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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	M16-904

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	45
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	45
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Administered intramuscularly as an injection

Arm title	Leuprolide Acetate - Treament Naïve

Arm description:

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

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

Dosage and administration details:

Administered intramuscularly as an injection

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

Baseline characteristics

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

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

End points

End points reporting groups

Reporting group title	Leuprolide Acetate - Previously Treated

Reporting group description:

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

Reporting group title	Leuprolide Acetate - Treament Naïve

Reporting group description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

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

End point description:

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

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

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

End point type	Primary

End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses per protocol are presented in the data table.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

Weeks 12, 20, 24, 44, and 48

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

Weeks 12, 20, 24, 44, and 48

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

Statistical analyses

No statistical analyses for this end point

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

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

	the Physical Signs of Puberty

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

Full analysis set; n=non missing observations.

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

Full analysis set; n=observed cases.

End point type	Secondary

End point timeframe:

Weeks 72, 96, 120, and 144

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

Weeks 72, 96, 120, and 144

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

Weeks 72, 96, 120, and 144

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Leuprolide Acetate - Treament Naïve

Reporting group description:

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

Reporting group title	Leuprolide Acetate - Previously Treated

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported