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:

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:
(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.

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

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