



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	L-CP07-167
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 84
Worldwide total number of subjects	84
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	83
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

Subjects who received at least 1 dose of study drug.

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

Dosage and administration details:

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

Arm title	Leuprolide Acetate 11.25 mg - Previous Treatment
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Arm description:

Subjects who received at least 1 dose of study drug.

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

Dosage and administration details:

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

Arm title	Leuprolide Acetate 30 mg - Treatment Naive
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Arm description:

Subjects who received at least 1 dose of study drug.

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

Dosage and administration details:

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

Arm title	Leuprolide Acetate 30 mg - Previous Treatment
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Arm description:

Subjects who received at least 1 dose of study drug.

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

Dosage and administration details:

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

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

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

End point title	Percentage of Participants With Suppression of Peak Stimulated Luteinizing Hormone (<4 mIU/mL) From Month 2 Through Month 6 ^[1]
End point description: Percentage of participants with suppression of peak stimulated luteinizing hormone that was measured after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test at Month (Mo) 2, 3, and 6. The analysis was performed according to a life table method. Subjects who withdrew without peak-stimulated luteinizing hormone ≥ 4 mIU/mL were censored at their last measurement of peak-stimulated luteinizing hormone. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement of peak stimulated luteinizing hormone at Mo 2 or afterward defined as the intent-to-treat population.	
End point type	Primary
End point timeframe: Month 2 through 6	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive data were summarized for this end point per protocol.	

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

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

No statistical analyses for this end point

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

End point title	Percentage of Participants with Suppression of Basal Estradiol <20 pg/mL by Visit
End point description: Percentage of participants with suppression of estradiol, out of the number of girls with at least 1 estradiol measurement at each visit (n/N%). Only girls are analyzed in this outcome measure. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population. N=the number of patients with available data at each time point.	
End point type	Secondary
End point timeframe: Month 1, 2, 3 and 6	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Secondary
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End point timeframe:

Month 1, 2, 3 and 6

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

Statistical analyses

No statistical analyses for this end point

Secondary: Peak-stimulated Luteinizing Hormone Concentration by Visit

End point title	Peak-stimulated Luteinizing Hormone Concentration by Visit
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline, Month 1, 2, 3 and 6

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Suppression of the Physical Signs of Puberty (Breast Development) at Month 6
End point description:	
Percentage of participants with suppression of breast development, out of the number of girls with pubertal staging of breast development (n/N%). Only girls are analyzed in this outcome measure. Breast development was rated from Stage 1 (early development) through Stage 5 (full development) according to a Tanner Staging pictogram. Girls entering the study with fully developed breasts (Stage 5) were excluded from this analysis. Observed data were used with no imputation for missing data. Subjects must have received at least 1 dose of study drug and had at least 1 postbaseline measurement defined as the intent-to-treat population.	
End point type	Secondary
End point timeframe:	
Month 6	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Secondary
End point timeframe:	
Month 6	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
End point timeframe:	
Baseline and Month 6	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Secondary
End point timeframe:	
Baseline to Month 6	

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Post-hoc
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End point timeframe:

Month 2 through 6

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Post-hoc
End point timeframe:	
Baseline to Month 6	

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Leuprolide Acetate 11.25 mg - Treatment Naive
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Reporting group description:

Subjects who received at least 1 dose of study drug.

Reporting group title	Leuprolide Acetate 30 mg - Treatment Naive
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Reporting group description:

Subjects who received at least 1 dose of study drug.

Reporting group title	Leuprolide Acetate 30 mg - Previous Treatment
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Reporting group description:

Subjects who received at least 1 dose of study drug.

Reporting group title	Leuprolide Acetate 11.25 mg - Previous Treatment
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Reporting group description:

Subjects who received at least 1 dose of study drug.

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

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

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

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

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

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

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

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

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

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

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

Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported