withdrawal of subjects who may need more time to reach hormonal suppression in response to long acting formulation; added procedures for rescreening. |
| 05 August 2020 | Major changes included: alternative study procedures related to subject safety in response to the COVID19 pandemic added throughout. The following alternative procedures were permitted per protocol:<br>If a subject could not come to the site because of an unforeseen circumstance (e.g., the COVID-19 pandemic), study visits could be conducted virtually by site staff (e.g., by phone or video) or by a qualified home healthcare nurse in a non-hospital/clinic environment (e.g., the subject's home) at the request of the investigator and with the agreement of the subject's parent or legal guardian. Patient-reported outcome entries could be administered by site staff over the phone and responses collected on paper (source) and transcribed into EDC or entered by site staff directly into an electronic collection system. AbbVie was to be notified if these changes occurred. Supplemental study case report forms were completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).<br>In unforeseen circumstances (e.g., the COVID-19 pandemic), the study drug injection could be administered and GnRHa stimulation test and required gonadotropins and sex steroids blood samples collection could be performed by a home healthcare nurse at the subject's home. If permitted by local regulations, provisioning of study drug and generic LA for stimulation test for direct to-patient and direct-frompatient transfer because of unforeseen circumstances (e.g., the COVID-19 pandemic) was available upon request. In the event of a home healthcare nurse performing the study drug injection at the subject's home, the injection site reaction assessment was to be conducted by the home healthcare nurse. AbbVie was to be notified if any of these situations occurred. |
| 05 August 2020 | (con't)<br>If a subject could not visit the site because of unforeseen circumstances (e.g., the COVID-19 pandemic), laboratory and PK samples could be collected by a home healthcare service and sent to the central laboratory. If the central laboratory could not be used to test samples because of unforeseen circumstances (e.g., the COVID-19 pandemic), laboratory samples could be collected and tested at a local laboratory. AbbVie was to be notified if any of these situations occurred. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported