Clinical trial results:
A Phase III, Multi-Center, Open Label, Single-Group Trial to Investigate the Efficacy and Safety of MK-8962 (Corifollitropin Alfa) in Combination With Human Chorionic Gonadotropin (hCG) for Initiation or Restoration of Puberty as Assessed by Increased Testicular Volume in Adolescent Males 14 to <18 Years Old With Hypogonadotropic Hypogonadism (MK-8962-043)

Summary

EudraCT number	2015-001878-18
Trial protocol	IT DK Outside EU/EEA
Global end of trial date	05 May 2020

Results information

Result version number	v1
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	8962-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03019575
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-8962-043

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000306-PIP01-08
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	05 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2020
Global end of trial reached?	Yes
Global end of trial date	05 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a single group study to investigate the efficacy and safety of corifollitropin alfa (CFA, MK-8962) in combination with human chorionic gonadotropin (hCG) for initiation or restoration of puberty assessed by increased testicular volume (TV) in adolescent males with hypogonadotropic hypogonadism (HH). The objectives of the study were: 1) To estimate the change from baseline in TV (measured as the sum of volumes of left and right testes by ultrasound) after 64 weeks of treatment with CFA (in combination with hCG for the last 52 weeks). 2) To evaluate the safety and tolerability of CFA over 64 weeks of treatment, including evaluation of development of antibodies to CFA.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2017
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	Brazil: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	17
EEA total number of subjects	1

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)	0
Adolescents (12-17 years)	17
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:

Male participants with Hypogonadotropic Hypogonadism (HH) aged 14 to <18 years were enrolled in the study. A total of 17 participants were allocated to the study treatment arm. Of 17 participants, 16 participants completed the study treatment.

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	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)

Arm description:

Participants received 100 µg (if body weight was ≤60 kg) or 150 µg (if body weight was >60 kg) of CFA as a subcutaneous (SC) injection once every 2 weeks for 64 Weeks (Day 1, Week 0 through Week 64) and 500-5000 IU of hCG reconstituted with 1 ml of 0.9% sodium chloride solution, as a SC injection twice a week for 52 weeks (last day of Week 12 through Week 64). The total treatment duration was 64 Weeks.

Arm type	Experimental
Investigational medicinal product name	Corifollitropin Alfa (CFA)
Investigational medicinal product code	
Other name	MK-8962, Elonva
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CFA administered 100 µg (if body weight ≤60 kg) or 150 µg (if body weight >60 kg) by SC injection, once every 2 weeks for 64 weeks (Day 1, Week 0 through Week 64).

Investigational medicinal product name	human Chorionic Gonadotropin (hCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

hCG 500-5000 IU reconstituted with 1 ml of 0.9% sodium chloride solution, as a SC injection twice a week for 52 weeks (last day of Week 12 through Week 64).

Number of subjects in period 1	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)
Started	17
Completed	17

Baseline characteristics

Reporting groups

Reporting group title	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)

Reporting group description:

Participants received 100 µg (if body weight was ≤60 kg) or 150 µg (if body weight was >60 kg) of CFA as a subcutaneous (SC) injection once every 2 weeks for 64 Weeks (Day 1, Week 0 through Week 64) and 500-5000 IU of hCG reconstituted with 1 ml of 0.9% sodium chloride solution, as a SC injection twice a week for 52 weeks (last day of Week 12 through Week 64). The total treatment duration was 64 Weeks.

Reporting group values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)	Total	
Number of subjects	17	17	
Age Categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: years			
arithmetic mean	15.5		
standard deviation	± 0.9	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	17	17	
Race Units: Subjects			
Multiple (Black Or African American, White)	1	1	
White	16	16	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	13	13	
Testicular Volume (TV) Units: mL			
arithmetic mean	2.2		
standard deviation	± 1.9	-	

End points

End points reporting groups

Reporting group title	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)

Reporting group description:

Participants received 100 µg (if body weight was ≤60 kg) or 150 µg (if body weight was >60 kg) of CFA as a subcutaneous (SC) injection once every 2 weeks for 64 Weeks (Day 1, Week 0 through Week 64) and 500-5000 IU of hCG reconstituted with 1 ml of 0.9% sodium chloride solution, as a SC injection twice a week for 52 weeks (last day of Week 12 through Week 64). The total treatment duration was 64 Weeks.

Primary: Change from Baseline in Log-Transformed Testicular Volume (TV) to Week 64

End point title	Change from Baseline in Log-Transformed Testicular Volume (TV) to Week 64[1]

End point description:

Participants underwent testicular ultrasound of left and right testes at pre-specified time points to measure TV. TV was measured as the sum of volumes of left and right testes. The linear mixed model with a fixed effect for baseline and Week 64 and a random effect for participant was used to calculate the mean change in log-transformed TV and associated 95% confidence intervals (CIs) from baseline to Week 64. The geometric mean ratio and its 95% CIs for TV were obtained by exponentiation. The ratio > 1 indicated an increase in TV from baseline. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had luteinizing hormone (LH) level ≤3 IU/L anytime in study, had at least 12 weeks of Corifollitropin Alfa (CFA) and 24 weeks of CFA plus human chorionic gonadotropin (hCG) treatment, have last TV value within 4 weeks from last dose of CFA were analyzed.

End point type	Primary

End point timeframe:

Baseline and Week 64

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: No between-group analysis were performed for this endpoint. A single-sided analysis will be presented on ClinicalTrials.gov NCT03019575.

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Fold change				
geometric mean (confidence interval 95%)	9.43 (7.44 to 11.97)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Experienced an Adverse Event (AE)

End point title	Number of Participants who Experienced an Adverse Event

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The number of participants who experienced an AE was reported. All participants who received at least 1 dose of study treatment were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 71 Weeks

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: No between-group analysis were performed for this endpoint. A single-sided analysis will be presented on ClinicalTrials.gov NCT03019575.

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Participants	16			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Discontinued Study Treatment Due to an AE

End point title	Number of Participants who Discontinued Study Treatment Due to an AE[3]

End point description:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The number of participants who discontinued study treatment due to an AE was reported. All participants who received at least 1 dose of study treatment were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 64 Weeks

Notes:

[3] - 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: No between-group analysis were performed for this endpoint. A single-sided analysis will be presented on ClinicalTrials.gov NCT03019575.

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Participants	1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Anti-Corifollitropin Alfa (CFA) Antibodies

End point title	Percentage of Participants with Anti-Corifollitropin Alfa (CFA) Antibodies[4]

End point description:

Blood samples were collected at pre-specified time points to assess anti-CFA antibodies. The percentage of participants with anti-CFA antibodies after administration of CFA and the corresponding 95% CIs using the Exact Binomial method of Clopper Pearson was not reported as planned since there were no participants who tested with confirmed anti-CFA antibodies during the study. All participants who received at least 1 dose of study treatment were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 71 Weeks

Notes:

[4] - 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: No between-group analysis were performed for this endpoint. A single-sided analysis will be presented on ClinicalTrials.gov NCT03019575.

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: Participants				

Notes:

[5] - No participants tested positive for anti-CFA antibodies during the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Inhibin B Concentration to Week 64

End point title	Change from Baseline in Serum Inhibin B Concentration to Week 64

End point description:

Serum Inhibin B concentration is a surrogate marker for spermatogenesis in males. Blood samples were collected at baseline and Week 64 post dose to report the mean change from baseline in serum inhibin concentration to Week 64. A mean change from baseline in serum inhibin B concentration to Week 64 was reported. A positive value indicated a higher serum inhibin concentration level. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, have last TV value within 4 weeks from last dose of CFA and had a baseline and at least 1 post baseline inhibin value were analyzed.

End point type	Secondary
End point timeframe: Baseline and Week 64	

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/L				
arithmetic mean (standard deviation)				
Baseline Baseline to Week 64	31.92 (± 35.30) 91.46 (± 59.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 36

End point title	Growth Velocity at Week 36

End point description:

Growth velocity is the rate of change in height measurement and is a marker for pubertal progress. Height was measured using a wall-mounted calibrated stadiometer. A mixed model was used to assess the overall growth velocity slope over the 36-week treatment period using the slopes estimated from an overall mixed random intercept and random slope model of height (cm) and time (yr) and age as covariates. All participants who had at least 1 dose of study treatment, had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline height records at Week 36 were analyzed.

End point type	Secondary
End point timeframe: Week 36	

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: cm/year				
least squares mean (standard error)	8.3 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 64

End point title	Growth Velocity at Week 64

End point description:

Growth velocity is the rate of change in height measurement and is a marker for pubertal progress. Height was measured using a wall-mounted calibrated stadiometer. A mixed model was used to assess the overall growth velocity slope over the 64-week treatment period using the slopes estimated from an overall mixed random intercept and random slope model of height (cm) and time (year) and age as covariates. All participants who had at least 1 dose of study treatment, had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline height records at Week 64 were analyzed.

End point type	Secondary

End point timeframe:

Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: cm/year				
least squares mean (standard error)	7.6 (± 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Stage (TS) of Pubertal Development for Pubic Hair to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Tanner Stage (TS) of Pubertal Development for Pubic Hair to Week 12, Week 36, and Week 64

End point description:

Male participants were assessed clinically for pubertal development using the TS for pubic hair (range: Tanner I-V). TS describes sexual maturity stages (no better or worse outcome) as: Tanner I: prepubertal state, Tanner II: small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum, Tanner III: hair becomes more coarse and curly, and begins to extend laterally, Tanner IV: adult-like hair quality, extending across pubis but sparing medial thighs and Tanner V: hair

extends to medial surface of the thigh. Percentage of participants was calculated as number of participants in each TS at each timepoint/ number of participants in population*100. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, have last TV value within 4 weeks from last dose of CFA were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Participants				
Baseline (BL) Tanner I	6			
BL Tanner II	6			
BL Tanner III	1			
BL Tanner IV	0			
BL Tanner V	0			
BL Tanner I to Week 12 Tanner I	5			
BL Tanner I to Week 12 Tanner II	1			
BL Tanner II to Week 12 Tanner II	5			
BL Tanner II to Week 12 Tanner III	1			
BL Tanner III to Week 12 Tanner III	1			
BL Tanner I to Week 36 Tanner II	2			
BL Tanner I to Week 36 Tanner III	4			
BL Tanner II to Week 36 Tanner II	2			
BL Tanner II to Week 36 Tanner III	4			
BL Tanner III to Week 36 Tanner IV	1			
BL Tanner I to Week 64 Tanner III	3			
BL Tanner I to Week 64 Tanner IV	1			
BL Tanner I to Week 64 Tanner V	2			
BL Tanner II to Week 64 Tanner III	1			
BL Tanner II to Week 64 Tanner IV	3			
BL Tanner II to Week 64 Tanner V	1			
BL Tanner II to Week 64 Missing	1			
BL Tanner III to Week 64 Tanner IV	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in TS of Pubertal Development for Genital Growth to Week 12, Week 36, and Week 64

End point title	Change from Baseline in TS of Pubertal Development for

	Genital Growth to Week 12, Week 36, and Week 64

End point description:

Male participants were assessed clinically for pubertal development using TS for genital growth (range: Tanner I-V). TS describes sexual maturity stages (no better/worse outcome) as: Tanner I: prepubertal (TV <1.5 ml; small penis), Tanner II: TV 1.6-6ml; skin on scrotum thins, reddens and enlarges; penis length unchanged, Tanner III: TV 6-12ml; scrotum enlarges further; penis begins to lengthen Tanner IV: TV 12-20ml; scrotum enlarges further and darkens; penis increases in length and circumference, and Tanner V: TV >20ml; adult scrotum and penis. Percentage of participants was calculated as number of participants in each TS at each timepoint/ number of participants in population*100. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, have last TV value within 4 weeks from last dose of CFA were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Participants				
Baseline (BL) Tanner I	12			
BL Tanner II	1			
BL Tanner III	0			
BL Tanner IV	0			
BL Tanner V	0			
BL Tanner I to Week 12 Tanner I	9			
BL Tanner I to Week 12 Tanner II	3			
BL Tanner II to Week 12 Tanner II	1			
BL Tanner I to Week 36 Tanner I	2			
BL Tanner I to Week 36 Tanner II	1			
BL Tanner I to Week 36 Tanner III	8			
BL Tanner I to Week 36 Tanner IV	1			
BL Tanner II to Week 36 Tanner II	1			
BL Tanner I to Week 64 Tanner II	1			
BL Tanner I to Week 64 Tanner III	4			
BL Tanner I to Week 64 Tanner IV	4			
BL Tanner I to Week 64 Tanner V	2			
BL Tanner I to Week 64 Missing	1			
BL Tanner II to Week 64 Tanner III	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Serum Concentration of CFA

End point title	Mean Serum Concentration of CFA

End point description:

Blood samples were collected at pre-specified time points to report the mean serum concentration of CFA. All enrolled participants in the study were analyzed.

End point type	Secondary

End point timeframe:

Predose on Days 1, 29, 85, 169, 253, 337; and postdose on Day 1 (6-24 hours), Day 3 (32-52 hours), Day 5 (72-120 hours), Day 8 (144-192 hours), Day 11 (216-264 hours), Day 449, and Day 456

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	17[6]			
Units: ng/L				
arithmetic mean (standard deviation)				
Predose Day 1 [n =16]	0.0 (± 0.0)			
Predose Day 29 [n =16]	480 (± 348)			
Predose Day 85 [n =17]	695 (± 1310)			
Predose Day 169 [n =17]	691 (± 1060)			
Predose Day 253 [n = 17]	301 (± 297)			
Predose Day 337 [n =16]	556 (± 1260)			
Postdose Day 1 (6-24 hours) [n =16]	4100 (± 2630)			
Postdose Day 3 (32-52 hours) [n =17]	5880 (± 1640)			
Postdose Day 4 (72-120 hours) [n=17]	4240 (± 1180)			
Postdose Day 8 (144-192 hours) [n =16]	2110 (± 864)			
Postdose Day 11 (216-264 hours) [n =17]	1150 (± 655)			
Postdose Day 449 [n =16]	864 (± 1290)			
Postdose Day 456 [n =16]	0.0 (± 0.0)			

Notes:

[6] - Day 1 predose and postdose samples for 1 participant were excluded due to biological implausibility.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Testicular Echogenicity to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Testicular Echogenicity to Week 12, Week 36, and Week 64

End point description:

Testicular Echogenicity was determined by evaluating the sonographic patterns obtained on testicular ultrasound of right and left testes at baseline, Week 12, Week 36 and 64. The sonographic patterns were assessed by central imaging unit by an independent radiologist and categorized as Hypoechoic (decreased echogenicity as compared to echogenicity at baseline), Isoechoic (same echogenicity as compared to echogenicity at baseline) and Hyperechoic (increased echogenicity as compared to echogenicity at baseline). The percentage of participants was calculated as number of participants in each sonographic pattern at specific time point / number of participants in population*100. All

participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, have last TV value within 4 weeks from last dose of CFA were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Participants				
Left Testes: Baseline (BL) to Week 12: Hypoechoic	2			
Left Testes: BL to Week 12: Isoechoic	10			
Left Testes: BL to Week 12: Hyperechoic	1			
Right Testes: BL to Week 12: Hypoechoic	1			
Right Testes: BL to Week 12: Isoechoic	12			
Left Testes: BL to Week 36: Hypoechoic	2			
Left Testes: BL to Week 36: Isoechoic	10			
Left Testes: BL to Week 36: Hyperechoic	1			
Right Testes: BL to Week 36: Hypoechoic	1			
Right Testes: BL to Week 36: Isoechoic	9			
Right Testes: BL to Week 36: Hyperechoic	3			
Left Testes: BL to Week 64: Hypoechoic	2			
Left Testes: BL to Week 64: Isoechoic	8			
Left Testes: BL to Week 64: Hyperechoic	3			
Right Testes: BL to Week 64: Isoechoic	10			
Right Testes: BL to Week 64: Hyperechoic	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Luteinizing Hormone (LH) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Luteinizing Hormone (LH) to Week 12, Week 36, and Week 64

End point description:

LH is a gonadotropin secreted from the anterior pituitary and is a marker for spontaneous puberty. Blood samples were collected at baseline, Week 12, Week 36 and Week 64 to report the mean change

from baseline in LH level to Weeks 12, 36 and 64. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline LH values at Weeks 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: IU/L				
arithmetic mean (standard deviation)				
Baseline	0.25 (± 0.24)			
Baseline to Week 12	-0.08 (± 0.15)			
Baseline to Week 36	-0.13 (± 0.25)			
Baseline to Week 64	-0.14 (± 0.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Calculated Free Testosterone (T) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Calculated Free Testosterone (T) to Week 12, Week 36, and Week 64

End point description:

Blood samples were collected at baseline, Week 12, Week 36 and Week 64 to report the mean change from baseline in T level to Weeks 12, 36 and 64. The change from baseline in T level to Week 12, 36, and 64 could not be calculated as planned because only 2 participants had baseline T level values which was insufficient to provide the trend change from baseline in T level to Week 12, 36, and 64. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline T value at Week 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: ng/L				
arithmetic mean (standard deviation)	()			

Notes:

[7] - Insufficient T data at BL to calculate reliable mean change from BL for T.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Testosterone (Total T) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Total Testosterone (Total T) to Week 12, Week 36, and Week 64

End point description:

Total T is a marker for progress of puberty in males. Total T levels increase during puberty as the testes respond to the gonadotropins. Blood samples were collected at baseline, Week 12, Week 36 and Week 64 post dose to report the mean change from baseline in Total T level to Weeks 12, 36 and 64. A negative value indicated a lower Total T level. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline Total T value at Week 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ug/L				
arithmetic mean (standard deviation)				
Baseline	0.11 (± 0.12)			
Baseline to Week 12	-0.01 (± 0.07)			
Baseline to Week 36	4.87 (± 3.97)			
Baseline to Week 64	5.31 (± 3.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Estradiol (E2) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Estradiol (E2) to Week 12, Week 36, and Week 64

End point description:

E2 levels rise during puberty in males when some of the T secreted is aromatized. Blood samples were collected at baseline, Week 12, Week 36 and Week 64 to report the mean change from baseline in E2 level to Weeks 12, 36 and 64. A positive value indicated a higher E2 level. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline E2 value at Week 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/L				
arithmetic mean (standard deviation)				
Baseline	9.51 (± 0.00)			
Baseline to Week 12	0.81 (± 2.90)			
Baseline to Week 36	37.57 (± 28.73)			
Baseline to Week 64	45.58 (± 41.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sex Hormone-Binding Globulin (SHBG) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Sex Hormone-Binding Globulin (SHBG) to Week 12, Week 36, and Week 64

End point description:

SHBG is a blood protein that controls the amount of T body tissues in males. SHBG is regulated by the ratio of T and E2 levels in addition to other factors (thyroid hormone status, dietary factors, certain diseases and medications). Blood samples were collected at baseline, Week 12, Week 36 and Week 64 to report the mean change from baseline in SHBG level to Weeks 12, 36 and 64. A negative value indicated a lower SHBG level. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline SHBG value at Week 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ug/dL				
arithmetic mean (standard deviation)				
Baseline	1.53 (± 0.91)			
Baseline to Week 12	0.04 (± 0.45)			
Baseline to Week 36	-0.53 (± 0.73)			
Baseline to Week 64	-0.68 (± 0.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Anti-Müllerian Hormone (AMH) to Week 12, Week 36, and Week 64

End point title	Change from Baseline in Anti-Müllerian Hormone (AMH) to Week 12, Week 36, and Week 64

End point description:

AMH is a marker for progress of puberty in males. Blood samples were collected at baseline, Week 12, Week 36 and Week 64 to report the mean change from baseline in AMH level to Weeks 12, 36 and 64. A negative value indicated a lower AMH level. All participants with at least 1 dose of study treatment who had a baseline and at least 1 post baseline TV value, had LH level ≤3 IU/L anytime in study, had at least 12 weeks of CFA and 24 weeks of CFA plus hCG treatment, had last TV value within 4 weeks from last dose of CFA and had a baseline and post baseline AMH value at Week 12, 36 and 64 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36, and Week 64

End point values	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ug/L				
arithmetic mean (standard deviation)				

Baseline	23.62 (± 11.07)			
Baseline to Week 12	17.98 (± 8.39)			
Baseline to Week 36	-10.23 (± 15.69)			
Baseline to Week 64	-15.83 (± 11.58)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 71 Weeks	
Adverse event reporting additional description:	
All participants who received at least one dose of study treatment were analyzed.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)
Reporting group description:	
Participants received 100 µg (if body weight was ≤60 kg) or 150 µg (if body weight was >60 kg) of CFA as a subcutaneous (SC) injection once every 2 weeks for 64 Weeks (Day 1, Week 0 through Week 64) and 500-5000 IU of hCG reconstituted with 1 ml of 0.9% sodium chloride solution, as a SC injection twice a week for 52 weeks (last day of Week 12 through Week 64). The total treatment duration was 64 Weeks.	

Serious adverse events	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			
subjects affected / exposed	1 / 17 (5.88%)		
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	Corifollitropin Alfa (CFA)+human Chorionic Gonadotropin (hCG)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)		
Vascular disorders			

Hot flush			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pruritus genital			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Scrotal disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Spermatocele			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	6		
Varicocele			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinitis allergic			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Investigations			
Blood prolactin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood testosterone decreased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Blood testosterone free increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Blood testosterone increased			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Human chorionic gonadotropin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oestradiol increased			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	5		
Testicular scan abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ultrasound testes abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Foot fracture			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Migraine			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		

Gingival oedema subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 2 / 17 (11.76%) 3		
Skin and subcutaneous tissue disorders Acanthosis nigricans subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all) Dermatitis contact subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Infections and infestations			

Gastroenteritis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tinea infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tracheitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Metabolism and nutrition disorders Hyperphagia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolic syndrome subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2016	Major changes of Amendment (AM) 1 included testicular ultrasound images to be read locally by the investigator or local radiologist at Visit 1/Screening, additional blood samples for total T and E2 at Study Visits 10, 11, 13 and 14, and allowed participants with previous GnRH, gonadotropins and androgen treatments to participate in the study.
19 June 2018	Major change of AM3 included addition of vials as a dosage form for hCG and sodium chloride solution.
26 June 2018	Major change of AM6 allowed for hCG dose titration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported