



Clinical trial results:

A 36 Month, Multi-Center, Open-Label Extension Study to Evaluate the Safety of Leuprolide Acetate 11.25 mg and 30 mg Formulations in Children with Central Precocious Puberty

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004494-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 08 January 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 13 May 2016 |
| First version publication date | 07 June 2015 |
| Version creation reason | • Correction of full data set potential timestamp and category issues |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | L-CP07-177 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00667446 |
| 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 | 08 January 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 08 January 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this extension study is to determine if leuprolide acetate (11.25 mg and 30 mg) is safe in treating children with Central Precocious Puberty over a longer period of time (36 months).

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 | 02 December 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: 72 |
| Worldwide total number of subjects | 72 |
| 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) | 72 |
| 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 who successfully completed and showed maintenance of luteinizing hormone suppression through the 6-month treatment period of the lead-in study L-CP07-167 (NCT00635817) received the same treatment in this study that they were previously assigned in the lead-in study.

Pre-assignment

Screening details:

At the end of the Treatment Period, participants who completed the study or prematurely discontinued from the study could enter the Safety Follow-Up Period.

Period 1

| | |
|------------------------------|------------------------------|
| Period 1 title | Treatment Period (36 months) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Leuprolide Acetate 3M Depot 11.25 mg |

Arm description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months (3M) apart during the Treatment Period.

| | |
|--|--|
| 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:

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

| | |
|------------------|-----------------------------------|
| Arm title | Leuprolide Acetate 3M Depot 30 mg |
|------------------|-----------------------------------|

Arm description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months (3M) apart during the Treatment Period.

| | |
|--|--|
| 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:

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

| Number of subjects in period 1 | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg |
|---------------------------------------|---|--------------------------------------|
| Started | 34 | 38 |
| Completed | 11 | 13 |
| Not completed | 23 | 25 |
| Personal reasons | 2 | 2 |
| Consent withdrawn by subject | - | 4 |
| Other | 2 | 2 |
| Therapeutic failure | 1 | 1 |
| Lost to follow-up | 1 | - |
| Not adequately suppressed on therapy | 3 | - |
| Ready to enter puberty based on age | 13 | 15 |
| Protocol deviation | 1 | 1 |

Period 2

| | |
|------------------------------|------------------------------------|
| Period 2 title | Safety Follow-up Period (12 weeks) |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Leuprolide Acetate 3M Depot 11.25 mg |

Arm description:

During the Safety Follow-Up Period participants were offered standard of care treatment as deemed appropriate by the investigator.

| | |
|--|--|
| 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:

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

| | |
|------------------|-----------------------------------|
| Arm title | Leuprolide Acetate 3M Depot 30 mg |
|------------------|-----------------------------------|

Arm description:

During the the Safety Follow-Up Period participants were offered standard of care treatment as deemed appropriate by the investigator.

| | |
|----------|--------------|
| 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:

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

| Number of subjects in period 2 | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg |
|---------------------------------------|---|--------------------------------------|
| Started | 28 | 26 |
| Completed | 28 | 25 |
| Not completed | 0 | 1 |
| No longer needed treatment | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Leuprolide Acetate 3M Depot 11.25 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months (3M) apart during the Treatment Period.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Leuprolide Acetate 3M Depot 30 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months (3M) apart during the Treatment Period.

| Reporting group values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | Total |
|------------------------|---|--------------------------------------|-------|
| Number of subjects | 34 | 38 | 72 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------|--------|--------|----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.5 | 8.45 | |
| standard deviation | ± 1.71 | ± 1.52 | - |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Female | 32 | 33 | 65 |
| Male | 2 | 5 | 7 |

End points

End points reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Leuprolide Acetate 3M Depot 11.25 mg |
| Reporting group description: Twelve intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months (3M) apart during the Treatment Period. | |
| Reporting group title | Leuprolide Acetate 3M Depot 30 mg |
| Reporting group description: Twelve intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months (3M) apart during the Treatment Period. | |
| Reporting group title | Leuprolide Acetate 3M Depot 11.25 mg |
| Reporting group description: During the Safety Follow-Up Period participants were offered standard of care treatment as deemed appropriate by the investigator. | |
| Reporting group title | Leuprolide Acetate 3M Depot 30 mg |
| Reporting group description: During the the Safety Follow-Up Period participants were offered standard of care treatment as deemed appropriate by the investigator. | |
| Subject analysis set title | Leuprolide Acetate 3M Depot 11.25 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Twelve intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months apart. Intention-to-treat, defined as patients who received at least 1 dose of study drug with at least 1 post-baseline measurement of any maintenance of suppression variable. | |
| Subject analysis set title | Leuprolide Acetate 3M Depot 30 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Twelve intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months apart. Intention-to-treat, defined as patients who received at least 1 dose of study drug with at least 1 post-baseline measurement of any maintenance of suppression variable. | |

Primary: Percentage of Participants With Suppression of Peak-Stimulated Luteinizing Hormone

| | |
|---|---|
| End point title | Percentage of Participants With Suppression of Peak-Stimulated Luteinizing Hormone ^[1] |
| End point description: Luteinizing Hormone (LH) suppression is defined as peak-stimulated LH < 4 mIU/mL. Peak-stimulated LH refers to the maximum LH concentration measured 30 and 60 minutes after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test. Participants who failed suppression at previous visit and prematurely discontinued were counted as having failed future visits also. Final visit is the participant's last visit closest to Month 36. Intention-to-treat, defined as patients who received at least 1 dose of study drug with at least 1 post-baseline measurement of any maintenance of suppression variable, & did not prematurely discontinue in the 1st 30 days due to inadequate suppression at Month 6 of the lead-in study. N = the number of patients with available data at each time point. | |
| End point type | Primary |
| End point timeframe: Day 1, Months 6, 12, 24, and 36 | |

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 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 33 | 38 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 [N= 32, 37] | 96.9 (83.78 to 99.92) | 100 (90.51 to 100) | | |
| Month 6 [N=32, 36] | 93.8 (79.19 to 99.23) | 100 (90.26 to 100) | | |
| Month 12 [N=31, 32] | 90.3 (74.25 to 97.96) | 96.9 (83.78 to 99.92) | | |
| Month 24 [N=16, 18] | 87.5 (64.65 to 98.45) | 100 (81.47 to 100) | | |
| Month 36 [N=9, 11] | 77.8 (39.99 to 97.19) | 100 (71.51 to 100) | | |
| Final Visit [N=33, 36] | 93.9 (79.77 to 99.26) | 100 (90.26 to 100) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Female Participants With Suppression of Basal Estradiol (Assay 1)

| | |
|-----------------|---|
| End point title | Percentage of Female Participants With Suppression of Basal Estradiol (Assay 1) |
|-----------------|---|

End point description:

The percentage of female participants with suppression of basal estradiol to prepubertal levels, defined as estradiol < 20 pg/mL.

The estradiol assay was changed in June of 2010, and the lower limit of quantitation (LLOQ) was increased from 1 pg/mL to 10 pg/mL. This outcome measure reports data for assays performed before this change occurred, with an LLOQ of 1 pg/mL. Final visit is the participant's last visit closest to Month 36. Intention-to-treat female population. N = the number of participants with available data at each time point.

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

End point timeframe:

Day 1, Months 3, 6, 9, 12, and 24

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 33 ^[2] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 [N=28, 30] | 96.4 (81.65 to 99.91) | 100 (88.43 to 100) | | |
| Month 3 [N=29, 33] | 100 (88.06 to 100) | 100 (89.42 to 100) | | |

| | | | | |
|------------------------|--------------------|--------------------|--|--|
| Month 6 [N=26, 25] | 100 (86.77 to 100) | 100 (86.28 to 100) | | |
| Month 9 [N=18, 18] | 100 (81.47 to 100) | 100 (81.47 to 100) | | |
| Month 12 [N=10, 12] | 100 (69.15 to 100) | 100 (73.54 to 100) | | |
| Month 24 [N=1, 0] | 100 (2.5 to 100) | 0 (0 to 0) | | |
| Final Visit [N=31, 33] | 100 (88.78 to 100) | 100 (89.42 to 100) | | |

Notes:

[2] - 0=NA for Month 24 for this group because no participants had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Female Participants With Suppression of Basal Estradiol (Assay 2)

| | |
|-----------------|---|
| End point title | Percentage of Female Participants With Suppression of Basal Estradiol (Assay 2) |
|-----------------|---|

End point description:

The percentage of female participants with suppression of basal estradiol to prepubertal levels, defined as estradiol < 20 pg/mL.

The estradiol assay was changed in June of 2010, and the lower limit of quantitation (LLOQ) was increased from 1 pg/mL to 10 pg/mL. This outcome measure reports data for assays performed after this change occurred, with an LLOQ of 10 pg/mL. Final visit is the participant's last visit closest to Month 36. Intention-to-treat female population. N = the number of participants with available data at each time point.

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

End point timeframe:

Months 6, 9, 12, 24, 30, and 36

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 33 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Month 6 [N=4, 6] | 100 (39.76 to 100) | 83.3 (35.88 to 99.58) | | |
| Month 9 [N=13, 10] | 61.5 (31.58 to 86.14) | 40 (12.16 to 73.76) | | |
| Month 12 [N=20, 15] | 45 (23.06 to 68.47) | 60 (32.29 to 83.66) | | |
| Month 24 [N=14, 15] | 50 (23.04 to 76.96) | 53.3 (26.59 to 78.73) | | |
| Month 30 [N=9, 15] | 33.3 (7.49 to 70.07) | 26.7 (7.79 to 55.1) | | |
| Month 36 [N=7, 11] | 28.6 (3.67 to 70.96) | 36.4 (10.93 to 69.21) | | |
| Final Visit [N=24, 26] | 29.2 (12.62 to 51.09) | 30.8 (14.33 to 51.79) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Male Participants With Suppression of Basal Testosterone

| | |
|---|--|
| End point title | Percentage of Male Participants With Suppression of Basal Testosterone |
| End point description: The percentage of male participants with suppression of basal testosterone to prepubertal levels, defined as testosterone < 30 ng/dL. Final visit is the participant's last visit closest to Month 36. Intention-to-treat male population. N = the number of participants with available data at each time point. | |
| End point type | Secondary |
| End point timeframe: Day 1, Months 3, 6, 9, 12, 24, 30, and 36 | |

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 ^[3] | 5 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 [N= 2, 5] | 100 (15.81 to 100) | 100 (47.82 to 100) | | |
| Month 3 [N=2, 5] | 100 (15.81 to 100) | 100 (47.82 to 100) | | |
| Month 6 [N=2, 5] | 100 (15.81 to 100) | 80 (28.36 to 99.49) | | |
| Month 9 [N=2, 5] | 100 (15.81 to 100) | 80 (28.36 to 99.49) | | |
| Month 12 [N=1, 5] | 100 (2.5 to 100) | 100 (47.82 to 100) | | |
| Month 24 [N=1, 3] | 100 (2.5 to 100) | 66.7 (9.43 to 99.16) | | |
| Month 30 [N=0, 1] | 0 (0 to 0) | 100 (2.5 to 100) | | |
| Month 36 [N=0, 1] | 0 (0 to 0) | 100 (2.5 to 100) | | |
| Final Visit [N=2, 5] | 100 (15.81 to 100) | 100 (47.82 to 100) | | |

Notes:

[3] - 0=NA for Month 30 and Month 36 for this group because no participants had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Peak-stimulated Luteinizing Hormone Concentration by Visit

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

End point description:

Peak-stimulated luteinizing hormone refers to the maximum luteinizing hormone concentration measured 30 and 60 minutes after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test. Final visit is the participant's last visit closest to Month 36. Intention-to-treat. N = the number of participants with available data at each time point.

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

End point timeframe:

Baseline of the lead-in study L-CP07-167, Day 1, Months 6, 12, 24, and 36

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|--------------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 33 | 38 | | |
| Units: mIU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline [N=33, 38] | 21.89 (± 38.46) | 10.16 (± 12.66) | | |
| Day 1 [N=32, 37] | 2 (± 1.03) | 1.49 (± 0.86) | | |
| Month 6 [N=32, 36] | 2.22 (± 1.16) | 1.62 (± 0.82) | | |
| Month 12 [N=31, 32] | 2.24 (± 1.2) | 1.58 (± 1.02) | | |
| Month 24 [N=14, 18] | 1.67 (± 0.97) | 0.88 (± 0.58) | | |
| Month 36 [N=7, 11] | 1.51 (± 0.85) | 0.91 (± 0.49) | | |
| Final Visit [N=33, 36] | 1.81 (± 1.13) | 1.15 (± 0.74) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Female Participants With Suppression of the Physical Signs of Puberty (Breast Development)

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

End point description:

The percentage of female participants with suppression of breast development. Breast development was rated from Stage 1 (early development) through Stage 5 (full development) according to a modified Tanner Staging pictogram. Suppression of breast development is defined as regression or no progression of breast development from Baseline (of the lead-in study L-CP07-167) according to pubertal staging. Girls entering the study with fully developed breasts (Stage 5) were excluded from this analysis. Final visit is the participant's last visit closest to Month 36. Intention-to-treat female population, excluding participants who entered the study at Stage 5. N = the number of participants with available data at each time point.

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

End point timeframe:

Baseline (of the lead-in study L-CP07-167), Day 1, Months 3, 6, 9, 12, 18, 24, 30, and 36

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 31 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 [N= 31, 31] | 90.3 (74.2 to 98) | 83.9 (66.3 to 94.5) | | |
| Month 3 [N=29, 31] | 86.2 (68.3 to 96.1) | 87.1 (70.2 to 96.4) | | |
| Month 6 [N=31, 30] | 90.3 (74.2 to 98) | 80 (61.4 to 92.3) | | |
| Month 9 [N=31, 28] | 87.1 (70.2 to 96.4) | 75 (55.1 to 89.3) | | |
| Month 12 [N=28, 26] | 85.7 (67.3 to 96) | 80.8 (60.6 to 93.4) | | |
| Month 18 [N=17, 20] | 82.4 (56.6 to 96.2) | 75 (50.9 to 91.3) | | |
| Month 24 [N=14, 16] | 78.6 (49.2 to 95.3) | 75 (47.6 to 92.7) | | |
| Month 30 [N=10, 16] | 90 (55.5 to 99.7) | 68.8 (41.3 to 89) | | |
| Month 36 [N=8, 12] | 87.5 (47.3 to 99.7) | 66.7 (34.9 to 90.1) | | |
| Final Visit [N=31, 31] | 83.9 (66.3 to 94.5) | 71 (52 to 85.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Male Participants With Suppression of the Physical Signs of Puberty (Testicular Volume and Genital Development)

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

End point description:

The percentage of male participants with suppression of testicular volume and genital staging. Testicular volume was calculated from the length, width and height of each testicle measured by ultrasound. External genital development (testes and penis) was rated from Stage 1 (early development) through Stage 5 (full development) according to a modified Tanner Staging pictogram. Suppression is defined as regression or no progression in both testicular volume and genital staging from Baseline (of the lead-in study L-CP07-167) according to pubertal staging. Boys entering the study with fully developed genitals (Stage 5) were excluded from this analysis. Final visit is the participant's last visit closest to Month 36. Intention-to-treat male population, excluding participants who entered the study at Stage 5. N = the number of participants with available data at each time point.

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

End point timeframe:

Baseline (of the lead-in study L-CP07-167), Day 1, Months 3, 6, 9, 12, 18, 24, 30, and 36

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|-----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 ^[4] | 5 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Day 1 [N= 2, 5] | 50 (1.3 to 98.7) | 40 (5.3 to 85.3) | | |
| Month 3 [N=2, 5] | 50 (1.3 to 98.7) | 60 (14.7 to 94.7) | | |
| Month 6 [N=2, 5] | 50 (1.3 to 98.7) | 60 (14.7 to 94.7) | | |
| Month 9 [N=2, 5] | 50 (1.3 to 98.7) | 40 (5.3 to 85.3) | | |
| Month 12 [N=1, 5] | 100 (2.5 to 100) | 60 (14.7 to 94.7) | | |
| Month 18 [N=1, 3] | 100 (2.5 to 100) | 100 (29.2 to 100) | | |
| Month 24 [N=1, 3] | 100 (2.5 to 100) | 33.3 (0.8 to 90.6) | | |
| Month 30 [N=1, 1] | 100 (2.5 to 100) | 100 (2.5 to 100) | | |
| Month 36 [N=0, 1] | 0 (0 to 0) | 100 (2.5 to 100) | | |
| Final Visit [N=2, 5] | 50 (1.3 to 98.7) | 20 (0.5 to 71.6) | | |

Notes:

[4] - 0=NA for Month 36 for this group because no participants had available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Growth Rate

| | |
|--|-------------------------------------|
| End point title | Change from Baseline in Growth Rate |
| End point description: | |
| Baseline growth rate was the growth rate in the one year prior to Day 1 of the lead-in study L-CP07-167. Growth rates were calculated as the ratio of the change in height to the change in chronological age with an approximate 6-month interval for Day 1, Months 6, 12, 18, 24, 30, 36 and the Final Treatment Visit. Intention-to-treat with available growth rate data. N = participants with available data at each time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (the 1 year prior to the start of treatment in the lead-in study), and Day 1, Months 6, 12, 18, 24, 30, and 36 | |

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|--|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 32 | 38 | | |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline [N=32, 38] | 7.2 (± 3.96) | 7.53 (± 2.81) | | |
| Change from Baseline at Day 1 [N=32, 38] | -1.67 (± 3.9) | -1.65 (± 3.43) | | |
| Change from Baseline at Month 6 [N=32, 37] | -1.66 (± 3.78) | -2.04 (± 2.95) | | |
| Change from Baseline at Month 12 [N=28, 32] | -1.99 (± 3.9) | -2.28 (± 2.88) | | |
| Change from Baseline at Month 18 [N=18, 23] | -2.21 (± 4.29) | -2.06 (± 2.4) | | |
| Change from Baseline at Month 24 [N=15, 19] | -2.36 (± 4.85) | -1.59 (± 2.2) | | |
| Change from Baseline at Month 30 [N=11, 17] | -1.86 (± 5.45) | -2.13 (± 2.33) | | |
| Change from Baseline at Month 36 [N=8, 13] | -2.64 (± 5.93) | -2.19 (± 2.41) | | |
| Change from Baseline at Final Visit [N=32, 38] | -2.27 (± 3.78) | -2.64 (± 2.65) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Change From Baseline in Bone Age/Change From Baseline in Chronological Age

| | |
|---|---|
| End point title | Ratio of Change From Baseline in Bone Age/Change From Baseline in Chronological Age |
| End point description: | |
| <p>Bone age was determined by left hand/wrist bone age radiographs that were evaluated using the Fels Method by a central reader. The ratio of change from Baseline in bone age (BA)/change from Baseline in chronological age (CA) was calculated using the following formula:</p> <p>(BA at Post-baseline Treatment Visit - BA at Baseline) / (CA at Post-baseline Treatment Visit - CA at Baseline). Intention-to-treat with available bone age data. N = participants with available data at each time point.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (of the lead-in study L-CP07-167), and Day 1, Months 12, 24, and 36 | |

| End point values | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | | |
|--------------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 33 | 37 | | |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|------------------------|---------------|---------------|--|--|
| Day 1 [N=32, 37] | 0.51 (± 0.56) | 1.02 (± 1.27) | | |
| Month 12 [N=32, 32] | 0.52 (± 0.33) | 0.62 (± 0.37) | | |
| Month 24 [N=14, 17] | 0.53 (± 0.3) | 0.72 (± 0.34) | | |
| Month 36 [N=5, 11] | 0.43 (± 0.15) | 0.64 (± 0.3) | | |
| Final Visit [N=33, 32] | 0.48 (± 0.28) | 0.56 (± 0.3) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

37 months

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Leuprolide Acetate 3M Depot 11.25 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 11.25 mg administered 3 months apart.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Leuprolide Acetate 3M Depot 30 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Twelve intramuscular injections of leuprolide acetate for depot suspension 30 mg administered 3 months apart.

| Serious adverse events | Leuprolide Acetate 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | |
|---|---|--------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 38 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 38 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 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 3M Depot 11.25 mg | Leuprolide Acetate 3M Depot 30 mg | |
|---|---|--------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 31 / 34 (91.18%) | 31 / 38 (81.58%) | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 3 / 38 (7.89%) | |
| occurrences (all) | 0 | 3 | |
| Injury, poisoning and procedural | | | |

| | | | |
|--|------------------|-----------------|--|
| complications | | | |
| Excoriation | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 38 (5.26%) | |
| occurrences (all) | 0 | 2 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 38 (5.26%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 6 / 38 (15.79%) | |
| occurrences (all) | 5 | 9 | |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 10 / 34 (29.41%) | 9 / 38 (23.68%) | |
| occurrences (all) | 17 | 18 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 5 / 38 (13.16%) | |
| occurrences (all) | 9 | 5 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 38 (5.26%) | |
| occurrences (all) | 1 | 2 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 38 (2.63%) | |
| occurrences (all) | 2 | 1 | |
| Eye disorders | | | |
| Myopia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 38 (5.26%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 38 (7.89%) | |
| occurrences (all) | 3 | 3 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 38 (7.89%) | |
| occurrences (all) | 2 | 3 | |
| Constipation | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 38 (2.63%) 2 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 38 (2.63%) 2 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 2 / 38 (5.26%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 4 / 38 (10.53%) 5 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 5 | 9 / 38 (23.68%) 9 | |
| Respiratory disorder subjects affected / exposed occurrences (all) | 1 / 34 (2.94%) 5 | 2 / 38 (5.26%) 2 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 4 | 5 / 38 (13.16%) 5 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 4 | 1 / 38 (2.63%) 1 | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 2 / 38 (5.26%) 2 | |
| Eczema subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 38 (2.63%) 1 | |
| Rash subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 1 / 38 (2.63%) 1 | |
| Rash papular | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 0 / 38 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 3 / 38 (7.89%) 3 | |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 4 | 5 / 38 (13.16%) 6 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 4 | 0 / 38 (0.00%) 0 | |
| Body tinea subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 0 / 38 (0.00%) 0 | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 5 | 4 / 38 (10.53%) 7 | |
| Ear infection subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 1 / 38 (2.63%) 1 | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 4 | 0 / 38 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 4 | 1 / 38 (2.63%) 2 | |
| Pharyngitis subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 6 | 1 / 38 (2.63%) 1 | |
| Pharyngitis streptococcal subjects affected / exposed occurrences (all) | 5 / 34 (14.71%) 5 | 4 / 38 (10.53%) 5 | |
| Sinusitis | | | |

| | | | |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 38 (5.26%) | |
| occurrences (all) | 3 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 34 (26.47%) | 5 / 38 (13.16%) | |
| occurrences (all) | 16 | 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 22 April 2009 | <p>Due to transition of the Lupron program from TAP Pharmaceutical Products Inc. to Abbott, the primary purpose of the amendment is document changes regarding Sponsor name, contact information, fax number and a revised timeline for reporting SAEs.</p> <ul style="list-style-type: none">-include convulsions as a rarely reported event-document that the commercially-available generic leuprolide acetate daily injection (Leuprolide Acetate Injection) will be used to conduct the GnRHa Stimulation test.-reduce the allowable visit window from +/- 7 days to +/- 3 days at each of the Months 3, 6, 9 and 12 study visits.-clarify which procedures are required at the Early Discontinuation Visit and which procedures are optional if previously preformed or may be performed at the discretion of the investigator based on clinical judgment.-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-at the Months 3 and 9 study visits, the blood collections for basal gonadotropin and sex steroids are relative to the Depot Injection. No stimulation tests are performed at these visits.-indicate that any storage temperatures that fall outside the allowable range of temperature excursions, as defined by the product label and/or the Package Inserts, are to be communicated to Abbott.-incorporate a longer study duration as a result of the enrollment period of the lead-in study, L-CP07-167, having been extended a few months-update criteria for withdrawal (accelerated progression of pubertal symptoms), exclusion (bone age ≥ 14.00 years for girls and ≥ 15.00 years for boys is exclusionary)-clarify premature discontinuation from trial, permitted/prohibited medications, AE and SAE procedures |
| 18 March 2010 | <p>The purpose of this amendment is to extend the treatment period from 12 months to a total of 36 months to allow subjects to continue to be treated with study medication until a 3-month Depot formulation of leuprolide acetate is approved for the clinical treatment of central precocious puberty and is commercially available. The amendment also allows for subjects currently in the Safety Follow-up Period receiving Lupron Depot as standard of care to resume treatment with the 3-month Depot Investigational Product for an additional 24 months of treatment, following IRB approval.</p> <ul style="list-style-type: none">-add study visits to reflect the amendment. Study procedures and assessments such as stimulation tests, physical exams, pelvic ultrasound (girls), etc. to be performed during the study, as well as the change in names from Post-Treatment Follow-Up Period and Post-Treatment Follow-Up Visit to Safety Follow-Up Period and Safety Follow-Up Visit-indicate that the current immunochemiluminometric assay (ICMA) used for the analysis of LH will be changed to the electrochemiluminescent (ECL) methodology, once the ICMA assay is no longer supported by the central laboratory-indicate that following the Month 9 study visit, sites will no longer be required to call the parent the day following each injection to assess for any injection site reactions any hormonal flare response to the study drug. Instead, the parent will call the site to report any reactions or flare. The site will still be required to assess reaction/flare on the day of the injection prior to the subject leaving the clinic, and assess at the following study visit or by asking the parent/subject-provide instructions on storing the frozen samples for LH, estradiol and testosterone, if not shipped on the same day as the day of the blood draw.-clarify study procedures and add 2 interim analyses when all subjects finish their Month 12 and Month 24 visits |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported