Amsterdam, 25 March 2021
EMA/CHMP/707542/2020
Committee for Medicinal Products for Human Use (CHMP)

Final Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Elonva

International non-proprietary name: Corifollitropin alfa

Procedure no.: EMEA/H/C/001106/P46/019

Marketing authorisation holder (MAH): Merck Sharp & Dohme B.V.

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 30 October 2020, the marketing authorisation holder (MAH) submitted a completed paediatric study for corifollitropin alfa (Elonva, EMEA/H/C/001106), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Elonva has been approved in females, for controlled ovarian stimulation (COS) by centralised procedure since 2010 (EMEA/H/C/001106).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study P043:MK8962,

"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)",

is part of an agreed Paediatric Investigation Plan (PIP) in the European Union (EU); EMEA-000306PIP01-08-M04 (decision P/0143/2019) and that the study is part of a clinical development program. This study was planned and executed as part of a PIP for corifollitropin alfa (CFA) per EU regulations.

The original PIP was issued in December 2008 and a PIP modification was agreed upon by the Paediatric Committee (PDCO) in AUG 2011 to extend the timelines for the planned clinical study. The PIP was modified in December 2013 to include two sequential, open-label, noncomparative studies in adult men with HH and in adolescent males with hypogonadotropic hypogonadism *(*HH), instead of one, two-staged study, primarily to facilitate better execution of the studies. This modified PIP was approved by PDCO in May 2014.

The part of the modified study studying adults was Study 031, an "*open-label, non-comparative, multi-centre safety and efficacy study of corifollitropin alfa (CFA) in association with hCG in male adults with hypogonadotrophic hypogonadism (HH)*" and included 18 adult males. CFA use resulted in doubling of the mean testicular volume and induction of spermatogenesis in 77% of adult males who remained azoospermic after treatment with hCG. The dose used in Study P031 was based on the results from Study 022, a "*Phase 1, open-label, repeated single dose, multicenter PK study in adult males with HH*".

In this assessment report, the study in adolescents (P043) is reviewed.

The MAH states in their cover letter that they are planning to submit a type II variation to update the product information to include the outcome of the PIP after finalization of this Article 46 application.

2.2. Information on the pharmaceutical formulation used in the study

No paediatric formulation for corifollitropin alfa was necessary. The pharmaceutical formulation used in the study were the currently registered formulations for Elonva in fertile women: 100 micrograms and 150 micrograms solution for injection in prefilled syringe.

For human Chorionic Gonadotropin (hCG) the commercially available formulations for Pregnyl were used: 1500 IU in 2 mL vial and 5000 IU in 2 mL vial.

2.3. Clinical aspects

2.3.1. Introduction

The disease

Hypogonadotropic hypogonadism (HH) is lack of, or inadequate, production of gonadotropins, follicle stimulating hormone (FSH) and luteinising hormone (LH), from the pituitary gland and can be caused by a primary defect in gonadotropin secretion by the pituitary gonadotrophs, or from absent or inadequate gonadotropin releasing hormone (GnRH) secretion by the hypothalamus. When gonadotropin deficiency occurs before puberty (prepubertal), puberty is delayed or absent.

Paediatric hypogonadotropic hypogonadism

Clinical presentation of hypogonadism at birth is rare, with abnormal genitalia occurring in ~1 in 4,500 live births. Hypogonadism established after birth, throughout childhood, is usually inapparent until pubertal age; at this point, the hypogonadal condition manifests as delayed puberty. The prevalence of delayed puberty in the general population has not been thoroughly assessed. In this context, it is important to note that the current definition of delayed puberty is based on an arbitrary cut-off of 14 years. Using this definition, early studies have found a prevalence of delayed puberty of <2% among boys in the United States (Salonia et al, Nat Rev Dis Primers. 2019).

Treatment of adolescents

The primary goal in the treatment of male HH is to increase testosterone (T) levels (either through the administration of exogenous T, or by using hCG to stimulate LH receptors on Leydig cells of the testes and induce the production of endogenous T from Leydig cells). This leads to a pubertal growth spurt and the development of male secondary sexual characteristics. Another important goal is to stimulate spermatogenesis to support fertility; this requires treatment with FSH to stimulate the proliferation and maturation of Sertoli cells in the testes, initiated before hCG treatment.

Historically, boys with HH were given exogenous testosterone to induce the development of male secondary sexual characteristics. However, boys that are not exposed to FSH may miss a critical state of testicular development with regard to spermatogenesis.

Currently, modern treatment protocols for adolescent males with HH use a 3-staged approach:

- a short period of treatment with FSH-only to promote Sertoli cell proliferation and maturation,
- followed by treatment with a combination of FSH and hCG to stimulate Leydig cell function and increase T production until testicular volumes attain adult size,
- after which gonadotropin therapy can be stopped and T supplementation can be used to maintain male secondary sexual characteristics until fertility is desired.

This approach allows for both the induction of puberty and maturation of Sertoli cells in early onset HH so that spermatogenesis and future fertility are not compromised.

Inhibin B has been shown to be a useful surrogate for monitoring spermatogenic activity in boys treated with hCG when semen analysis is not feasible.

The product

Elonva, corifollitropin alfa [CFA] is a recombinant gonadotropin, consisting of the α-subunit of human FSH and a hybrid subunit composed of the sequence of the α-subunit of human FSH and the carboxy-terminal peptide (CTP) part of the α-subunit of the hCG. It has the same mechanism of action as FSH, but different pharmacokinetic (PK) properties. A single injection of corifollitropin alfa replaces 7 days of daily recombinant FSH. Since treatment of HH in males usually requires long-term treatment, the use of CFA may result in fewer medication errors and improved compliance. Both CFA and recFSH act at the same FSH receptor in the ovary or testes, therefore either can be used for gonadal stimulation. CFA has been approved in females, for controlled ovarian stimulation (COS) in 69 countries since 2010.

2.3.2. Clinical study

Clinical study number and title:

(P043:MK8962): 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.

Description

This was a multicenter, open-label, single-group study evaluating the treatment of corifollitropin alfa (MK-8962) in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis in adolescent males with HH.

The rationale for the pretreatment with CFA instead of hCG in HH adolescents is to mimic the gonadotropin pattern of normal puberty, ie, to stimulate FSH receptors on Sertoli cells with CFA prior to the stimulation of LH receptors on Leydig cells with hCG to induce testicular growth, masculinization, and preservation of future fertility in male adolescents.

Methods

Objectives and endpoints

Table 1 Objectives and endpoints

Primary Objectives	Primary Endpoints
To estimate the change from baseline in testicular volume (measured as the sum of volumes of left and right testes by ultrasound) after 64 weeks of treatment with MK-8962 (in combination with hCG for the last 52 weeks).	Change from baseline (Day 1) to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound).

To evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962.	Development of anti-MK-8962 antibodies, and adverse events, laboratory assessments, and vital sign measurements.
Secondary objectives	**Secondary endpoints**
To evaluate the following parameters over 64 weeks of treatment with corifollitropin alfa (in combination with hCG for the last 52 weeks) in adolescent males with HH:	
1) The change from baseline in inhibin B concentrations.	1) Change from baseline in serum inhibin B concentrations at Week 64.
2) Growth velocity (height)	2) Growth velocity at Weeks 36 and 64.
3) The change from baseline in Tanner Stage of pubertal development	3) Tanner Stage of pubertal development at Weeks 12, 36, and 64.
4) The change from baseline in levels of endocrine parameters [ie, LH, calculated free testosterone [T], Total T, estradiol (E2), sex hormone-binding globulin (SHBG), and anti-müllerian hormone (AMH)].	4) Changes from baseline in endocrine parameters LH, Total T, T, E2, SHBG, and AMH at Weeks 12, 36, and 64.
5) Testicular sonographic pattern reflecting pubertal development.	5) Characterization of testicular sonographic pattern reflecting pubertal development through 64 weeks of treatment.
6) The pharmacokinetics (PK) of MK-8962 (based on serum MK-8962 concentrations).	6) Characterization of MK-8962 PK (based on serum MK-8962 concentrations) through 64 weeks of treatment.

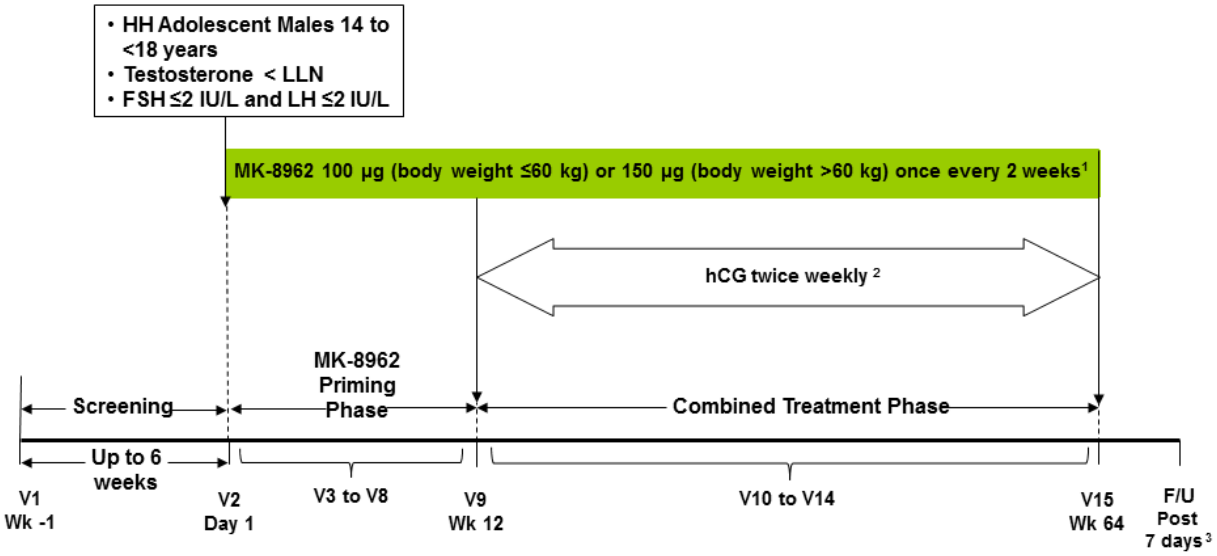
Assessor's comment:

The primary efficacy endpoint selected for this study, i.e. change from baseline in testicular volume, is considered adequate.

The secondary efficacy endpoints are considered adequate parameters for evaluation of the pubertal development.

Study design

Figure 1 Study Design Diagram



1. During the course of the trial, for subjects receiving MK-8962 100 µg, the dose of MK-8962 should be adjusted to 150 µg if the subject's body weight increases by 2 kg or more from the previous visit to a value greater than 60 kg. For subjects receiving MK-8962 150 µg, the dose should not be down-titrated for the rest of the trial regardless of any changes in body weight.
2. During the Combined Treatment Phase, the dose of hCG may be titrated between 500-5000 IU twice weekly to keep the testosterone and E2 levels within acceptable ranges. A dose of hCG outside of this range may be appropriate in certain subjects, based on the subject's Total T and/or E2 levels and/or any clinically relevant signs or symptoms (e.g., gynecomastia, breast pain and/or tenderness), and will require prior consultation with the Sponsor.
3. Follow-up visit should be at least 21 days (but no more than 45 days) after the last dose of MK-8962 and at least 7 days after the last dose of hCG

E2 = estradiol; F/U = follow-up visit; FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HH = hypogonadotropic hypogonadism; LH = luteinizing hormone; LLN = lower limit of normal

Duration of treatment

The total duration of the study was 73 weeks, the active treatment period was 64 weeks.

Study population /Sample size

This was an estimation study. Approximately 15 subjects were to be enrolled.

Assuming a screen failure rate of approximately 50-60%, approximately 30-40 subjects were to be screened to enrol approximately 15 subjects. Assuming a discontinuation rate of 30%, it was estimated that 10 subjects will complete. If the discontinuation rate exceeded 30%, enrolment was to be reopened to assure the target number of completers. The total number of enrolled subjects was not to exceed 35.

A total of 17 male adolescents were allocated to CFA (priming period) for 12 weeks and combined treatment with CFA and hCG for 52 weeks.

Adolescent male participants who met the following key criteria were eligible to participate in the study:

Inclusion Criteria

1. 14 to <18 years of age at the time when consent/assent was signed, with treatment to begin before the subject's 18th birthday.
2. Diagnosis of HH (either isolated or associated with panhypopituitarism), either congenital or acquired with onset before puberty.
   Note: Subjects with drug-induced HH (e.g., misuse of anabolic steroids, chronic use of glucocorticoids or narcotic analgesics, etc.) are excluded.
3. Bilateral pre-gonadarche testes as defined by testicular volume <4.0 mL for each testicle, as determined by ultrasound and assessed by a qualified investigator (if qualified) or local radiologist with appropriate training and expertise in reading testicular ultrasound.
   Note: subjects with a volume of <4.0 mL in one testicle and a volume of 4-8 mL in the other testicle are considered to be pre-gonadarche and may participate, if there is no history or evidence of a primary testicular disorder (see exclusion criteria 1 and 2).
4. Circulating levels of Total T less than the LLN of 8.3 nmol/L as specified by the central laboratory for a young healthy adult male.
5. FSH ≤2 IU/L and LH ≤2 IU/L.
6. Inhibin B levels ≤35 pg/mL. Note: if the subject has inhibin B levels >35 pg/mL and meets all of the other inclusion/exclusion criteria, either a GnRH agonist (GnRHa) stimulation test or GnRH IV infusion test may be performed. The subject may be enrolled if either of the following is met:
   1) GnRH agonist (GnRHa) stimulation test: LH level of <3 IU/L at all of the following time points: 0, 60, 120, and 180 minutes after subcutaneous administration of a GnRH agonist, eg., 500 µg of leuprolide acetate.
   2) GnRH IV infusion test: LH peak <5.8 IU/L and FSH peak <4.6 IU/L at all of the following time points: 0, 15, 30, 45, 60 and 120 minutes during intravenous infusion of GnRH 100 micrograms over 120 minutes.

Exclusion Criteria

1. History of bilateral cryptorchidism (maldescended testes) or unilateral cryptorchidism treated after the age of 2 years.
2. History or presence of clinically significant testicular problems (e.g., epididymitis, orchitis, testicular torsion, varicocele Grade III, testicular atrophy, occlusive azoospermia, etc) that in the opinion of the investigator would impair the subject's response to treatment or has had known damage or injury to the vas deferens.
3. Previous treatment with GnRH, gonadotropins (e.g., hCG, FSH) or androgens (e.g., T, etc.).
   Note: Use of GnRH and gonadotropins for diagnostic testing purposes only was allowed. Subjects with use of hCG and androgen therapy before 2 years old could have been included in the study. Subjects with transient use of androgens (i.e., for less than 2 weeks) that was stopped at least 6 months before signing informed consent could have also been included in the trial.
4. Untreated or inadequately treated pituitary or hypothalamic tumour.
5. Uncontrolled endocrinopathies, including thyroid, adrenal, and pituitary disorders not on stable replacement therapies (i.e., subject has not been on stable doses for at least 3 months).

Note: The subject with a free T4 level outside the normal laboratory range at the time of screening was excluded but may have been rescreened once he had been on a stable dose of replacement therapies for at least 3 months.

6. History of active pituitary hypersecretion as evidenced by hyperprolactinemia or Cushing's disease, or acromegaly, or any other active pituitary hypersecretion syndrome. Note: Subjects were treated and are clinically stable, with no evidence of hypersecretion for at least 12 months before screening, may have participated.
7. Hypophysectomy within a period of 12 months before the start of screening.
8. Had an allergy/sensitivity to gonadotropins or its/their excipients.

Assessor's comment:

The inclusion criteria are acceptable and reflect the pre-puberty HH population with pre-gonadarche testes.

The exclusion criteria are appropriate. Subjects were to be naïve for earlier treatment with testosterone, hCG, FSH or GnRH. The currently listed contraindication for FSH use in adult males with HH is primary testicular insufficiency, which is considered covered by these exclusion criteria aiming to exclude non-endocrine disorders.

Treatment

Table 2 Study Medication

Intervention, route and type of use	Unit Dose and Frequency	Treatment period
Corifollitropin alfa (CFA; MK-8962); subcutaneous (SC) injection; Experimental medication	Body weight ≤60 kg: 100 µg Body weight >60 kg: 150 µg once every 2 weeks	Day 1 (Week 0) through Week 64. The last dose was to be administered on the last day of Week 62 (Day 435).
hCG* SC injection Standard of care	500-5000 IU twice a week	The first dose was to be administered on the last day of Week 12 (Day 85). Treatment was to be continued from Week 13 through Week 64.

* Note: A dose of hCG outside this range may be appropriate in certain subjects, based on the subject's Total T and/or E2 levels and/or any clinically relevant signs or symptoms (e.g., gynecomastia, breast pain, and/or tenderness), and required prior consultation with the Sponsor.

Assessor's comment

This was an open label, single-group study where all participants received the same treatment and no comparison was made with placebo or other FSH treatment.

The dose in relation to weight is the same as the current posology for women.

Statistical Methods

The primary analysis for testicular volume was based on the Full Analysis Set (FAS) population. The primary efficacy endpoint was the mean change from Day 1 (Baseline) in log-transformed testicular volume was analysed using a mixed model with a fixed effect for baseline and time point and a random effect for each participant. The geometric mean increase in testicular volume and its 95% confidence intervals (CI) were obtained by exponentiation.

The mean change from the first day of combined treatment (Week 12) to Week 64 in log-transformed testicular volume was also analysed using a mixed model with a fixed effect for time point. For each time point, the mean change from Week 12 to that time point and the associated 95% CI were calculated. The geometric mean increase in testicular volume and its 95% CI were obtained by exponentiation.

The analyses for all secondary efficacy endpoints were conducted on the FAS population.

The change in serum inhibin B concentrations after Weeks 12, 36, and 64 were summarized. Growth velocity over the 36- and 64-week treatment periods was extracted using the slopes estimated from an overall mixed random intercept and random slope model of height (cm) and time (in years) and age as covariates. Tanner Staging was recorded for both testicular volume and pubic hair at baseline, Weeks 12, 36, and 64. Serum concentrations of hormones (LH, total T, E2, SHBG, and AMH) were summarized by assessment. Sonographic testicular patterns were listed and any changes over time were described.

The PK analysis was conducted in the All-Subjects-Pharmacokinetically-Evaluable group. Serum CFA concentrations were obtained using a solid phase enzyme-immunoassay specific for CFA. Descriptive statistics for the serum concentrations by time-point were calculated.

Safety analyses were performed in the ASaT population, which consisted of all participants who received at least 1 dose of study medication. Safety and tolerability were assessed by clinical review of relevant endpoints including AEs, presence of MK-8962 antibodies, predefined limits of change (PDLCs), laboratory tests, and vital signs.

Assessor's comment

The primary analysis will be performed in the full analysis set using a mixed model. Secondary endpoints will be analysed with similar models. This is considered acceptable.

Note (last paragraph): participants were not randomized as this was a one-arm uncontrolled study.

Results

Recruitment/ Number analysed

A total of 17 male subjects aged between 14 and 17 years were allocated across 9 sites in 4 countries.

Table 3 Disposition of Subjects

	n
Screened	25
Screen failures	8

Allocated	17
Subjects who entered the Priming Period	17
Subjects who entered the Combined Treatment Period	17
Subjects who completed the Combined Treatment Period	16
Discontinued	1 (due to SAE)

Table 4 Protocol deviations

	n
Subjects with one or more clinically important protocol deviations	8
Two or more consecutive occurrences of a change of the hCG and/or MK-8962 dose without a dose titration by the Principal Investigator (PI)	1
hCG dosing non-compliance of two or more consecutive occurrences (dose and window): doses less than 1000 IU or greater than 10,000 IU per week and/or <2 doses administered within any 1-week span that was NOT driven by a dose titration by the PI.	1
Failure to obtain a value for PK or secondary endpoint parameters (i.e., FSH, LH, hCG, inhibin-B, AMH, Total T, E2, and SHBG) at baseline, after at least 8 weeks of treatment with MK-8962 only, OR after at least 12 weeks of combined treatment with MK-8962 and hCG.	5
Missing scheduled serum sample for assessment of anti-MK-8962 antibodies and were not taken within two weeks of the date of the protocol-specified visit.	1
Testicular ultrasound not performed at baseline (not collected prior to first witnessed dose of MK-8962 or within 24 hours after the first witnessed dose of MK-8962)	1

No important protocol deviations were classified as serious GCP compliance issues.

Table 5 Subjects analysed

	n
All subjects	17
Pharmacokinetic analysis: ASaT (all subjects as treated)	17
Safety analysis: ASaT	17
Efficacy Analysis	
FAS (full analysis set) Excluded from FAS: • Had no baseline or no post-baseline testicular volume measurement • Had at least one LH value >3 IU/L anytime during the study or missing LH values at Week 64 • Received <36 weeks of corifollitropin alpha or >4 weeks from last corifollitropin alpha dose when last measurement was taken	13 4 • 1 • 2 • 1
MITT (modified intent-to-treat)	16

Excluded from MITT: • Had no baseline or no post-baseline testicular volume measurement at ≥ 36 weeks of treatment	• 1
Completers Excluded from completers: • Discontinued study medication before completing 64 weeks of treatment	16 • 1

Baseline data

The 17 subjects were recruited in 9 centres in the following countries: Mexico (n=1), Brazil (n=4), Russia (n=11) and Italy (n=1).

Demographic characteristics

All participants were prepubertal adolescent males with:

- a mean age of 15.5 years
- with a mean height of 161.4 cm
- mean testicular volume of 2.2 mL (range: 0.6-7.4 mL)
- prepubertal levels of FSH (0.5 IU/L; range 0.3 - 1.9 IU/L), LH (0.2 IU/L; range 0.1- 0.9 IU/L), Inhibin B (44.9 ng/L; range 11.0 - 155.0 ng/L) and total T (0.1 µg/L; range 0.0 - 0.4 µg/L)
- and Tanner I for genital development (with the exception of 1 participant with Tanner II genitalia) and Tanner I, II or III pubic hair.
- Weight was ≤60 kg for 11 subjects and >60 kg for 6 subjects
- BMI was 21.9 kg/m^2
- Race: 16 subjects were white, 1 was multiple
- Ethnicity: 13 were not Hispanic or Latino, 4 were Hispanic or Latino

Medical history

All participants had 1 or more endocrine disorders pertaining to the pituitary gland reported in their medical history: 14 had HH without olfaction deficit/olfactive bulb hypoplasia, 2 had rare diseases associated with HH and 1 had a diagnosis of unknown origin.

Assessor's comment

The 17 participants can be considered representative of pre-pubertal HH patients.

Concomitant medications

The most frequent concomitant medications included levothyroxine, somatropin, hydrocortisone, and desmopressin. These reported concomitant medications were expected in this subject population of HH patients.

Compliance

All participants were 100% compliant (ie, no missed injections) with CFA during the priming period and combined treatment period. Although hCG compliance was not specifically collected, an increase in hCG levels was observed after Week 12 and maintained throughout the rest of the study.

Extent of exposure

All participants received 6 or 7 doses of CFA before starting hCG. During the combined treatment period, participants received CFA with 500 to 5000 IU of hCG. In 2 participants, the dose of CFA was increased per protocol from 100 to 150 µg. The majority of participants received CFA for ≥52 weeks (n=16), 1 participant received CFA for '>36 weeks to 48 weeks'.

Efficacy results

Primary Efficacy Endpoint – Testicular Volume Change

Testicular volume was measured as the sum of volumes of left and right testes by ultrasound.

Priming period

In the priming period, the mean testicular volume changed from a geometric mean of 1.4 mL to 2.5 mL (mean fold increase of 1.83 (95% CI of 1.58, 2.13)):

Table 6 Analysis of Testicular Volume (mL) Change from Baseline to Week 12

	N	Baseline				Week 12				Model† Based Geometric Mean Ratio	
		Geometric Mean	Mean	SD	Median	Geometric Mean	Mean	SD	Median	Ratio‡	(95% CI)
Corifollitropin Alfa	13	1.4	1.5	0.7	1.5	2.5	2.8	1.7	2.4	1.83	(1.58, 2.13)

N = Number of participants included in the analysis. CI = Confidence Interval.
†Based on a mixed model that includes fixed effects for log-transformed baseline and time point, and a random effect for subject by the analysis of the log transformed data.
‡Ratio >1 indicates an increase from baseline.

Source: [P043MK8962: adam-adsl; adtsv]

Assessor's comment

In the priming period on CFA alone, to stimulate FSH receptors on Sertoli cells, the mean testicular volume (measured as the sum of volumes of left and right testes by ultrasound) at week 12 was almost doubled from a geometric mean of 1.4 mL to 2.5 mL.

Overall treatment period

During the overall treatment period, the increase noted in testicular volume at Week 64 changed from a geometric mean of 1.4 mL to 12.9 mL, mean fold increase of 9.43 mL (95% CI of 7.44, 11.97).

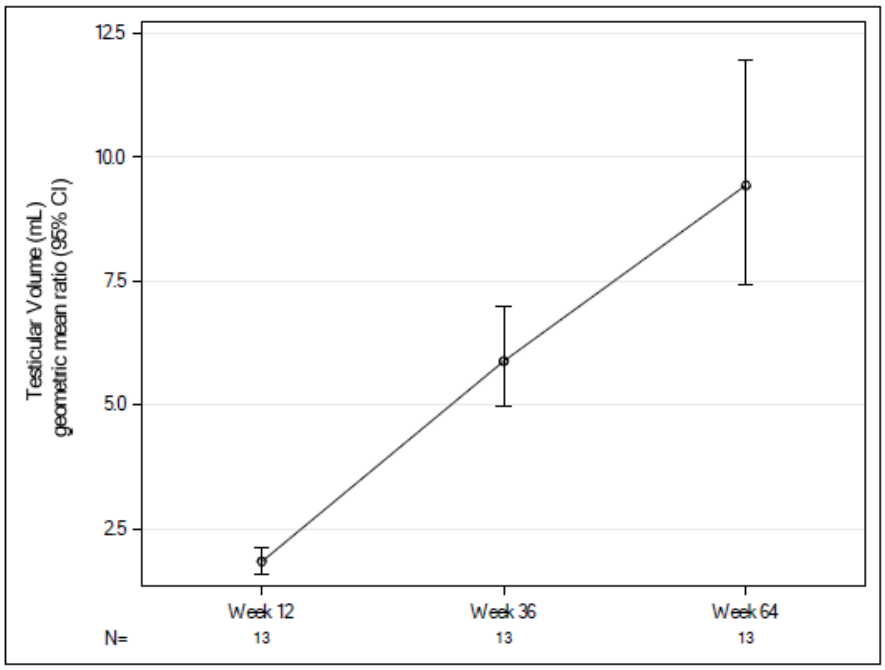
Table 7 Analysis of Testicular Volume (mL) Change from Baseline to Week 64

	N	Baseline				Week 64				Model† Based Geometric Mean Ratio	
		Geometric Mean	Mean	SD	Median	Geometric Mean	Mean	SD	Median	Ratio‡	(95% CI)
Corifollitropin Alfa + Corifollitropin Alfa/hCG	13	1.4	1.5	0.7	1.5	12.9	14.5	6.8	12.7	9.43	(7.44, 11.97)

N = Number of participants included in the analysis. CI = Confidence Interval.
†Based on a mixed model that includes fixed effects for log-transformed baseline and time point, and a random effect for subject by the analysis of the log transformed data.
‡Ratio >1 indicates an increase from baseline.

Source: [P043MK8962: adam-adsl; adtsv]

Figure 2 Analysis of Testicular Volume Change Over Time



Note: The geometric mean of testicular volume at baseline was 1.4 mL.

During the overall treatment period, mean testicular volume (measured by ultrasound) increased, with the largest increase noted at Week 64.

The mean testicular volume achieved at the end of Week 64 was less than the testicular volume observed at the end of normally-timed puberty. This reflected the exposure to gonadotropins for 64 weeks, while normal puberty lasts for 2 to 3 years. At Week 64, 3 participants had a change of testicular volume of ≥20 mL from baseline.

Assessor's comment

During the combined CFA/hCG treatment, the testicular volume continued to increase until end of study (Week 64) to 12.9 mL, mean fold increase of 9.43 mL (95% CI of 7.44, 11.97) compared to baseline.

The applicant noted that the mean testicular volume achieved at the end of Week 64 (geometric mean 12.9 mL) was less than the testicular volume observed at the end of normally-timed puberty, but that this is as expected considering the exposure to gonadotropins for 64 weeks, while normal puberty lasts

for 2 to 3 years. This explanation can be accepted (according to Rohany et al (2017) testicular volume observed at the end of normally-timed puberty is ≥24 mL).

Symmetry in testes growth

The increase in mean testicular volume during the overall treatment period was symmetric in both testes:

Table 8 Analysis of Testicular Volume (mL) Change from Week 12 by Time Point and Laterality

Timepoint	N	Week 12				Timepoint				Model† Based Geometric Mean Ratio	
		Geometric Mean	Mean	SD	Median	Geometric Mean	Mean	SD	Median	Ratio‡	(95% CI)
Left Testis											
Week 36	13	1.2	1.4	0.8	1.1	4.0	4.4	2.0	3.4	3.21	(2.76, 3.73)
Week 64	13	1.2	1.4	0.8	1.1	6.5	7.2	3.3	5.8	5.22	(4.15, 6.55)
Right Testis											
Week 36	13	1.3	1.4	0.9	1.3	4.0	4.5	2.2	4.1	3.20	(2.76, 3.71)
Week 64	13	1.3	1.4	0.9	1.3	6.4	7.3	3.6	7.1	5.08	(4.22, 6.11)

N = Number of participants included in the analysis. CI = Confidence Interval.
†Based on a mixed model that includes fixed effects for log-transformed baseline and time point, and a random effect for subject by the analysis of the log transformed data.
‡Ratio >1 indicates an increase from week 12.

Source: [P043MK8962: adam-adsl; adtsv]

Assessor's comment

The testes growth was symmetrical.

Body weight and dose

Participants who began the study weighing ≤60 kg (and received 100 µg CFA), and participants who began the study weighing >60 kg (and received 150 µg CFA), had similar increases in mean testicular volume:

Table 9 Summary of Testicular Volume (mL) Change by Weight

	N	Baseline			Week 64		
		Mean (SD)	Median	[Min, Max]	Mean (SD)	Median	[Min, Max]
Weight (kg)							
≤ 60 kg at baseline†	8	1.4 (0.7)	1.4	[0.6, 2.8]	13.7 (6.8)	12.1	[6.4, 25.6]
> 60 kg at baseline	5	1.7 (0.9)	1.6	[0.9, 3.0]	15.6 (7.5)	15.8	[5.8, 23.6]

†two subjects who had received 100 µg corifollitropin alfa had their dose increased to 150 µg as their body weight increased by 2 kg or more from the previous visit to a value greater than 60 kg.

Source: [P043MK8962: adam-adsl; adtsv]

Assessor's comment

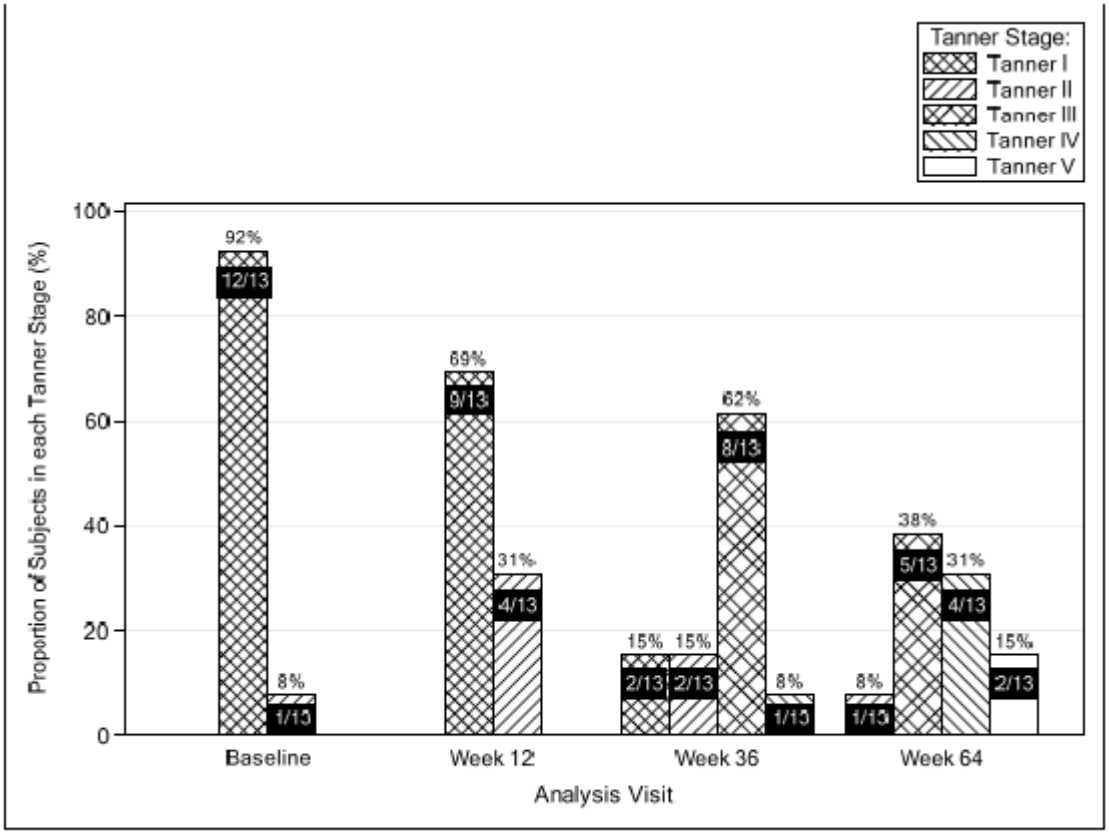
Weight (and consequent dose of CFA) did not affect testicular growth in these patients: similar increases in mean testicular volume were seen, regardless of body weight at baseline.

Secondary efficacy endpoints

Tanner Stage of Development

At the start of the study, 12 participants (92.3%) in the FAS were prepubertal (Tanner I) and 1 participant was in early puberty (Tanner II) for genital growth. At Week 64, 1 participant was in early puberty (Tanner II), 5 participants were in mid puberty (Tanner III), and 6 participants were in late puberty (Tanner IV/V):

Figure 3 Summary of Tanner Stage Over Time (Genital Growth)



One participant had a missing value at Week 64.

Source: [P043MK8962: adam-adsl; adtsv]

At Week 64, all participants had pubic hair development ranging from Tanner III to V indicating pubertal progress.

Testosterone

Total T levels increased in response to hCG administered starting from Week 12. Mean total T levels at Week 64 (5.42 µg/L) were within the normal range (1 – 12 µg/L) observed in adolescent boys undergoing normally timed puberty:

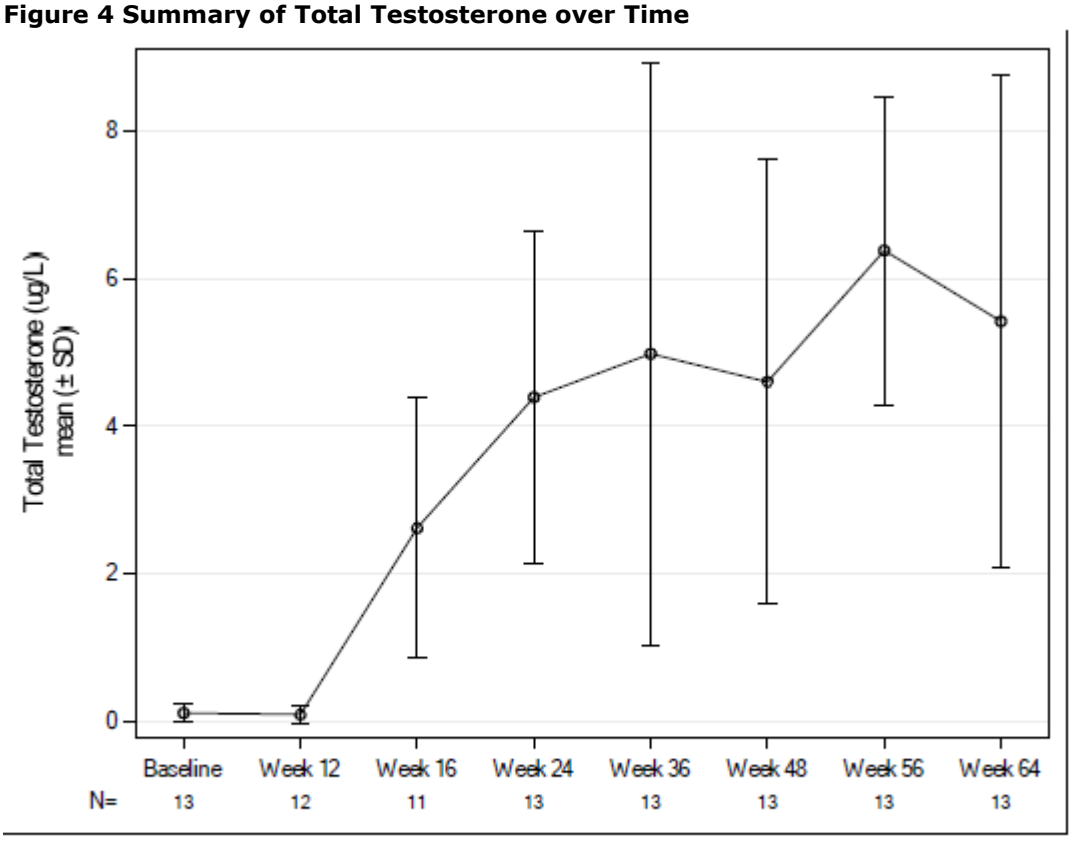
Table 10 Summary of Total Testosterone (ug/L) Change from Baseline by Time Point

			Observed Value							Change from Baseline					
Timepoint	N	n (%)	Geometric Mean	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV
Baseline	13	4 (30.8)	0.06	0.11 (0.12)	0.01	0.09	0.12	[0.01, 0.43]	1.09						
Priming Period															
Week 12	12	4 (33.3)	0.05	0.09 (0.12)	0.01	0.06	0.10	[0.01, 0.37]	1.29	-0.01 (0.07)	-0.03	0.00	0.00	[-0.12, 0.17]	-11.59
Combined Treatment Period															
Week 16	11	0 (0.0)	1.81	2.62 (1.77)	0.46	2.54	4.47	[0.29, 4.95]	0.68	2.50 (1.83)	0.39	2.46	4.46	[-0.14, 4.94]	0.73
Week 24	13	0 (0.0)	3.61	4.39 (2.26)	3.29	4.27	5.16	[0.61, 8.66]	0.52	4.28 (2.28)	3.23	4.15	4.93	[0.59, 8.65]	0.53
Week 36	13	0 (0.0)	2.91	4.98 (3.95)	1.30	4.21	6.86	[0.06, 14.69]	0.79	4.87 (3.97)	1.28	3.98	6.43	[0.00, 14.68]	0.81
Week 48	13	0 (0.0)	3.36	4.60 (3.01)	3.03	4.25	5.56	[0.29, 11.26]	0.65	4.49 (3.05)	2.85	4.16	5.55	[0.17, 11.25]	0.68
Week 56	13	0 (0.0)	6.03	6.38 (2.09)	5.85	6.57	7.26	[3.00, 10.49]	0.33	6.27 (2.09)	5.73	6.14	7.10	[2.98, 10.37]	0.33
Week 64	13	0 (0.0)	2.93	5.42 (3.34)	4.55	6.08	7.26	[0.12, 9.90]	0.62	5.31 (3.31)	4.54	5.97	7.11	[0.00, 9.89]	0.62

CV = Coefficient of Variation=SD/Mean.
N = number of subjects with baseline and post-baseline results. n = number of subjects with a value below the Lower Limit of Quantification (LLOQ). Q1 = 25th percentile.
Q3 = 75th percentile. SD = Standard Deviation.
Values below the LLOQ have been set to 1/2 times the LLOQ.

Source: [P043MK8962: adam-adsl; adeh]

Figure 4 Summary of Total Testosterone over Time



Source: [P043MK8962: adam-adsl; adeh]

Growth velocity

Participants demonstrated increased linear growth in response to hCG, indicative of pubertal changes:

Table 11 Summary of Growth Velocity (cm/year) at Week 64

Treatment	N	Week 64[†]			Model[‡] Based	
		Mean (SD)	Median	[Min, Max]	Overall Growth (SD[§])	SE
Corifollitropin Alfa + Corifollitropin Alfa/hCG	12	7.4 (3.7)	7.5	[-0.2, 14.6]	7.6 (3.5)	1.0

[†]Growth Velocity at Week 64 = change from baseline in height/(duration in days from date of baseline measurement to date of Week 64 measurement/365.25)
[‡]Based on a mixed random intercept and random slope model of height (cm) and time (in years) and age as covariate.
[§]Based on model-based estimates.
N = number of subjects with height records both at baseline and Week 64; SE = standard error.

Source: [P043MK8962: adam-adsl; advs]

Growth velocity at Week 64 (7.4 cm/year) was as expected in HH boys who were responding to therapy.

The participants started at a mean pretreatment height of 160.1 cm ±10.5 cm. At the end of the study, mean height was 169.3 cm ±8.4 cm.

The applicant noted that boys undergoing normally-timed puberty have been reported to have a mean prepubertal height of 156 cm at age 13, with increases from 5 cm/year to 7 cm/year during the first year of puberty. For participants in this study, mean baseline height was greater than 156 cm, reflecting the fact that they were older than 13 at the beginning of the study.

Estradiol and Sex Hormone-Binding Globulin

The increased estradiol observed in response to treatment was consistent with the changes in total T levels and reflect peripheral aromatization of T. No participant reported an AE of gynecomastia.

Table 12 Summary of Estradiol (ng/L) Change from Baseline by Time Point

			Observed Value							Change from Baseline					
Timepoint	N	n (%)	Geometric Mean	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV
Baseline	13	13 (100.0)	9.51	9.51 (0.00)	9.51	9.51	9.51	[9.51, 9.51]	0.00						
Priming Period															
Week 12	13	12 (92.3)	10.07	10.31 (2.90)	9.51	9.51	9.51	[9.51, 19.98]	0.28	0.81 (2.90)	0.00	0.00	0.00	[0.00, 10.47]	3.61
Combined Treatment Period															
Week 16	11	5 (45.5)	15.69	17.51 (8.33)	9.51	19.64	24.97	[9.51, 30.42]	0.48	8.00 (8.33)	0.00	10.13	15.47	[0.00, 20.92]	1.04
Week 24	13	3 (23.1)	28.07	33.91 (19.40)	21.87	32.87	39.92	[9.51, 73.94]	0.57	24.40 (19.40)	12.36	23.37	30.41	[0.00, 64.44]	0.79
Week 36	13	0 (0.0)	40.78	47.08 (28.73)	28.74	37.46	53.49	[19.46, 122.07]	0.61	37.57 (28.73)	19.23	27.95	43.98	[9.95, 112.57]	0.76
Week 48	13	2 (15.4)	33.74	39.57 (21.18)	31.30	35.59	47.40	[9.51, 89.54]	0.54	30.06 (21.18)	21.80	26.08	37.89	[0.00, 80.04]	0.70
Week 56	13	0 (0.0)	52.33	57.44 (25.77)	41.17	46.00	72.61	[22.69, 110.65]	0.45	47.93 (25.77)	31.66	36.49	63.10	[13.19, 101.14]	0.54
Week 64	13	2 (15.4)	41.10	55.09 (41.09)	26.82	49.79	81.04	[9.51, 143.79]	0.75	45.58 (41.09)	17.31	40.28	71.53	[0.00, 134.29]	0.90

CV = Coefficient of Variation=SD/Mean.
N = number of subjects with baseline and post-baseline results. n = number of subjects with a value below the Lower Limit of Quantification (LLOQ). Q1 = 25th percentile.
Q3 = 75th percentile. SD = Standard Deviation.
Values below the LLOQ have been set to 1/2 times the LLOQ.
The SDs for the change from baseline values are identical to that of the observed values because the baseline values are all nearly identical.

Source: [P043MK8962: adam-adsl; adeh]

The production of SHBG in the liver is regulated by the ratio of T and E2 levels (among other). During male puberty, a change in the T/E2 ratio in favour of T leads to a decrease in SHBG levels as observed in the participants in this study in response to administration of hCG:

Table 13 Summary of Sex Hormone-Binding Globulin (ug/dL) Change from Baseline by Time Point

			Observed Value							Change from Baseline					
Timepoint	N	n (%)	Geometric Mean	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV	Mean (SD)	Q1	Median	Q3	[Min, Max]	CV
Baseline	13	0 (0.0)	1.31	1.53 (0.91)	0.99	1.24	1.86	[0.44, 3.57]	0.60						
Priming Period															
Week 12	13	0 (0.0)	1.34	1.57 (0.92)	0.72	1.57	2.18	[0.62, 3.43]	0.58	0.04 (0.45)	-0.28	-0.12	0.32	[-0.60, 0.93]	11.45
Combined Treatment Period															
Week 36	12	0 (0.0)	0.84	0.96 (0.49)	0.49	0.95	1.40	[0.41, 1.76]	0.51	-0.53 (0.73)	-0.52	-0.41	-0.03	[-2.15, 0.13]	-1.38
Week 64	13	0 (0.0)	0.76	0.85 (0.44)	0.49	0.75	0.93	[0.35, 1.69]	0.51	-0.68 (0.76)	-0.76	-0.53	-0.25	[-2.70, 0.36]	-1.11

CV = Coefficient of Variation=SD/Mean.
N = number of subjects with baseline and post-baseline results. n = number of subjects with a value below the Lower Limit of Quantification (LLOQ). Q1 = 25th percentile.
Q3 = 75th percentile. SD = Standard Deviation.
Values below the LLOQ have been set to 1/2 times the LLOQ.

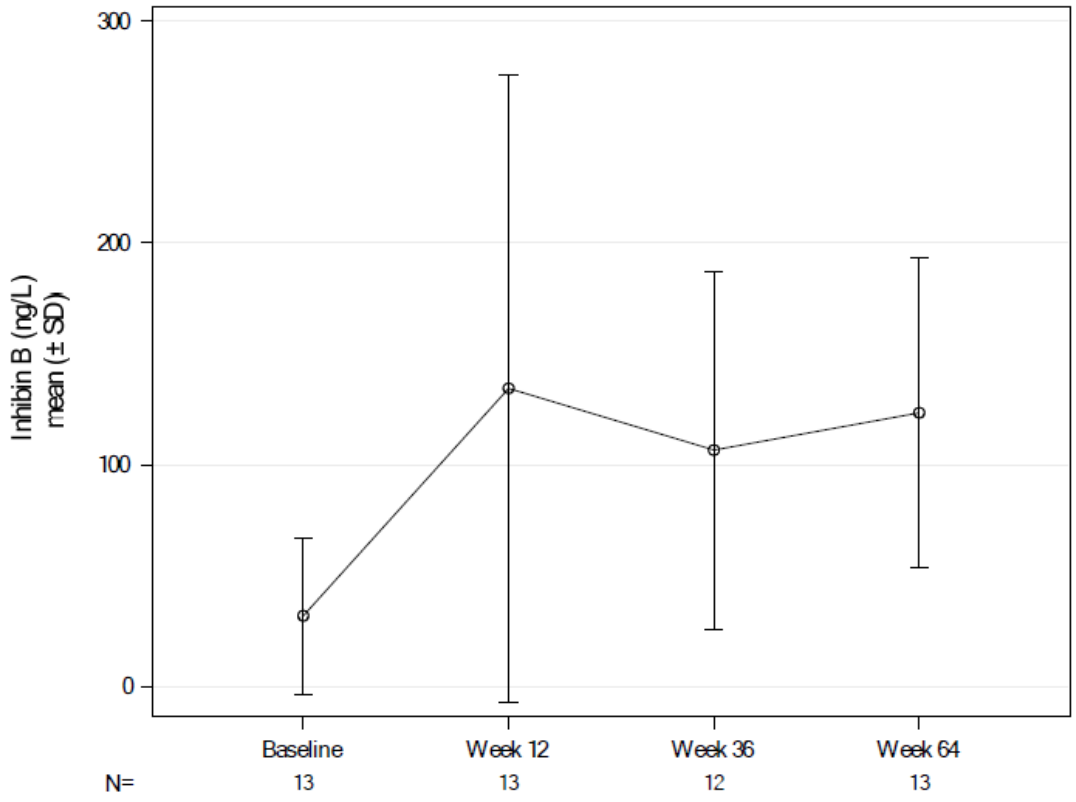
Source: [P043MK8962: adam-adsl; adeh]

Inhibin B Concentration

Increased serum inhibin B is a surrogate marker of spermatogenesis. Increase in inhibin B levels shows proliferation of Sertoli cells, which are associated with sperm-producing capacity, by CFA treatment. The inhibin B response suggests that the testicles had matured and that the transition from Antimullerian Hormone (AMH) to inhibin B production in the testicles associated with puberty had occurred.

There was a mean increase in inhibin B levels at Week 12 that was maintained through Week 64:

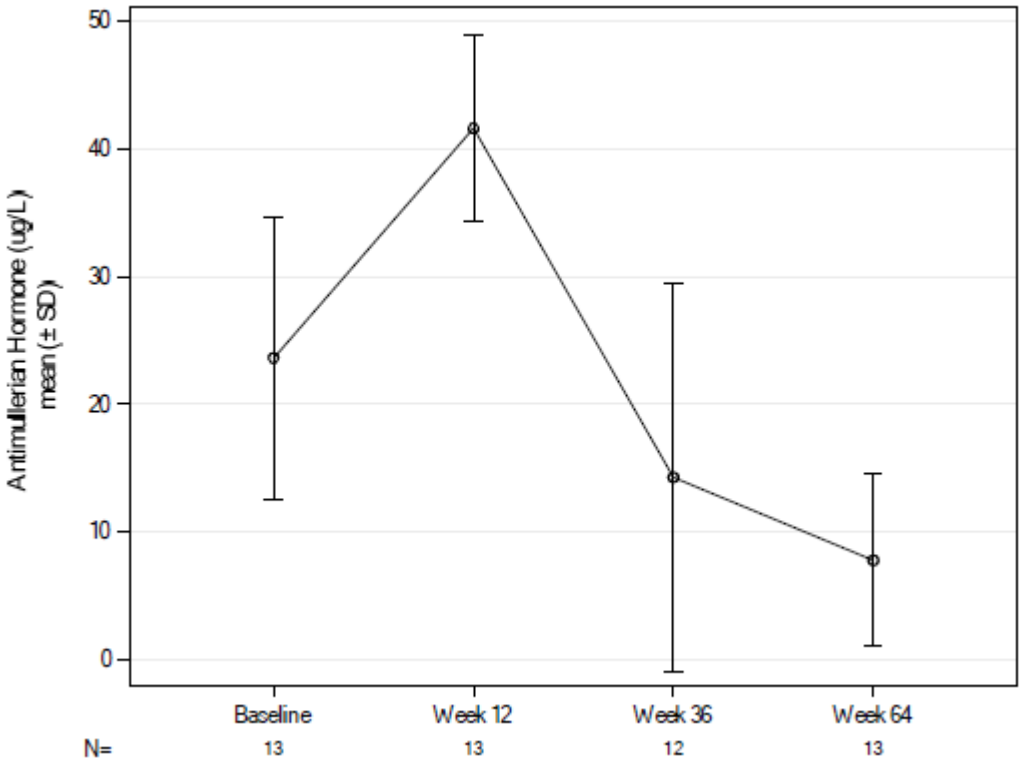
Figure 5 Summary of Inhibin B Over Time



Antimullerian Hormone

There was an initial increase in AMH during the priming period, which is consistent with stimulation by CFA alone. After Week 12, when CFA was combined with hCG, mean AMH levels decreased, with the lowest AMH value at Week 64.

Figure 6 Summary of Antimullerian Hormone Over Time



Assessor's comment

The results from the secondary objectives were supportive of the primary endpoint and suggestive of induced puberty:

- All subjects went to higher Tanner stages (III, IV and V) during the course of the study.
- Growth velocity from baseline to Week 64 was 7.4 cm/year.
- Testosterone levels increased from Week 12 in response to hCG: mean total T level at Week 64 was 5.42 µg/L. Variations in testosterone levels were within the normal range (1 – 12 µg/L) observed in adolescent boys.
- Changes in E2 (increase) and SHBG levels (decrease) were consistent with increased testosterone production.
- Serum inhibin B levels, a surrogate marker of spermatogenesis, increased on CFA alone. The decreased Anti Mullerian Hormone (AMH) levels increased on CFA alone and decreased after hCG was added, suggesting a transition from AMH to inhibin B production in the testicles, in line with normal puberty.

Pharmacokinetic Results

Table 14 Descriptive Summary Statistic Values of Corifollitropin Alfa Serum Concentrations

Descriptive Summary Statistic Values of Corifollitropin Alfa Serum Concentrations Following Administration of 100 µg (Body Weight Less Than 60 kg) or 150 µg (Body Weight Greater Than 60 kg) of Corifollitropin Alone Once Every 2 Weeks for 12 Weeks, and Then Following by Co-administration of Corifollitropin (Once Every 2 Weeks) with hCG (Twice Weekly) for 52 Weeks to Adolescent Males 14 to <18 Years Old with HH

Period	TRT	Visit	Time	N	AM (ng/L)	SD (ng/L)	Min (ng/L)	Median (ng/L)	Max (ng/L)	GM (ng/L)	GMCV (%)
Priming Period	CFA	Single Dose Administration of CFA									
		Predose	Predose	16[a]	0.00	0.00	0.00	0.00	0.00	0.00	0.00
		Visit 2	6-24hr	16[a]	4100	2630	797	4410	10800	3200	93.0
		Visit 3	32-52hr	17	5880	1640	3450	5880	9190	5700	28.8
		Visit 4	72-120hr	17	4240	1180	2500	3890	7560	4100	26.5
		Visit 5	144-192hr	16[b]	2110	864	974	1980	4600	2000	41.0
		Visit 6	216-264hr	17	1150	655	406	1020	3280	1000	52.5
		Multiple Dose Administration of CFA Alone or CFA with hCG									
		Visit 8	Predose	16[c]	480	348	0.00	422	1540	NC	NC
		Visit 9	Predose	17	695	1310	0.00	443	5630	NC	NC
Combined Treatment Period	CFA with hCG	Visit 11	Predose	17	691	1060	0.00	367	3490	NC	NC
		Visit 12	Predose	17	301	297	0.00	358	866	NC	NC
		Visit 13	Predose	16[d]	556	1260	0.00	173	5170	NC	NC
		Visit 15	Postdose	16[d]	864	1290	0.00	459	4700	NC	NC
		Follow-up	Follow-Up	16[d]	0.00	0.00	0.00	0.00	0.00	NC	NC

AM = Arithmetic Mean; GM = Geometric Mean; GMCV = CV% of geometric mean; NC = Not able to be calculated; SD = Standard Deviation; TRT = Treatment
[a] A predose and 6-24 hr postdose serum sample from a single subject were excluded from the descriptive summary statistical analysis due to biological implausibility.
[b] A serum sample from a single subject was not collected at Visit 5.
[c] A serum sample from a single subject collected at Visit 8 was not considered evaluable and was excluded from the descriptive summary statistical analysis.
[d] A subject was discontinued prior to Visit 13.

No comparison was made by the Applicant between the groups receiving 100 µg and 150 µg. The following ranges of trough values (based on visits 8-13) are derived from the individual listing.

<u>Trough data (visit 8-13) subjects receiving 100 µg:</u>
Subject 8962-043_: 0 – 432 ng/L
Subject 8962-043_: 0 – 566 ng/L
Subject 8962-043_: 0 – 1430 ng/L
Subject 8962-043_: 370 – 603 ng/L
Subject 8962-043_: 0 – 2035 ng/L
Subject 8962-043_: 0 – 531 ng/L
Subject 8962-043_: 0 – 1541 ng/L
Subject 8962-043_: 0 – 0 ng/L
Subject 8962-043_: 0 – 758 ng/L
Subject 8962-043_: 442 – 822 ng/L
Subject 8962-043_: 0 – 381 ng/L

<u>Trough data (visit 8-13) subjects receiving 150 µg:</u>
Subject 8962-043_: 0 – 415 ng/L
Subject 8962-043_: 417 – 625 ng/L
Subject 8962-043_: 0 – 3489 ng/L
Subject 8962-043_: 0 – 0 ng/L
Subject 8962-043_: 473 – 5627 ng/L
Subject 8962-043_: 393 – 2623 ng/L

Assessor's comment

Mean pre-dose (trough) CFA serum concentrations ranged from 301 ng/L to 864 ng/L and were generally similar, after repeated dosing with CFA alone and co-administered with hCG, i.e. mean and median concentrations at visit 8 and 9 (CFA alone) were similar to concentrations at visits 11-13 (CFA + hCG). CFA serum concentrations appeared comparable in participants with body weights ≤60 kg

receiving 100 µg doses of CFA and participants with body weights >60 kg receiving 150 µg doses of CFA, as far as can be concluded based on limited data without available statistical analyses on the comparison between the groups receiving 100 µg and 150 µg.

Overall conclusion on efficacy (applicant)

Primary Efficacy Endpoint

• In the FAS population (N=13), treatment with CFA for 64 weeks (administered alone for 12 weeks and then in combination with hCG from Weeks 12 to 64) induced testicular growth and development in adolescent males with HH.

Secondary Efficacy Endpoints

- Increased T levels, increased growth velocity, and progression of secondary sexual characteristics (Tanner III, IV, and V) indicated appropriate responses to hCG by the Leydig cells of the participants' testes. Changes in E2 and SHBG were consistent with increased T production.
- Increased serum inhibin B levels, a surrogate marker of spermatogenesis, and decreased AMH levels were consistent with pubertal progression and indicate that future fertility may be preserved.
- Mean predose (trough) CFA serum concentrations ranged from 301 ng/mL to 864 ng/mL and were generally similar, after repeated dosing with CFA alone and coadministered with hCG. CFA serum concentrations were comparable in participants with body weights ≤60 kg receiving 100 μg doses of CFA and participants with body weights >60 kg receiving 150 µg doses of CFA.

Overall conclusion on efficacy (Rapporteur)

The applied regimen of 12 weeks of pretreatment with Elonva and subsequently 52 weeks of Elonva/hCG combined was seen to induce puberty in the efficacy analysis population, based on increase in testicular volume. The results from the secondary objectives were supportive of an induction of pubertal development and induction of spermatogenesis.

Safety results

Brief Summary of Adverse Events

During the study, 16 out of 17 participants were reported with one or more AEs. Nine participants had drug-related AEs and 1 participant discontinued study medication due to a SAE:

Table 15 Adverse Event Summary

	Priming (CFA, 12 wks)	Combined (CFA/hCG, 52 wks)	Total (CFA + CFA/hCG, 64 wks)
Subjects in population	17	17	17
with one or more adverse events	10 (58.8)	15 (8 8.2)	16 (94.1)
with no adverse event	7 (41.2)	2 (11.8)	1 (5.9)
with drug-related† adverse events	2 (11.8)	8 (47.1)	9 (52.9)
with serious adverse events	-	1 (5.9)	1 (5.9)
with serious drug-related adverse events	-	-	-
who died	-	-	-
who died due to a drug-related adverse event	-	-	-
discontinued drug due to an adverse event	-	1 (5.9)	1 (5.9)
discontinued drug due to a drug-related adverse event	-	-	-
discontinued drug due to a serious adverse event	-	1 (5.9)	1 (5.9)
discontinued drug due to a serious drug-related adverse event	-	-	-

Most Frequently Reported Adverse Events

In the overall treatment period, the most frequently reported AEs (>20%) were spermatocele (n=5, 29.4%), increased E2 (n=5, 29.4%), increased blood T (n=4, 23.5%), and headache (n=4, 23.5%). Laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. One participant had an AE of increased E2 reported related to an accidental hCG overdose.

In the priming period, the most frequently reported AEs (>10%) were headache (n=3, 17.6%) and rhinorrhea (n=2, 8%).

Table 16 Subjects With Adverse Events

	Priming (CFA, 12 wks) n (%)	Combined (CFA/hCG, 52 wks) n (%)	Total (CFA + CFA/hCG, 64 wks) n (%)
Subjects in population	17	17	17
with one or more adverse events	10 (58.8)	15 (88.2)	16 (94.1)
with no adverse events	7 (41.2)	2 (11.8)	1 (5.9)
Blood and lymphatic system disorders		**2 (11.8)**	**2 (11.8)**
Anaemia		1 (5.9)	1 (5.9)
Iron deficiency anaemia		1 (5.9)	1 (5.9)
Congenital, familial and genetic disorders		**1 (5.9)**	**1 (5.9)**
Hydrocele		1 (5.9)	1 (5.9)
Endocrine disorders		**1 (5.9)**	**1 (5.9)**
Hypothyroidism		1 (5.9)	1 (5.9)
Gastrointestinal disorders	**2 (11.8)**	**2 (11.8)**	**4 (23.5)**
Abdominal pain		1 (5.9)	1 (5.9)
Dental caries	1 (5.9)		1 (5.9)
Diarrhoea		2 (11.8)	2 (11.8)
Gingival oedema		1 (5.9)	1 (5.9)
Vomiting	1 (5.9)	1 (5.9)	2 (11.8)
General disorders and administration site conditions	**1 (5.9)**	**3 (17.6)**	**4 (23.5)**
Injection site pain	1 (5.9)		1 (5.9)
Oedema peripheral		1 (5.9)	1 (5.9)
Peripheral swelling		1 (5.9)	1 (5.9)
Pyrexia		1 (5.9)	1 (5.9)
Infections and infestations	**2 (11.8)**	**5 (29.4)**	**7 (41.2)**
Gastroenteritis		1 (5.9)	1 (5.9)
Nasopharyngitis		2 (11.8)	2 (11.8)
Respiratory tract infection		1 (5.9)	1 (5.9)
Respiratory tract infection viral	1 (5.9)		1 (5.9)
Rhinitis	1 (5.9)		1 (5.9)
Tinea infection		1 (5.9)	1 (5.9)
Tracheitis		1 (5.9)	1 (5.9)
Upper respiratory tract infection		2 (11.8)	2 (11.8)
Injury, poisoning and procedural complications	**1 (5.9)**	**1 (5.9)**	**2 (11.8)**
Accidental overdose		1 (5.9)	1 (5.9)
Foot fracture	1 (5.9)		1 (5.9)
Investigations		**9 (52.9)**	**9 (52.9)**
Blood prolactin increased		1 (5.9)	1 (5.9)
Blood testosterone decreased		2 (11.8)	2 (11.8)
Blood testosterone free increased		2 (11.8)	2 (11.8)
Blood testosterone increased		4 (23.5)	4 (23.5)
Human chorionic gonadotropin increased		1 (5.9)	1 (5.9)
Oestradiol increased		5 (29.4)	5 (29.4)
Testicular scan abnormal		1 (5.9)	1 (5.9)
Ultrasound testes abnormal		1 (5.9)	1 (5.9)
Metabolism and nutrition disorders	**1 (5.9)**	**1 (5.9)**	**2 (11.8)**
Hyperphagia	1 (5.9)		1 (5.9)
Metabolic syndrome		1 (5.9)	1 (5.9)
Musculoskeletal and connective tissue disorders	**1 (5.9)**	**1 (5.9)**	**2 (11.8)**
Back pain		1 (5.9)	1 (5.9)
Myalgia	1 (5.9)		1 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**1 (5.9)**	**1 (5.9)**

		1 (5.9)	1 (5.9)
Nervous system disorders	**3 (17.6)**	**3 (17.6)**	**6 (35.3)**
Cerebrovascular disorder		1 (5.9)	1 (5.9)
Headache	3 (17.6)	1 (5.9)	4 (23.5)
Migraine		1 (5.9)	1 (5.9)
Presyncope	1 (5.9)		1 (5.9)
Renal and urinary disorders		**1 (5.9)**	**1 (5.9)**
Dysuria		1 (5.9)	1 (5.9)
Reproductive system and breast disorders		**7 (41.2)**	**7 (41.2)**
Pruritus genital		1 (5.9)	1 (5.9)
Scrotal disorder		1 (5.9)	1 (5.9)
Spermatocele		5 (29.4)	5 (29.4)
Varicocele		1 (5.9)	1 (5.9)
Respiratory, thoracic and mediastinal disorders	**3 (17.6)**	**1 (5.9)**	**4 (23.5)**
Nasal congestion		1 (5.9)	1 (5.9)
Rhinitis allergic	1 (5.9)		1 (5.9)
Rhinorrhoea	2 (11.8)		2 (11.8)
Skin and subcutaneous tissue disorders	**1 (5.9)**	**3 (17.6)**	**4 (23.5)**
Acanthosis nigricans		1 (5.9)	1 (5.9)
Acne		1 (5.9)	1 (5.9)
Dermatitis contact	1 (5.9)		1 (5.9)
Pruritus		1 (5.9)	1 (5.9)
Vascular disorders	**1 (5.9)**		**1 (5.9)**
Hot flush	1 (5.9)		1 (5.9)

Drug-related adverse events

In the overall treatment period, drug-related AEs (as determined by the investigator) were reported for 9 participants. Seven participants had AEs related to hCG that included increased blood T and increased E2; 2 participants had AEs related to CFA that included vomiting, injection site pain, and hot flush; and 1 participant had an AE related to both CFA and hCG (acne).

	Relationship to CFA, hCG or both	Corifollitropin Alfa + Corifollitropin Alfa/hCG n (%)
n (%)		
Subjects in population		17
With one or more drug-related adverse events	Overall	9 (52.9)
	CFA	2 (11.8)
	CFA + hCG	1 (5.9)
	hCG	7 (41.2)
Gastrointestinal disorders	**Overall**	**1 (5.9)**
Vomiting	CFA	1 (5.9)
General disorders and administration site conditions	**Overall**	**2 (11.8)**
Injection site pain	CFA	1 (5.9)
Peripheral swelling	hCG	1 (5.9)
Investigations	**Overall**	**6 (35.3)**
Blood testosterone free increased	hCG	2 (11.8)
Blood testosterone increased	hCG	4 (23.5)
Oestradiol increased	hCG	5 (29.4)
Skin and subcutaneous tissue disorders	**Overall**	**1 (5.9)**
Acne	CFA+hCG	1 (5.9)
Vascular disorders	**Overall**	**1 (5.9)**
Hot flush	CFA	1 (5.9)

Intensity

- All AEs were mild to moderate in intensity. AEs reported with moderate intensity included acne, allergic rhinitis, back pain, foot fracture, hyperphagia, migraine, nasopharyngitis, scrotal disorder, tinea infection, and vomiting.

- Both acne and vomiting were considered possibly related to study medication.
- There were no AEs with severe intensity reported.

Serious adverse events

There were no deaths reported in this study.

There was one SAE in the study. One participant had an SAE of a recurrent disease. This participant had a medical history of this condition. This SAE led to discontinuation of study medication and was considered by the investigator not related to study medication. The SAE was treated, and the participant completed the study off study medication.

Discontinuations Due to Adverse Events

One participant discontinued study medication due to an SAE (see above).

Adverse Events of Special Interest

Prespecified AEs of special interest included anti-MK-8962 antibodies (ie, anti-drug antibodies; ADA), and hypersensitivity reactions.

- *Anti-MK-8962 Antibodies*

  There were no cases of confirmed anti-MK-8962 antibodies.

- *Hypersensitivity Reactions*

  There were 3 participants with hypersensitivity AEs: gingival oedema and rhinitis allergic (n=1), Dermatitis contact (n=1) and Pruritus (n=1).

All AEs were mild in intensity, except for allergic rhinitis (moderate), considered not related to study medication by the investigator, and resolved while the participant was still on study medication.

Events of Clinical Interest

- *Overdose*

  One participant overdosed with hCG. The investigator provided instructions to up titrate the participant's hCG from 1500 IU to 2000 IU, and parent mistakenly gave the participant a dose of 5000 IU hCG (the entire contents of the 5000 IU vial) instead of 2000 IU for 6 doses (2 weeks). The participant had an AE of increased estradiol during this period.

- *Hepatic Safety*

  No participants met the biochemical criteria for drug-induced livery injury.

- *Cerebrovascular disorder*

  One participant underwent a routine endocrine evaluation and was discovered to have elevated prolactin levels and a minimal disorder of cerebral blood flow. The AE was ongoing and stable at the final visit. The investigator assessed the AE as not related to study medication and it was mapped to the PT of cerebrovascular disorder.

- *Participant Narratives*

  A narrative was written for 2 participants: 1 participant who discontinued study medication due to a SAE, and 1 participant who was accidently overdosed with hCG (administered by legal guardian).

Assessor's comments

Sixteen of the 17 participants experienced at least one AE. Overall, the most common AEs (>20%) were spermatocele (n=5), increased E2 (n=5), increased blood T (n=4), and headache (n=4). One participant had an AE of increased E2 related to an accidental hCG overdose. In the priming period, the most frequently reported AEs (>10%) were headache (n=3) and rhinorrhoea (n=2).

Nine participants had drug-related AEs. Seven participants had AEs related to hCG that included increased blood T and increased E2; 2 participants had AEs related to CFA that included vomiting, injection site pain, and hot flush; and 1 participant had an AE related to both CFA and hCG (acne).

It was stated that laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. However, changes over time for endocrine laboratory values (T, E2, and SHBG) were expected to change while participants underwent puberty. Beside the case of hCG overdose, it is not clear why the investigators reported some of these changes as adverse events. The applicant is asked to clarify (see section 4 "Additional clarification requested").

All AEs were mild to moderate in intensity.

One participant had an SAE of a recurrent disease. He discontinued study medication but remained in the study.

There were no deaths reported in this study.

Safety results showed that the treatment was safe and well-tolerated.

<u>Clinical laboratory</u>

The changes over time for blood chemistry (ALP and creatinine), haematology and prespecified endocrine laboratory values (T, E2, and SHBG) were expected to change while participants underwent puberty.

Safety ranges for each parameter were used to identify markedly abnormal chemistry or haematology values during the study:

- 5 participants had 1 value >1.5 x ULN for ALP
- The last serum creatinine values for 3 participants met the PDLC criterion of increase in creatinine of ≥0.3 mg/dL from baseline; however, all 3 values were below the ULN (1.2 mg/dL).
- No participants met the PDLC criteria for ALT, AST, bilirubin, or drug-induced liver injury.
- One participant met the PDLC criterion of last haemoglobin value (12.2 g/dL) (baseline 13.7 g/dL; NR: 12.7 g/dL–18.1 g/dL) at Week 36. Haematocrit had decreased by 5% from baseline (to 38%) and was slightly below the LLN (39.5%). The MCV was unchanged and was within the NR at all measurements. A subsequent CBC sample obtained at Week 64 was clotted and no repeat samples were obtained.

- Elevated prolactin levels (NR: 130-600 mIU/L) were noted for 1 participant during a routine clinical evaluation scheduled in accordance with local clinical practice guidelines for the management of patients with hypopituitarism. On Day 295, an AE of 'blood prolactin increased' was first noted (2445 mIU/L). A pituitary MRI revealed no changes from previous scans. This participant had an associated AE of cerebrovascular disorder. Repeat prolactin levels were stable (Day 301; 2301 mIU/L, Day 307; 2506 mIU/L, Day 352; 2092 mIU/L). The AE of elevated prolactin was considered not related to study medication.

Assessor's comments

Clinical laboratory data did not show unexpected values or changes due to study medication.

Overall conclusion on safety (applicant)

- Antibodies to CFA were not detected.
- Nine participants reported AEs that were considered by the investigator to be drug-related. Most of these were considered related to hCG.
- The most frequently reported AEs were spermatocele, increased E2, increased blood T, and headache.
- One participant had a SAE that was considered not related to study medication by the investigator.
- The incidence of hypersensitivity AEs was low and resolved while on study medication.

Overall conclusion on safety Rapporteur

The results showed that the treatment was safe, and no unexpected drug-related adverse events occurred, although one issue needs clarification:

It was stated that laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. However, changes over time for endocrine laboratory values (T, E2, and SHBG) were expected to change in participants who were treated to induce development of puberty. Beside the case of hCG overdose, it is not clear why the investigators reported some of these changes as adverse events. The applicant is asked to clarify (see section 4 "Additional clarification requested").

2.3.3. Discussion on clinical aspects

Elonva, corifollitropin alfa [CFA] is a recombinant gonadotropin, which has the same mechanism of action as FSH, but different PK properties. A single injection of corifollitropin alfa replaces 7 days of daily recFSH. It can be agreed that is an advantage to the patient as the use of corifollitropin alfa may result in fewer medication errors and improved compliance in the long-term HH treatment.

In the clinical development plan, based on the results from Study 022 (Phase 1, open-label, repeated single dose, multicenter PK study in adult males with HH), the CFA dose in Study 031 was determined. In Study 031, an open-label, non-comparative, multi-centre safety and efficacy study of corifollitropin in association with hCG in male adults with hypogonadotrophic hypogonadism, CFA was evaluated in 18 adult males with HH. CFA use more than doubled the mean testicular volume and induced spermatogenesis in 77% of adult males who remained azoospermic after treatment with hCG. Study

P031 has been published (Nieschlag et al. Reproductive Biology and Endocrinology (2017)) but has not been submitted as yet to the Rapporteur.

Currently, Elonva (corifollitropin alfa) is not approved for use in men. However, recFSH preparations (follitropin) are approved for use in adult men: *<RecFSH> is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy*.

The rationale for the pre-treatment with CFA instead of hCG in HH adolescents was to mimic the gonadotropin pattern of normal puberty, i.e. to stimulate FSH receptors on Sertoli cells with CFA prior to the stimulation of LH receptors on Leydig cells with hCG to induce testicular growth, masculinization, and adequate spermatogenesis. In the current study, 17 adolescent boys (14 to 17 years old) with HH were treated 12 weeks with CFA alone and then combined with hCG 52 weeks).

Seventeen subjects were recruited from the following countries: Mexico (n=1), Brazil (n=4), Russia (n=11) and Italy (n=1). All subjects (100.0%) were treated, 16 (94.1%), completed the study on study medication, and 1 (5.9%) completed the study off study medication. A total of 13 of 17 participants met the criteria for the efficacy population.

The subjects were all pre-pubertal, with a mean testicular volume of 2.2 mL, measured by ultrasound. Currently, the mean testicular volume before the onset of puberty in boys with normally-timed puberty has been determined to be 0.6 mL (i.e., testicular volume of ~1.2 mL), which is smaller. The applicant explained that testes grow throughout childhood, and as treatment in adolescent males with HH is typically delayed beyond onset of normally-timed puberty, the baseline testicular volume in these males with HH prior to therapy is likely to be larger than 1.2 mL reflecting continued prepubertal growth prior to the start of treatment. This explanation can be accepted.

Efficacy

The primary endpoint for efficacy was shown by increase in testicular volume, measured as the sum of volumes of left and right testes by ultrasound. In the priming period, the mean testicular volume changed from a geometric mean of 1.4 mL to 2.5 mL (mean fold increase of **1.83** (95% CI of 1.58, 2.13)). During the overall treatment period, the increase noted in testicular volume at Week 64 changed from a geometric mean of 1.4 mL to 12.9 mL, mean fold increase of **9.43** (95% CI of 7.44, 11.97). The applicant noted that the mean testicular volume achieved at the end of Week 64 (geometric mean 12.9 mL) was less than the testicular volume observed at the end of normally-timed puberty but that this is as expected considering the exposure to gonadotropins for 64 weeks, while normal puberty lasts for 2 to 3 years. This explanation can be accepted (according to Rohany et al (2017) testicular volume observed at the end of normally-timed puberty is ≥24 mL).

The results from the secondary objectives were supportive of the primary endpoint. All subjects went to higher Tanner stages (III, IV and V) during the course of the study. Growth velocity from baseline to Week 64 was 7.4 cm/year. Testosterone levels increased from Week 12 in response to hCG: mean total T level at Week 64 was 5.42 µg/L. Variations in testosterone levels were within the normal range (1 – 12 µg/L) observed in adolescent boys. Changes in E2 (increase) and SHBG levels (decrease) were consistent with increased testosterone production. Serum inhibin B levels, a surrogate marker of spermatogenesis, increased on CFA alone. The decreased Antimullerian Hormone (AMH) levels increased on CFA alone and decreased after hCG was added, suggesting a transition from AMH to inhibin B production in the testicles, in line with normal puberty

Safety

Safety was also a primary endpoint. The treatment was well tolerated. There were no severe AEs and no SAEs, except one SAE of recurrence of pre-existing condition leading to discontinuation. Sixteen of

the 17 participants experienced at least one AE. Overall, the most common AEs (>20%) were spermatocele (n=5), increased E2 (n=5), increased blood T (n=4), and headache (n=4). Laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. One participant had an AE of increased E2 related to an accidental hCG overdose. In the priming period, the most frequently reported AEs (>10%) were headache (n=3) and rhinorrhea (n=2).

Nine participants had drug-related AEs. Seven participants had AEs related to hCG that included increased blood T and increased E2; 2 participants had AEs related to CFA that included vomiting, injection site pain, and hot flush; and 1 participant had an AE related to both CFA and hCG (acne).

All AEs were mild to moderate in intensity.

One participant had an SAE of a recurrent disease. He discontinued study medication but remained in the study.

There were no deaths reported in this study.

The results showed that the treatment was safe, and no unexpected drug-related adverse events occurred, although one issue needs clarification: It was stated that laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. However, changes over time for endocrine laboratory values (T, E2, and SHBG) were expected to change while participants underwent puberty. Beside the case of hCG overdose, it is not clear why the investigators reported some of these changes as adverse events. The applicant is asked to clarify (see section 4 "Additional clarification requested").

Antibodies to CFA were not detected.

Pharmacokinetics

After repeated dosing of CFA alone and co-administered with hCG, predose (trough) CFA serum concentrations are generally similar.

3. Rapporteur's overall conclusion and recommendation

Study P043 was a one-armed open-label study conducted to assess safety and efficacy of Elonva (corifollitropin) in association with hCG in 17 male adolescents (14 to 18 years of age) with hypogonadotrophic hypogonadism.

Regarding efficacy, the applied regimen of 12 weeks of pre-treatment with Elonva and subsequently 52 weeks of Elonva/hCG combined showed to induce puberty (measured by increase in testicular volume) in all 13 patients included in the efficacy population. The results from the secondary objectives were supportive of an induction of pubertal development and induction of spermatogenesis.

As to safety, the results showed that the treatment was safe and no unexpected drug-related adverse events occurred in the 17 included participants, although one issue with regard to changes over time for endocrine laboratory values needs clarification (see section 4 "Additional clarification requested").

The results from PIP study P043 do not impact the benefit-risk profile of Elonva.

The Rapporteur welcomes the subsequent submission of the type II variation to update the Product Information with the results of the Art 46 study as proposed by the company.

However, as part of this Art 46 procedure the MAH should provide the requested additional clarification, see section 4 "Additional clarification requested".

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide the additional clarification as part of this procedure. (see section 4 "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following question as part of this procedure:

1. It was stated that laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. However, changes over time for endocrine laboratory values (T, E2, and SHBG) were expected to change in participants who are treated to induce development of puberty. Beside the case of hCG overdose, it is not clear why the investigators reported some of these changes as adverse events. The applicant is asked to clarify.

The timetable is a 30-day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1

It was stated that laboratory AEs for increased T and E2 levels were reported at the investigator's discretion. However, changes over time for endocrine laboratory values (T, E2, and SHBG) were expected to change in participants who are treated to induce development of puberty. Beside the case of hCG overdose, it is not clear why the investigators reported some of these changes as adverse events. The applicant is asked to clarify.

Applicant's response

Based on the information provided in the protocol and presentations at Investigators' meetings, Investigators were aware that treatment with corifollitropin alfa and human chorionic gonadotropin (hCG) will induce normal pubertal changes including increases in testosterone and estradiol levels, and reductions in sex hormone-binding globulin (SHBG) levels, in adolescent males with hypogonadotropic hypogonadism.

Investigators were allowed to titrate the dose of hCG based on testosterone and estradiol levels. The protocol defined acceptable levels of total testosterone and estradiol in response to treatment with hCG based on the assays from the central laboratory used (Section 5.2.1.2: ≤950 ng/dL for total testosterone, and <56 pg/mL for estradiol). Investigators used their discretion to report total testosterone and/or estradiol measurements that were above these cut-offs as AEs. Investigators reported AEs of increased testosterone and/or estradiol if the values were above the cut-offs; with the exception of one participant, each of these reports was followed by a reduction in the dose of hCG in response. There were no AEs reported for changes in SHBG.

One participant had total testosterone and estradiol levels that were above the cut-offs defined above, and his dose of hCG was decreased; however, no AEs of increased testosterone or estradiol were reported for this participant.

Assessment of the applicant's response

The applicant explained that in the protocol total testosterone and estradiol levels in response to treatment were given and that investigators were free to report reported changes beyond these cut-off levels as adverse events if they considered this of interest. This explanation is acceptable.

Conclusion

Issue solved.

6. Updated Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

Study P043 was a one-armed open-label study conducted to assess safety and efficacy of Elonva (corifollitropin) in association with hCG in 17 male adolescents (14 to 18 years of age) with hypogonadotrophic hypogonadism.

Regarding efficacy, the applied regimen of 12 weeks of pre-treatment with Elonva and subsequently 52 weeks of Elonva/hCG combined showed to induce puberty (measured by increase in testicular volume) in the efficacy population. The results from the secondary objectives were supportive of an induction of pubertal development and induction of spermatogenesis.

As to safety, the results showed that the treatment was safe, and no unexpected drug-related adverse events occurred in the 17 included participants.

The results from PIP study P043 do not impact the benefit-risk profile of Elonva.

The Rapporteur welcomes the subsequent submission of the type II variation to update the Product Information with the results of the Art 46 study as proposed by the company.