Clinical trial results:
Study of Lupron Depot In The Treatment of Central Precocious Puberty

Summary

EudraCT number	2014-004495-36
Trial protocol	Outside EU/EEA
Global end of trial date	22 April 2009

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	M90-516

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00660010
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	Kristof Chwalisz MD, AbbVie, kristof.chwalisz@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	22 April 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2009
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 Lupron (leuprolide acetate) is safe and effective in treating children with Central Precocious Puberty (CPP), and to assess long term effects of leuprolide acetate treatment after therapy is discontinued.

Protection of trial subjects:

Prior to the initiation of any screening or study-specific procedures, the investigator or his representative explained the nature of the study to the subject and the subject's parent or legal guardian and answered all questions regarding this study. The informed consent statement was reviewed and signed and dated by the subject's parent or legal guardian and by the person who administered the informed consent.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	31 January 1991
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: 55
Worldwide total number of subjects	55
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)	2
Children (2-11 years)	53
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: -

Pre-assignment

Screening details:

This study included 1 treatment group and subjects were assigned the initial dosage depending on their weight. The minimum starting dose was 7.5 mg every 28 days. Study drug was discontinued either when puberty occurred at 12 years +- 6 months for males and 11 years +- 6 months for females or at the discretion of the investigator.

Period 1

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

Arms

Arm title	Leuprolide Acetate 1 Month Depot

Arm description:

Leuprolide acetate dosing was initiated at 300 mcg/kg (minimum dose 7.5 mg) administered intramuscularly (IM) every 28 days. Incremental adjustments to dosing at 3.75 mg increments were made at each visit.

Arm type	Experimental
Investigational medicinal product name	Leuprolide acetate
Investigational medicinal product code	
Other name	Lupron
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Leuprolide acetate was administered monthly by intramuscular injection starting at 300 mcg/kg with adjustments of 3.75 mg upward, at subsequent clinic visits based on physical and laboratory parameters. Dosing continued until New Drug Application (NDA) was approved, or until subject no longer required leuprolide acetate to treat CPP.

Number of subjects in period 1	Leuprolide Acetate 1 Month Depot
Started	55
Completed	46
Not completed	9
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Noncompliance with visit schedule	3
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Leuprolide Acetate 1 Month Depot
Reporting group description:	
Leuprolide acetate dosing was initiated at 300 mcg/kg (minimum dose 7.5 mg) administered intramuscularly (IM) every 28 days. Incremental adjustments to dosing at 3.75 mg increments were made at each visit.	

Reporting group values	Leuprolide Acetate 1 Month Depot	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
<= 18 years	55	55	
Between 18 and 65 years	0	0	
>= 65 years	0	0	
Age continuous Units: years			
arithmetic mean	6.9		
standard deviation	± 1.86	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	6	6	

End points

End points reporting groups

Reporting group title	Leuprolide Acetate 1 Month Depot

Reporting group description:

Leuprolide acetate dosing was initiated at 300 mcg/kg (minimum dose 7.5 mg) administered intramuscularly (IM) every 28 days. Incremental adjustments to dosing at 3.75 mg increments were made at each visit.

Primary: Percentage of Subjects (n/N) With Suppression of Clinical Sexual Characteristics According to Tanner Staging (Breast Development in Females)

End point title	Percentage of Subjects (n/N) With Suppression of Clinical Sexual Characteristics According to Tanner Staging (Breast Development in Females)[1]

End point description:

Suppression of clinical sexual characteristics was defined as regression (improvement) or no progression of breast development in females. Tanner staging is a scale of physical development that defines primary and secondary sex characteristics including size of breasts. The final visit occurred at a mean age +/- SD of 11.05 +/- 1.14 years (range, 6.96 to 12.95 years). The intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. The starting population comprised 49 females (breast development suppression). Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Primary

End point timeframe:

Week 4, Week 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

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 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Percentage of subjects				
number (not applicable)				
Breast development suppression - Week 4 N=44	81.8			
Breast development suppression-Week 48 N=47	80.9			
Breast development suppression -Week 96 N=41	87.8			
Breast development suppression-Week 144 N=29	82.8			
Breast development suppression - Week 192 N=18	66.7			
Breast development suppression -Week 240 N=13	76.9			
Breast development suppression-Final Visit N=48	77.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects (n/N) With Suppression of Clinical Sexual Characteristics According to Tanner Staging (Genital Development in Males)

End point title	Percentage of Subjects (n/N) With Suppression of Clinical Sexual Characteristics According to Tanner Staging (Genital Development in Males)[2]

End point description:

Suppression of clinical sexual characteristics was defined as regression (improvement) or no progression of genital development in males. Tanner staging is a scale of physical development that defines primary and secondary sex characteristics including size of genitals. The final visit occurred at a mean age +/- SD of 12.35 +/-1.35 years (range, 10.71 to 14.07 years). The intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. The starting population comprised 6 males (genital development suppression). Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Primary

End point timeframe:

Week 4, Week 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

Notes:

[2] - 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 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage of subjects				
number (not applicable)				
Genital development suppression - Week 4 N=5	80			
Genital development suppression - Week 48 N=6	83.3			
Genital development suppression - Week 96 N=6	83.3			
Genital development suppression - Week 144 N=4	75			
Genital development suppression - Week 192 N=4	75			
Genital development suppression - Week 240 N=3	66.7			
Genital development suppression - Final Visit N=6	83.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Peak Stimulated Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) Concentrations

End point title	Mean Peak Stimulated Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) Concentrations

End point description:

Mean peak stimulated visit LH and FSH concentrations were assessed according to the DELFIA (registered trademark) assay. The final visit for measurement of both hormone concentrations occurred at a mean age +/- SD of 11.13 +/- 1.23 (range, 6.73 to 14.07) years. The intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. The starting population comprised 49 females and 6 males. Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 24, 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: mIU/mL				
arithmetic mean (standard deviation)				
Peak stimulated LH at Baseline N=55	35 (± 21.32)			
Peak stimulated LH at Week 4 N = 55	0.8 (± 0.57)			
Peak stimulated LH at Week 12 N = 54	1.1 (± 1.77)			
Peak stimulated LH at Week 24 N = 53	0.8 (± 0.79)			
Peak stimulated LH at Week 48 N = 54	0.6 (± 0.47)			
Peak stimulated LH at Week 96 N = 46	0.4 (± 0.33)			
Peak stimulated LH at Week 144 N = 36	0.4 (± 0.24)			
Peak stimulated LH at Week 192 N = 20	0.4 (± 0.25)			
Peak stimulated LH at Week 240 N = 17	0.4 (± 0.62)			
Peak stimulated LH at Final Visit N = 55	0.8 (± 3.29)			
Peak stimulated FSH at Baseline N=55	13.3 (± 5.58)			
Peak stimulated FSH at Week 4 N = 55	0.9 (± 0.44)			
Peak stimulated FSH at Week 12 N = 54	1.1 (± 0.61)			
Peak stimulated FSH at Week 24 N = 53	1.2 (± 0.84)			
Peak stimulated FSH at Week 48 N = 54	1.2 (± 0.58)			
Peak stimulated FSH at Week 96 N = 46	1.4 (± 0.79)			
Peak stimulated FSH at Week 144 N = 36	1.4 (± 0.73)			
Peak stimulated FSH at Week 192 N = 20	1.3 (± 0.76)			
Peak stimulated FSH at Week 240 N = 17	1.4 (± 0.67)			
Peak stimulated FSH at Final Visit N = 55	1.7 (± 1.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Stimulated Estradiol Concentrations in Females

End point title	Mean Stimulated Estradiol Concentrations in Females

End point description:

Mean estradiol concentrations were assessed according to the DELFIA (registered trademark) assay. The lower limit of quantitation for estradiol is 5 pg/mL and measurements below this limit are given a value of 5 pg/mL. The final visit for measurement estradiol concentrations occurred at a mean age +/- SD of 10.93 +/- 1.27 (range, 5.59 to 13.24) years. All females in the intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 24, 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: pg/mL				
arithmetic mean (standard error)				
Mean stimulated estradiol at baseline N=49	15.3 (± 18.73)			
Mean stimulated estradiol at Week 4 N=48	5 (± 0)			
Mean stimulated estradiol at Week 12 N=47	6 (± 6.56)			
Mean stimulated estradiol at Week 24 N=47	5 (± 0)			
Mean stimulated estradiol at Week 48 N=47	5 (± 0)			
Mean stimulated estradiol at Week 96 N=39	5 (± 0)			
Mean stimulated estradiol at Week 144 N=31	5 (± 0)			
Mean stimulated estradiol at Week 192 N=15	5 (± 0)			
Mean stimulated estradiol at Week 240 N=13	5 (± 0)			
Mean stimulated estradiol at Final Visit N=49	5 (± 0.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Stimulated Testosterone Concentrations in Males

End point title	Mean Stimulated Testosterone Concentrations in Males

End point description:

Mean stimulated testosterone concentrations were assessed according to the DELFIA (registered trademark) assay. The final visit for measurement of testosterone occurred at a mean age +/- SD of 12.34 +/- 1.16 (range, 11.14 to 14.07) years. All males in the intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 24, 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/dL				
arithmetic mean (standard deviation)				
Mean stimulated testosterone at baseline N=6	347.7 (± 121.86)			
Mean stimulated testosterone at Week 4 N=6	18 (± 12.39)			
Mean stimulated testosterone at Week 12 N=6	14.2 (± 7.05)			
Mean stimulated testosterone at Week 24 N=6	13.8 (± 6.15)			
Mean stimulated testosterone at Week 48 N=6	17.3 (± 11.64)			
Mean stimulated testosterone at Week 96 N=6	24.8 (± 19.92)			
Mean stimulated testosterone at Week 144 N=5	21.6 (± 19.5)			
Mean stimulated testosterone at Week 192 N=4	24 (± 17.19)			
Mean stimulated testosterone at Week 240 N=3	25.3 (± 24.01)			
Mean stimulated testosterone at Final Visit N=6	24.2 (± 17.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Ratio of Bone Age to Chronological Age

End point title	Mean Ratio of Bone Age to Chronological Age

End point description:

Bone age was determined by radiography of the wrist according to the Fels Method. The mean ratio of bone age to chronological age provides information about the slowing of bone age progression. A score = 1 indicates that bone age is equal to chronological age. The intent-to-treat (ITT) population and safety analysis set were identical for the treatment period. Study drug was discontinued at the initiation of puberty. N=subjects with evaluable data at given time point.

End point type	Secondary

End point timeframe:

Week 24 and Week 48 (Year 1), yearly for 5 years (Week 240), and Final Visit

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: ratio				
arithmetic mean (standard deviation)				
Ratio at Baseline N=53	1.5 (± 0.3)			
Ratio at Week 24 N=53	1.5 (± 0.25)			
Ratio at Week 48 N=51	1.4 (± 0.18)			
Ratio at Week 96 N=44	1.3 (± 0.15)			
Ratio at Week 144 N=31	1.2 (± 0.12)			
Ratio at Week 192 N=26	1.2 (± 0.11)			
Ratio at Week 240 N=16	1.2 (± 0.1)			
Ratio at Final Visit N=53	1.2 (± 0.11)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Posttreatment Height (ht.) Compared to Standard Population and as Predicted From Ht. at Baseline (BL)

End point title	Posttreatment Height (ht.) Compared to Standard Population and as Predicted From Ht. at Baseline (BL)

End point description:

Height was measured by stadiometer and was standardized for age according to standard growth charts. A standardized score of 0 indicated a mean ht. equivalent to mean of a standard population from 2000 CDC standardized ht. charts. Height gain was calculated as ht. - predicted ht. from the Bayley-Pinneau method on the basis of bone age at baseline. Final adult ht. was determined by measurement at final adult ht., if available, or by ht. collected during the follow-up period associated with a growth velocity <1 cm/year or a bone age >14 yrs in females or >15 yrs in males. For the follow-up posttreatment period, the ITT population=40 subjects and the safety population=55 subjects who received at least 1 injection of study drug during the treatment period. Study drug was discontinued at the initiation of puberty. The mean age of subjects at final questionnaire completion was 24.76 years with a range of 18.87 to 26.66. N=subjects with evaluable data at given time point.

End point type	Other pre-specified

End point timeframe:

Final ht. (measured or provided for final questionnaire in subjects >= 18 years of age) or near final adult ht. (<1 cm/year or bone age > 14 years for females or > 15 years for males)

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: cm				
arithmetic mean (standard error)				
Near final adult ht. standardized score N=33	-0.2 (± 1.2)			
Near final ht.gain from predicted ht. at BL N=29	3.2 (± 5.37)			

Final adult ht.standardized score N=19	0 (± 1.13)			
Final adult ht.gain from predicted ht. at BL N=17	3.9 (± 5.05)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Time to or Mean Age at Regular Menses in Females After Treatment

End point title	Mean Time to or Mean Age at Regular Menses in Females After Treatment

End point description:

Regular menses was defined as 3 or more consecutive days of menstrual-like bleeding and was defined by the investigator's clinical judgment. During the posttreatment period, data were obtained from 32 female subjects. Twenty-seven subjects reported the start of menses, but only 26 subjects reported a menses start date.

End point type	Other pre-specified

End point timeframe:

Posttreatment during the follow-up period (subjects observed every 6 months until physical and laboratory observations are at pubertal levels)

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: years				
arithmetic mean (standard deviation)				
Time to regular menses	1.5 (± 0.53)			
Age at regular menses	12.9 (± 0.89)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Female Subjects Who Reported Regular Menses at Adulthood

End point title	Number of Female Subjects Who Reported Regular Menses at Adulthood

End point description:

Subjects were required to complete final adult questionnaire to provide information on adult reproductive function. Regular menses was defined as 3 or more consecutive days of menstrual-like bleeding. A long-term follow-up questionnaire was sent to all subjects who completed at least 1 visit in the posttreatment follow-up period or who discontinued treatment because they entered puberty naturally at the appropriate age. Twenty female subjects (mean age 24.76 years, range 18.87 to 26.66 years) and 0 male subjects completed the questionnaire.

End point type	Other pre-specified

End point timeframe:

Posttreatment data were collected from the final adult questionnaire (subjects >= 18 years of age)

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
number (not applicable)				
No. of subjects with regular menses as adults	16			
No. of subjects without regular menses as adults	4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Who Reported Pregnancies at Final Questionnaire

End point title	Number of Subjects Who Reported Pregnancies at Final Questionnaire

End point description:

The final questionnaire was completed by 20 females who were at least 18 years of age. The subjects reported on total number of pregnancies resulting in live births or number of miscarriages (spontaneous or elective) and whether the subject was currently pregnant. A long-term follow-up questionnaire was sent to all subjects who completed at least 1 visit in the posttreatment follow-up period or who discontinued treatment because they entered puberty naturally at the appropriate age. Twenty female subjects (mean age 24.76 years, range 18.87 to 26.66 years) and 0 male subjects completed the questionnaire.

End point type	Other pre-specified

End point timeframe:

Posttreatment data were collected from the final adult questionnaire (subjects >= 18 years of age)

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Subjects				
number (not applicable)				
Number of subjects who reported being pregnant	7			
Number of subjects who were currently pregnant	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Pregnancies Reported by Subjects at Final Questionnaire

End point title	Number of Pregnancies Reported by Subjects at Final Questionnaire

End point description:

The final questionnaire was completed by 20 female subjects who were at least 18 years of age. The total number of pregnancies were reported. A long-term follow-up questionnaire was sent to all subjects who completed at least 1 visit in the posttreatment follow-up period or who discontinued treatment because they entered puberty naturally at the appropriate age. Twenty female subjects (mean age 24.76 years, range 18.87 to 26.66 years) and 0 male subjects completed the questionnaire.

End point type	Other pre-specified

End point timeframe:

Posttreatment data were collected from the final adult questionnaire (subjects >= 18 years of age)

End point values	Leuprolide Acetate 1 Month Depot			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Pregnancies				
number (not applicable)				
Number of pregnancies	12			
Number of live births	6			
Number of miscarriages	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each investigator monitored each subject for clinical and laboratory evidence of adverse events at Weeks 4, 8, 12, 24, 36, 48, and then every 6 months until the study drug was discontinued.

Adverse event reporting additional description:

Adverse events were reported from onset after the first injection of study drug through 30 days after treatment was completed. Treatment completion was defined as 28 days after the final study drug injection. The posttreatment follow-up period did not require the reporting of adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	COSTART
Dictionary version	COSTART

Reporting groups

Reporting group title	Leuprolide acetate 1 Month Depot

Reporting group description:

Leuprolide acetate dosing was initiated at 300 mcg/kg (minimum dose 7.5 mg) administered intramuscularly (IM) every 28 days. Incremental adjustments to dosing at 3.75 mg increments were made at each visit.

Serious adverse events	Leuprolide acetate 1 Month Depot		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 55 (12.73%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoma	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart arrest	Additional description: COSTART body system is cardiovascular system		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Repair of ventriculoperitoneal shunt	Additional description: COSTART body system was not classified since it was a surgical repair.		

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Aggravation reaction	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Personality disorder	Additional description: COSTART body system is nervous system		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone Disorder	Additional description: COSTART body system is musculoskeletal system		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture	Additional description: COSTART body system is musculoskeletal system		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia	Additional description: COSTART body system is respiratory system		

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Leuprolide acetate 1 Month Depot		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 55 (90.91%)		
Vascular disorders			
Vasodilatation	Additional description: COSTART body system is cardiovascular system		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	8		
Fever	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	14 / 55 (25.45%)		
occurrences (all)	35		
Injection site reaction	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Injection site pain	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	18		
Pain	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	32		
Reaction unevaluable	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	8		
Edema	Additional description: COSTART body system is metabolic and nutritional disorders		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		

Immune system disorders			
Allergic reaction	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	10		
Reproductive system and breast disorders			
Menstrual disorder	Additional description: COSTART body system is urogenital system		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	7		
Leukorrhea	Additional description: COSTART body system is urogenital system		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	24		
Respiratory, thoracic and mediastinal disorders			
Cough increased	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	36		
Epistaxis	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	17		
Psychiatric disorders			
Emotional Lability	Additional description: COSTART body system is nervous system		
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	46		
Depression	Additional description: COSTART body system is nervous system		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Nervousness	Additional description: COSTART body system is nervous system		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	7		
Investigations			
Weight gain	Additional description: COSTART body system is metabolic and nutritional disorders		
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	10		
Weight loss	Additional description: COSTART body system is metabolic and nutritional disorders		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Injury, poisoning and procedural			

complications			
Accidental injury	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	32		
Nervous system disorders			
Headache	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	25 / 55 (45.45%)		
occurrences (all)	146		
Dizziness	Additional description: COSTART body system is nervous system		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Lymphadenopathy	Additional description: COSTART body system is hemic and lymphatic system		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Ear pain	Additional description: COSTART body system is special senses		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	7		
Eye disorders			
Eye disorder	Additional description: COSTART body system is special senses		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	38		
Diarrhea	Additional description: COSTART body system is digestive system		
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	9		
Dyspepsia	Additional description: COSTART body system is digestive system		
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Nausea	Additional description: COSTART body system is digestive system		
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	14		
Vomiting	Additional description: COSTART body system is digestive system		

subjects affected / exposed	13 / 55 (23.64%)		
occurrences (all)	18		
Skin and subcutaneous tissue disorders			
Body odor	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Acne	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	27		
Rash	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	32		
Hirsutism	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Pruritus	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Skin disorder	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	8		
Urticaria	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Growth retarded	Additional description: COSTART body system is metabolic and nutritional disorders		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
Arthralgia	Additional description: COSTART body system is musculoskeletal system		
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Pathological fracture	Additional description: COSTART body system is musculoskeletal system		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Myalgia	Additional description: COSTART body system is musculoskeletal system		

subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Infections and infestations			
Flu syndrome	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	19 / 55 (34.55%)		
occurrences (all)	49		
Infection	Additional description: COSTART body system is body as a whole		
subjects affected / exposed	13 / 55 (23.64%)		
occurrences (all)	24		
Pharyngitis	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	29 / 55 (52.73%)		
occurrences (all)	142		
Sinusitis	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	17		
Rhinitis	Additional description: COSTART body system is respiratory system		
subjects affected / exposed	14 / 55 (25.45%)		
occurrences (all)	60		
Herpes zoster	Additional description: COSTART body system is skin and appendages		
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	8		
Otitis media	Additional description: COSTART body system is special senses		
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	37		
Urinary tract infection	Additional description: COSTART body system is urogenital system		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Vaginitis	Additional description: COSTART body system is urogenital system		
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	49		
Metabolism and nutrition disorders			
Increased appetite	Additional description: COSTART body system is digestive system		
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 1993	• Incorporated the Phase 4 protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study drug was discontinued usually at the initiation of puberty (12 years for males and 11 years for females) with the concurrence of the investigator, or at the discretion of the investigator. Adverse events are coded with the COSTART dictionary.

Notes: