Clinical trial results:
An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty

Summary

EudraCT number	2015-001607-30
Trial protocol	Outside EU/EEA
Global end of trial date	14 July 2014

Results information

Result version number	v2 (current)
This version publication date	07 April 2016
First version publication date	11 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	Debio8206-CPP-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01467882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Debiopharm International, S.A.
Sponsor organisation address	Case postale 5911, Chemin Messidor 5-7, Lausanne, Switzerland, 1002
Public contact	Dr Eija Lundström, Debiopharm International, S.A., 41 21321 0111, eija.lundstrom@debiopharm.com
Scientific contact	Dr Eija Lundström, Debiopharm International, S.A., 41 21321 0111, eija.lundstrom@debiopharm.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	15 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of triptorelin pamoate (embonate) 22.5 mg 6-month formulation IM in achieving LH suppression to prepubertal levels (defined as serum LH ≤ 5 IU/L 30 minutes after SC GnRH agonist stimulation [leuprolide acetate 20 µg/kg SC]) at Month 6 (Day 169) in children with CPP.

Protection of trial subjects:

After being fully informed about the trial, ethics-approved parental informed consent was signed in conformation with the Declaration of Helsinki and local laws was obtained from one or both parents (as per local requirements), by the liable parent or by the legal guardian prior to any study procedures. Assent was also collected from children aged 7 or more years. Participants were allowed to be withdrawn voluntarily or if the investigator determined the child's safety or well-being was at risk.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2012
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: 28
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Chile: 15
Worldwide total number of subjects	44
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)	44
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:

A group of 39 girls and 5 boys (44 children) with central precocious puberty (CPP) were enrolled by 13 centers in the USA, Chile, and Mexico.

Pre-assignment

Screening details:

Girls up to age 9 and boys up to age 10 were screened for a diagnosis of central precocious puberty.

Period 1

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

Arms

Arm title	Children

Arm description:

All children enrolled

Arm type	Experimental
Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two intramuscular (IM) injections of triptorelin pamoate 22.5 mg 6-month formulation

Number of subjects in period 1	Children
Started	44
Completed	44

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
Children (2-11 years)	44	44	
Age continuous Units: years			
arithmetic mean	7.41		
standard deviation	± 1.28	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	5	5	

End points

End points reporting groups

Reporting group title	Children
Reporting group description: All children enrolled	
Subject analysis set title	All Children - Luteinizing Hormone
Subject analysis set type	Full analysis
Subject analysis set description: All children with luteinizing hormone values	
Subject analysis set title	All Children - Follicle Stimulating Hormone
Subject analysis set type	Full analysis
Subject analysis set description: All children with follicle stimulating hormone values	
Subject analysis set title	Girls
Subject analysis set type	Sub-group analysis
Subject analysis set description: All girls enrolled	
Subject analysis set title	Boys
Subject analysis set type	Sub-group analysis
Subject analysis set description: All boys enrolled	
Subject analysis set title	AOC Subset
Subject analysis set type	Sub-group analysis
Subject analysis set description: Acute-on-chronic (AOC) Subset, defined as 50% of the population randomly assigned	

Primary: Percentage of children with LH suppression to prepubertal levels 30 minutes after leuprolide stimulation at month 6

End point title	Percentage of children with LH suppression to prepubertal levels 30 minutes after leuprolide stimulation at month 6[1]
End point description:	
End point type	Primary
End point timeframe: at month 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: Statistical analysis was conducted; two sided 95% confidence interval is provided in the data table. Database constraints require only comparative groups to populate the statistical analysis module. Therefore, because this was a single arm study, the database can only state "no statistical analyses for this end point" which, while inaccurate, may appear in the record.

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Percentage				
number (confidence interval 93.18%)	93.18 (81.34 to 98.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children with LH suppression to prepubertal levels 30 minutes after leuprolide stimulation at months 1, 2, 3, 9 and 12

End point title	Percentage of children with LH suppression to prepubertal levels 30 minutes after leuprolide stimulation at months 1, 2, 3, 9 and 12

End point description:

End point type	Secondary

End point timeframe:

at months 1, 2, 3, 9 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)				
Month 1	95.45			
Month 2	95.45			
Month 3	95.45			
Month 9	95.45			
Month 12	97.73			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children maintaining LH suppression at prepubertal levels 30 minutes after leuprolide stimulation from month 6 to 12

End point title	Percentage of children maintaining LH suppression at prepubertal levels 30 minutes after leuprolide stimulation from month 6 to 12

End point description:

End point type	Secondary

End point timeframe:

from Month 6 to Month 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)	93.18			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children with LH suppression (LH ≤ 4 IU/L)30 minutes after leuprolide stimulation at months 1, 2, 3, 6, 9 and 12

End point title	Percentage of children with LH suppression (LH ≤ 4 IU/L)30 minutes after leuprolide stimulation at months 1, 2, 3, 6, 9 and 12

End point description:

End point type	Secondary

End point timeframe:

at months 1, 2, 3, 6, 9 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)				
Month 1	95.45			
Month 2	95.45			
Month 3	93.18			
Month 6	90.91			
Month 9	93.18			
Month 12	97.73			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children maintaining LH suppression at </= 4 IU/L 30 minutes after leuprolide stimulation from month 6 to 12

End point title	Percentage of children maintaining LH suppression at </= 4 IU/L 30 minutes after leuprolide stimulation from month 6 to

	12

End point description:

End point type	Secondary

End point timeframe:
from month 6 to 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)	90.91			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in luteinizing hormone (LH) and follicle stimulating hormone (FSH) at months 1, 2, 3, 6, 9, and 12

End point title	Change from baseline in luteinizing hormone (LH) and follicle stimulating hormone (FSH) at months 1, 2, 3, 6, 9, and 12

End point description:

End point type	Secondary

End point timeframe:
at months 1, 2, 3, 6, 9, and 12

End point values	All Children - Luteinizing Hormone	All Children - Follicle Stimulating Hormone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: IU/L				
arithmetic mean (standard deviation)				
Month 1	-25.21 (± 20.28)	-8.85 (± 4.15)		
Month 2	-25.25 (± 20.41)	-8.8 (± 4.2)		
Month 3	-25.17 (± 20.53)	-8.13 (± 4.26)		
Month 6	-23.06 (± 22.17)	-6.66 (± 4.61)		
Month 9	-25.24 (± 20.49)	-7.87 (± 4.27)		

Month 12	-25.15 (± 20.5)	-6.99 (± 4.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in estradiol levels at months 1, 2, 3, 6, 9, and 12

End point title	Change from baseline in estradiol levels at months 1, 2, 3, 6, 9, and 12

End point description:

End point type	Secondary

End point timeframe:

at Months 1, 2, 3, 6, 9, and 12

End point values	Girls			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: ng/L				
arithmetic mean (standard deviation)				
Month 1	-31.87 (± 27.82)			
Month 2	-31.24 (± 31.8)			
Month 3	-32.15 (± 28.65)			
Month 6	-28.18 (± 31.26)			
Month 9	-30.08 (± 27.44)			
Month 12	-29.74 (± 28.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in testosterone levels at months 1, 2, 3, 6, 9, and 12

End point title	Change in testosterone levels at months 1, 2, 3, 6, 9, and 12

End point description:

End point type	Secondary

End point timeframe:

at months 1, 2, 3, 6, 9, and 12

End point values	Boys			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/dL				
arithmetic mean (standard deviation)				
Month 1	-306.96 (± 184.06)			
Month 2	-290.7 (± 214.81)			
Month 3	-319.2 (± 177.04)			
Month 6	-317.62 (± 178.11)			
Month 9	-315.54 (± 183.98)			
Month 12	-301.86 (± 205.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children with prepubertal estradiol or testosterone levels at months 1, 2, 3, 6, 9, and 12

End point title	Percentage of children with prepubertal estradiol or testosterone levels at months 1, 2, 3, 6, 9, and 12

End point description:

End point type	Secondary

End point timeframe:

at months 1, 2, 3, 6, 9, and 12

End point values	Children	Girls	Boys	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	44	39	5	
Units: percentage of participants				
number (not applicable)				
Month 1	86.36	87.18	80	
Month 2	88.37	89.47	80	
Month 3	93.18	92.31	100	
Month 6	81.82	79.49	100	
Month 9	81.82	82.05	80	
Month 12	79.55	79.49	80	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children without higher basal LH and estradiol or testosterone 2 days after second triptorelin injection

End point title	Percentage of children without higher basal LH and estradiol or testosterone 2 days after second triptorelin injection

End point description:

End point type	Secondary

End point timeframe:

at 2 days after second triptorelin injection (Day 171)

End point values	AOC Subset			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: percentage of participants				
number (not applicable)	13.64			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in height-for-age Z-score and percentile per 2000 CDC growth charts at months 6 and 12

End point title	Change from baseline in height-for-age Z-score and percentile per 2000 CDC growth charts at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:

At months 6 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change in Z-score at Month 6	0.05 (± 0.2)			
Change in Percentile at Month 6	1.01 (± 3.21)			
Change in Z-score at Month 12	0 (± 0.27)			
Change in Percentile at Month 12	0.91 (± 4.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in growth velocity at months 6 and 12

End point title	Change in growth velocity at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:

At months 6 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: cm/year				
arithmetic mean (standard deviation)				
Month 6	6.84 (± 2.33)			
Month 12	6.05 (± 1.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants without bone age / chronological age ratio increase from baseline at months 6 and 12

End point title	Percentage of participants without bone age / chronological age ratio increase from baseline at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:

At months 6 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)				
Month 6	63.64			
Month 12	95.45			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of children achieving stabilisation of sexual maturation at months 6 and 12

End point title	Percentage of children achieving stabilisation of sexual maturation at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:

At months 6 and 12

End point values	Children			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)				
Month 6	90.91			
Month 12	88.64			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of girls with regression of uterine length at months 6 and 12

End point title	Percentage of girls with regression of uterine length at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:
At months 6 and 12

End point values	Girls			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: percentage of participants				
number (not applicable)				
Month 6	69.23			
Month 12	76.92			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of boys with absence of progression of testis volumes at months 6 and 12

End point title	Percentage of boys with absence of progression of testis volumes at months 6 and 12

End point description:

End point type	Secondary

End point timeframe:
At months 6 and 12

End point values	Boys			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: percentage of participants				
number (not applicable)				
Month 6	100			
Month 12	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	Children
Reporting group description: All children enrolled	

Serious adverse events	Children		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 44 (2.27%)		
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	Children		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 44 (45.45%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2011	The amendment was required to improve some practical and pharmacovigilance-related aspects of the study. 1. Further to a shortage of leuprolide acetate on the US market, the suppliers initially identified were removed from the protocol and study centers were able to purchase any commercial leuprolide acetate. In addition, the number of alcohol pads in the injection kit was no longer specified to accommodate different suppliers. 2. The total volume of the vial of water for injection was no longer specified to accommodate different suppliers. 3. The CT scan or MRI of the brain initially to be performed at screening could be replaced by a brain CT or MRI performed within three months of the first IMP injection. 4. Reporting of SAEs to the Sponsor was corrected to comply with the Sponsor's pharmacovigilance procedure (contact person). 5. Reporting of SAEs in case of premature discontinuation was included to accomodate the triptorelin 6-month sustained-release formulation (reporting period of 7 months [6 months + 30 days] after the last triptorelin administration).
25 January 2012	The amendment was required because the blood volume necessary for measurement of hormone levels post-leuprolide stimulation had increased from 1 mL to 2 mL. In addition, inclusion criterion No. 7 was modified to allow parental signature of informed consent as per local requirements. 1. Two mL of blood instead of 1 mL were required post-leuprolide stimulation because of the minimal blood volume requirement of the analytical device. Despite this increase, the volume sampled per child remained within the limits recommended by the European ethical guidelines (Directive 2001/20/EC related to GCP) and were in accordance with ICH guidelines for clinical studies in a pediatric population. 2. Inclusion criterion No. 7 was modified (bold characters) to read: "Informed consent signed by one parent or both parents (as per local requirements), by the liable parent or by the legal guardian (when applicable); assent signed by the child if ≥ 7 years".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported