22 April 2022
EMA/329358/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elonva

International non-proprietary name: corifollitropin alfa

Procedure No. EMEA/H/C/001106/II/0061

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMH	anti-müllerian hormone
ART	assisted reproductive technology
ASaT	all subjects as treated
AUCss	area under the concentration or response time curve (at steady state)
BMI	body mass index
CFA	corifollitropin alfa (MK-8962)
CHH	congenital hypogonadotropic hypogonadism
CI	confidence interval
Cmax	maximum concentration
Cmin	minimum (trough) concentration
COS	controlled ovarian stimulation
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CSR	clinical study report
CTP	carboxy-terminal peptide
CV	coefficient variation
ECI	event of clinical interest
E2	estradiol
FAS	Full Analysis Set
FSH	follicle stimulating hormone
FSH-IR	follicle stimulating hormone-immunoreactivity
GCP	Good Clinical Practice
GnRH	gonadotropin releasing hormone
hCG	human chorionic gonadotropin, choriogonadotropin beta
HH	hypogonadotropic hypogonadism
HPG	hypothalamic pituitary gonadotrope
IHH	idiopathic hypogonadotropic hypogonadism
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

	Human Use
IRB	Institutional Review Board
IR	immunoreactivity
IRC	Independent Review Charter for review of ultrasound images of the testes
IU	international unit
KS	Kallmann syndrome
LH	luteinizing hormone
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
OHSS	ovarian hyperstimulation syndrome
PD	pharmacodynamic(s)
PDCO	Paediatric Committee (the European Medicines Agency's scientific committee responsible for providing scientific expertise and defining paediatric needs)
PDLC	predefined limits of changes
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
QoL	quality of life
recFSH	recombinant human follicle stimulating hormone (FSH)
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SHBG	sex hormone-binding globulin
sSAP	supplemental statistical analysis plan
T	testosterone
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Organon N.V. submitted to the European Medicines Agency on 16 July 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG) for Elonva, based on final results of the paediatric study P043. Study P043 was an open-label, non-comparative, multi-center safety and efficacy study of corifollitropin alfa in association with hCG in male adolescents with hypogonadotropic hypogonadism, part of the paediatric investigation plan; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement some minor editorial and formatting changes throughout the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMEA-000306PIP01-08-M04 (decision P/0143/2019) on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0143/2019 was completed. The PDCO issued an opinion on compliance for the PIP P/0143/2019.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	16 July 2021
Start of procedure:	14 August 2021
CHMP Rapporteur Assessment Report	8 October 2021
PRAC Rapporteur Assessment Report	8 October 2021
CHMP Co-Rapporteur Critique	20 October 2021
PRAC members comments	20 October 2021
PRAC endorsed relevant sections of the assessment report	28 October 2021
CHMP members comments	29 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	5 November 2021
Request for supplementary information (RSI)	11 November 2021
CHMP Rapporteur Assessment Report	24 March 2022
PRAC Rapporteur Assessment Report	24 March 2022
PRAC members comments	30 March 2022
PRAC endorsed relevant sections of the assessment report	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur (Joint) Assessment Report	14 April 2022
CHMP Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hypogonadotropic hypogonadism (HH) is lack of, or inadequate, production of gonadotropins, i.e. 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. This results in insufficient testicular function and deficiencies in endogenous testosterone production and spermatogenesis. When gonadotropin deficiency occurs before puberty (prepubertal), puberty is delayed or absent.

Claimed therapeutic indication

Current indication

Elonva 100 mcg and 150 mcg has been approved in females, for controlled ovarian stimulation (COS). In the treatment of women of reproductive age, the dose of Elonva (100 and 150 mcg) is based on weight and age.

Claimed indication

Based on the final results of the paediatric study P043, the Applicant initially requested for the following extension of the indication:

"Elonva is indicated for the treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG)."

The following posology is proposed:

"*Paediatric population*

In the treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism, the dose of Elonva is based on body weight.

For males weighing less than or equal to 60 kg: 100 micrograms of Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG in males weighing less than or equal to 60 kg. For patients initiating therapy with 100 micrograms, consider increasing the dose if their body weight increases to greater than 60 kg during the course of treatment.

For males weighing more than 60 kg: 150 micrograms of Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG, in males weighing greater than 60 kg."

Epidemiology

HH is a very rare condition. It is estimated that the incidence of CHH is 1-10:100,000 live births and approximately 2/3 and 1/3 of cases are caused by Kallmann syndrome (KS) and idiopathic HH, respectively (Fraietta R et al; Hypogonadotropic hypogonadism revisited. Clinics (Sao Paulo). 2013;68 Suppl 1:81-8).

Biologic features

Male HH is characterized by impaired secretion of the pituitary gonadotropins, FSH, and LH,

HH can be the result of failed secretion of the pituitary gonadotropins, FSH and LH, by the pituitary or absent or inadequate GnRH secretion by the hypothalamus, resulting in insufficient testicular function and deficiencies in testosterone and spermatogenesis.

Typically, FSH and LH secretion begins shortly before birth and a neonatal surge in these hormones in response to a robust secretion of GnRH from the hypothalamus is indicative of an intact and functional hypothalamic pituitary gonadotrope (HPG) axis. Following this neonatal surge in the secretion of GnRH and subsequently of FSH and LH, GnRH secretion from the hypothalamus decreases to very low levels throughout childhood. An initial event during puberty is the increase in the frequency and amplitude of pulsatile GnRH secretion, followed by the pulsatile secretion of FSH (initially) and LH from pituitary gonadotropes, and hence the stimulation of the testes and ultimate development of sexual maturity.

The clinical manifestations of HH depend on the stage of development at which the deficiency occurs (pre- or post-pubertal). When the deficiency occurs before puberty (prepubertal), the pubertal transition is delayed or absent. The condition can be congenital or acquired and can occur in isolation, idiopathic hypogonadotropic hypogonadism (IHH), in association with anosmia/hyposmia, KS, or as part of a multiple pituitary hormone deficiency syndrome.

Clinical presentation, diagnosis

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 investigated. 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).

Management

Treatment of adolescent males with HH

Currently, no FSH treatment is approved for adolescent males with HH.

FSH treatment of adult patients with HH:

- RecFSH has shown to be an effective and safe drug for several indications including adult male HH. RecFSH (Puregon) is approved for the treatment of deficient spermatogenesis in adult males who are infertile due to hormonal insufficiency and is administered concomitantly with hCG for 3 to 4 months before any improvement in spermatogenesis is expected. To assess response, semen analysis is recommended 4 to 6 months after the start of treatment. If a patient has not responded after this period, combination therapy may be continued for 18 months or longer to achieve spermatogenesis. Puregon is to be given at a dose of 450 IU/week preferably divided into 3 doses of 150 IU concomitantly with hCG. Although not indicated for use in adolescent males, recFSH has been used to induce puberty in adolescent males with HH, while hCG is approved for induction of puberty in adolescent males with HH.
- RecFSH Gonal-F is approved for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy. It is noted that for the lack of LH, hCG is given instead of LH. LH and hCG share the same alfa subunit and bind on the Leydig cell receptors, but hCG has half-life of 36 hours, while half live of LH is only 30 minutes. Gonal-F should be given at a dose of 150 IU three times a week, concomitantly with hCG, for a minimum of 4 months. If after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis.

The primary goal in the treatment of adolescent 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.

2.1.2. About 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 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 injections. Elonva 100 and 150 mcg is approved through centralised procedure (EU/1/09/609/001-002) in January 2010 for Controlled Ovarian Stimulation (COS) in combination with a Gonadotropin Releasing Hormone (GnRH) antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program.

Regarding the currently requested indication in adolescents with HH, the Applicant claimed that since treatment of HH in males usually requires long-term FSH 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. However, it is noted that currently the recFSH is not approved for treatment of adolescent males with HH, but only in adult patients with HH.

CFA has been approved in females for controlled ovarian stimulation (COS) in 69 countries since 2010.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

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) for corifollitropin alfa (CFA) in the European Union (EU); EMEA-000306PIP01-08-M04 (decision P/0143/2019).

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

One of the modified studies was Study P031, an "*open-label, non-comparative, multi-centre safety and efficacy study of corifollitropin alfa (CFA) in association with hCG in male adults with hypogonadotropic 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 P022, a "*Phase 1, open-label, repeated single dose, multicenter PK study in adult males with HH*" and was in general adequately substantiated.

2.1.4. General comments on compliance with GCP

The Applicant stated that the submitted studies were in compliance with GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC (Table 1).

Table 1 Tabular overview of clinical studies

Country List – Non-EU Members	Study/Protocols
Australia	P031
Brazil	P043
Mexico	P043
Russia	P043
South Africa	P043

2.3.2. Pharmacokinetics

This extension of indication to adolescent males with HH is based on the following clinical studies:

Study P022 (also known as study 38801) was an open label repeated single dose study in healthy adult men (incorrectly indicated as HH males in Table 2 below). Four single dose SC injections of 15 µg were given with 4 weeks interval.

Study P022 was already submitted in support of the currently registered indication in women and is not included in the current submission.

Study P031, a Phase 3 study, assessed PK, PD, efficacy, and safety of corifollitropin alfa (CFA, Elonva®, MK-8962) in combination with hCG in azoospermic adult men with HH. The dose to be used in study P043 was based on studies P022 and P031. CFA was administered at 150 µg once every 2 weeks.

Study P043 was a Phase 3, single-group, open-label efficacy and safety study in adolescent males (14 to less than 18 years of age) with HH. In this study, CFA was administered alone (once every 2 weeks) for the first 12 weeks and in combination with hCG (twice weekly) for the following 52 weeks. The dose of CFA is based on weight, and a single dose of 100 µg (body weight ≤60 kg) or 150 µg (body weight >60 kg) was administered subcutaneously in the abdominal wall once every 2 weeks in the morning on the same day of the week. This dosing regimen was selected based on population PK modeling of the results of studies P022 and P031.

The extension of the indication to adolescent males was supported by 2 Pop PK studies. At first, a Pop PK analysis was performed in adult males with hypogonadotropic hypogonadism (HH), based on a Phase 1 study in healthy adult men (study P022, also indicated as study 38801) and a Phase 3 study in azoospermic adult men with HH (study P031). Subsequently, the model in adult males was extended with data from a Phase 3 study in adolescent males with HH (study P043). An overview of the studies included in the Pop PK analyses is shown in Table 2.

Table 2 Overview of studies included in population PK analysis

Study	Trial Objective	Trial Design	Treatment and Number of Subjects	Pharmacokinetic Assessments
38801	To assess the safety of MK-8962, to study single dose pharmacokinetics of MK-8962 and to obtain preliminary data on pharmacodynamics of MK-8962	Phase 1, open label, repeated single dose study in HH males	MK-8962 15 µg 4 single SC injections with 4 weeks interval N = 13	PK sampling after 1st and 3rd MK-8962 dose: pre-dose and 1, 2, 4, 6, 8, 10, 16, 24, 30, 36, 48, 72, 96, 144, 192, 240, 288 and 336 h post-dose
7937 (P031)	To assess the efficacy of 150 µg MK-8962 in combination with a twice weekly dose of hCG to increase testicular volume To assess the safety of this treatment	Open-label uncontrol-led trial in azoospermic men aged 18-50 years with HH	MK-8962 150 µg SC injection every other week + hCG 1500 – 3000 IU twice weekly following a 16 weeks pre-treatment phase with hCG only N = 18	PK sampling after the first MK-8962 dose: pre-dose and 6-24, 32-52, 96, 168 and 240 h post-dose Additional PK samples pre-dose before 3rd, 9th, 15th and 21st injection and at endpoint and follow up FSH samples: Pre-dose every 4 weeks
8962043 (P043)	To estimate the change from baseline in testicular volume after 64 weeks of treatment with MK-8962 (in combination with hCG for the last 52 weeks) and To evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962	a multi-center, open-label, single-group trial in adolescent males 14 to < 18 years old with HH.	MK-8962 SC injection every other week from (100 µg and 150 µg for body weight ≤ 60 kg and > 60 kg, respectively), day 1 through week 64 hCG 500 – 5000 IU twice weekly last day of week 12 through week 64. N = 17	PK sampling after the first MK-8962 dose: pre-dose, 6-24 h, 32-52 h, 72-120 h, 144-192 h, and 216-264 h post dose. Additional PK samples pre-dose samples before 7th, 13th, in week 12, 24, 36, 48, and 64, and a follow up sample > 7 days after discontinuation.

Abbreviations: FSH = Follicle stimulating hormone; hCG = human chorionic gonadotropin; HH = hypogonadotropic hypogonadism; IU = International units; N = number; SC = Subcutaneous; PK = Pharmacokinetic.

2.3.2.1 Paediatric PK/PD study P043

In study P043, a total of 17 male adolescents were allocated to CFA (priming period) for 12 weeks followed by combined treatment with CFA and hCG for 52 weeks. A total of 16 subjects completed the combined treatment period; 1 subject discontinued because of adverse effects. Subjects weighing ≤60 kg received a dose of 100 µg and subjects weighing > 60 kg received a dose of 150 µg. Body weight was ≤60 kg for 11 subjects and >60 kg for 6 subjects (overall range 34.3-91.6 kg, mean ± SD 57.7 ± 16.6 kg). PK sampling in study P043 was performed pre-dose and at 6-24 h, 32-52 h, 72-120 h, 144-192 h, and 216-264 h after the first dose and pre-dose before 7th and 13th day and in week 12, 24, 36, 48 and 64 and at > 7 days after discontinuation. 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'. The results from PK measurements in study P043 are shown in Table 3 below.

Table 3 Descriptive Summary Statistic Values of Corifollitropin Alfa Serum Concentrations in Adolescent Males 14 to <18 Years Old with HH (study P043)

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 between the groups receiving 100 µg and 150 µg.

No PK parameters such as AUC, Cmax and Cmin were calculated in study P043 using non-compartmental methods.

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, mean and median concentrations at visit 8 and 9 (CFA alone), respectively, 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 based on non-summarized, individual data.

2.3.2.2 POP PK modeling in adult men

The objectives of the analyses were to:

- Develop Population PK model for Elonva (MK-8962) in male patients in order to:
    - Obtain individual exposure estimates for patients in study P031 to support exploratory PKPD evaluations
    - Enable simulations of PK in adolescent male patients for different Elonva regimens
- Explore PK-PD relationships for endpoints of interest, specifically testicular volume and sperm count
- Assess what doses of MK-8962 would produce drug exposure above FSH-IR level of 4 IU/L

The population PK analysis in adult males included available CFA concentration-time data from studies P022 and P031. Additionally, FSH immunoreactivity (FSH-IR) data were included from study P031. In study P022, PK sampling was performed after the 1st and 3rd dose: pre-dose and 1,2,4,6,8,10,16,24,30,36,48,72, 96,144,192,240,288 and 336 h post-dose. In study P031, PK sampling was performed pre-dose and at 6-24, 32-52, 96, 168 and 240 h after the first dose, and pre-dose before the 3rd, 9th, 15th and 21st injection and at endpoint and follow up. FSH-IR samples were collected pre-dose every 4 weeks. The PK/PD dataset included available testicular volume, sperm count, testosterone and estradiol observations from study P031 to support exploration of potential associations.

For the modeling and simulation pertinent to this application, data on CFA PK in males were considered and based upon historical experience with Puregon (recombinant FSH which is approved for use in adult males), serum trough FSH immunoreactivity (FSH-IR) ≥ 4 IU/L was selected as the criteria to obtain the target exposure in adolescent male HH patients. Notably, cross reactivity of the FSH assay to CFA is known to occur owing to the structural similarity of CFA and FSH. Consequently, the historical population PK models have jointly described FSH and CFA kinetics and output pharmacokinetic targets expressed as FSH-IR. To this end, any target FSH-IR reflected endogenous FSH and CFA concentrations and not endogenous FSH alone.

CFA and FSH-IR were analysed using a non-linear mixed effects model. The starting point was the existing Pop PK model in females. In this model, pharmacokinetics were described using a one-compartment model with first order absorption from the subcutaneous depot and first order elimination. The model in females included also endogenous FSH. Endogenous FSH was however removed from the model because no measurable FSH is present prior to treatment in the HH male population. All original covariates were removed from the model, as they may not apply in a male population. FSH concentration data were integrated into the previous analysis by estimating a scaling factor between FSH and CFA concentrations. A scaling factor was estimated to scale between MK-8962 and FSH-IR concentration measurements. Based on the experience in women, body weight was planned to be tested as a covariate on CL and V a priori. Graphical exploration was then used to assess any remaining relationships between CFA PK parameters and the covariates age and BMI. A formulation component was also included to account for the use of different formulations between the two studies (non-protein free in study P022 and protein-free in study P031).

To quantify the impact of body weight on CFA and FSH-IR exposure, two types of simulations were performed:

- Deterministic simulation, in which AUC_{ss} values were calculated for MK-8962 and FSH-IR, based on the final model estimates for CL and any potential effect of body weight, given a range of Elonva doses for a range of body weights.
- Stochastic simulation, in which individual estimates of AUC_{ss} and C_{min} for MK- 8962 and FSH-IR were predicted at CFA doses of 100 µg and 150 µg once every two weeks for 1000 adolescent male patients aged from 14 to 18.

The simulations from the population PK model were subsequently used to explore the resulting exposure values obtained with different CFA doses in male patients of different body weight. Key assumptions that are implied in these simulations are:

1. Apart from the body weight effect on clearance (CL) and volume of distribution (V), the PK and PD are the same in adolescent and adult HH male patients;
2. CFA has similar PD compared to Puregon (recFSH) in HH male population;
3. Serum FSH-IR levels after treatment with CFA should be at least as high as after treatment with 2x225 IU or 3x150 IU Puregon per week. As treatment with 2x 225 IU or 3x150 IU Puregon per week resulted in a pre-dose value ≥ 4 IU/L (nadir), a trough FSH immunoreactivity levels ≥ 4 IU/L was selected as a criteria to select the dose and interval for adolescent males.

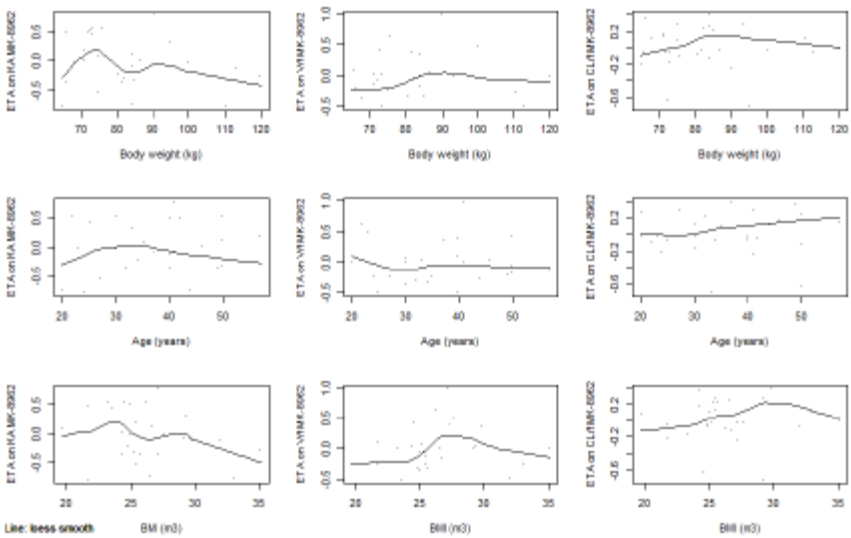
Data programming was conducted in SAS v 9.3. Population PK analysis was conducted in NONMEM v 7.2. Post processing of Pop PK analysis results as well as the complete PK-PD evaluation were conducted in R-Studio using R version 2.15.2.

Results

A total of 31 patients were included in the dataset for Pop PK analysis, 13 subjects from study P022 and 18 subjects from study P031. Three patients from study P022 were excluded because measurable CFA concentrations were present prior to treatment and these patients had elevated concentrations throughout the study. Furthermore, concentrations below the LLOQ were set to zero. The resulting dataset consisted of a total of 431 CFA concentrations and 229 FSH IR concentrations.

The final model was a one-compartment model with first order absorption. Body weight was added as a covariate on CL and V. Other covariates age and BMI were evaluated based on ETA estimates (see Figure 1).

Figure 1 Individual ETA estimates versus body weight, age and BMI in adult males

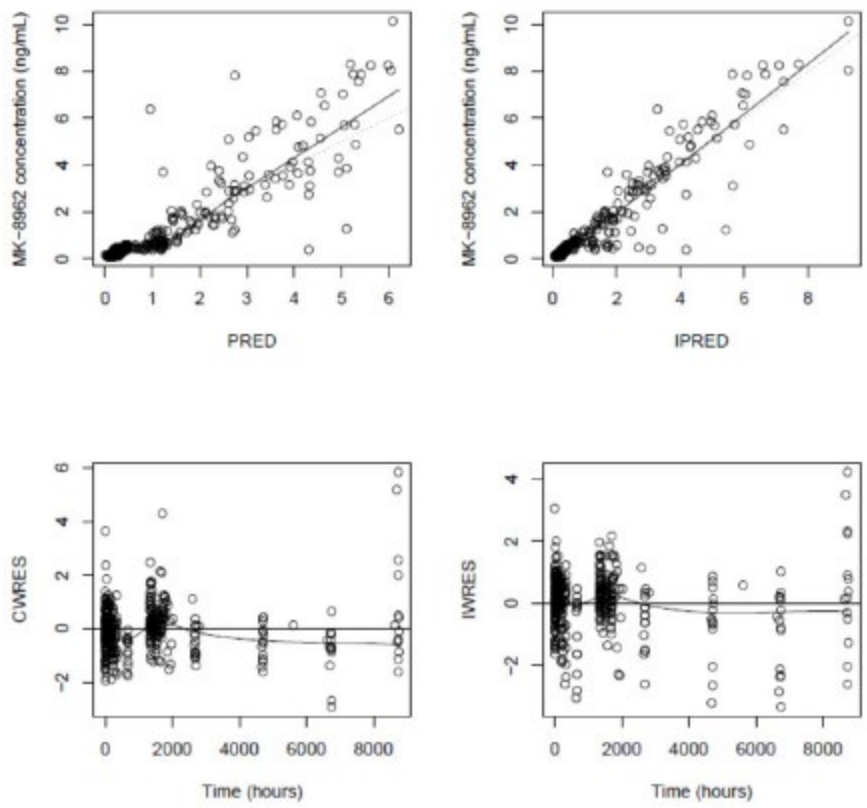


Parameter estimates for the final model are presented in Table 4. All fixed effect parameters, including the body weight effect, were estimated with relatively high precision. Goodness of fit plots are shown in Figure 2. The estimated relative bioavailability fraction accounting for formulation differences (26%, see Table 4) was consistent with the difference in exposure observed in a direct comparison between the protein-free and non-protein-free formulations in study P022 (AUC 20% higher for protein-free).

Table 4 Parameter estimates of final population PK model of adult males

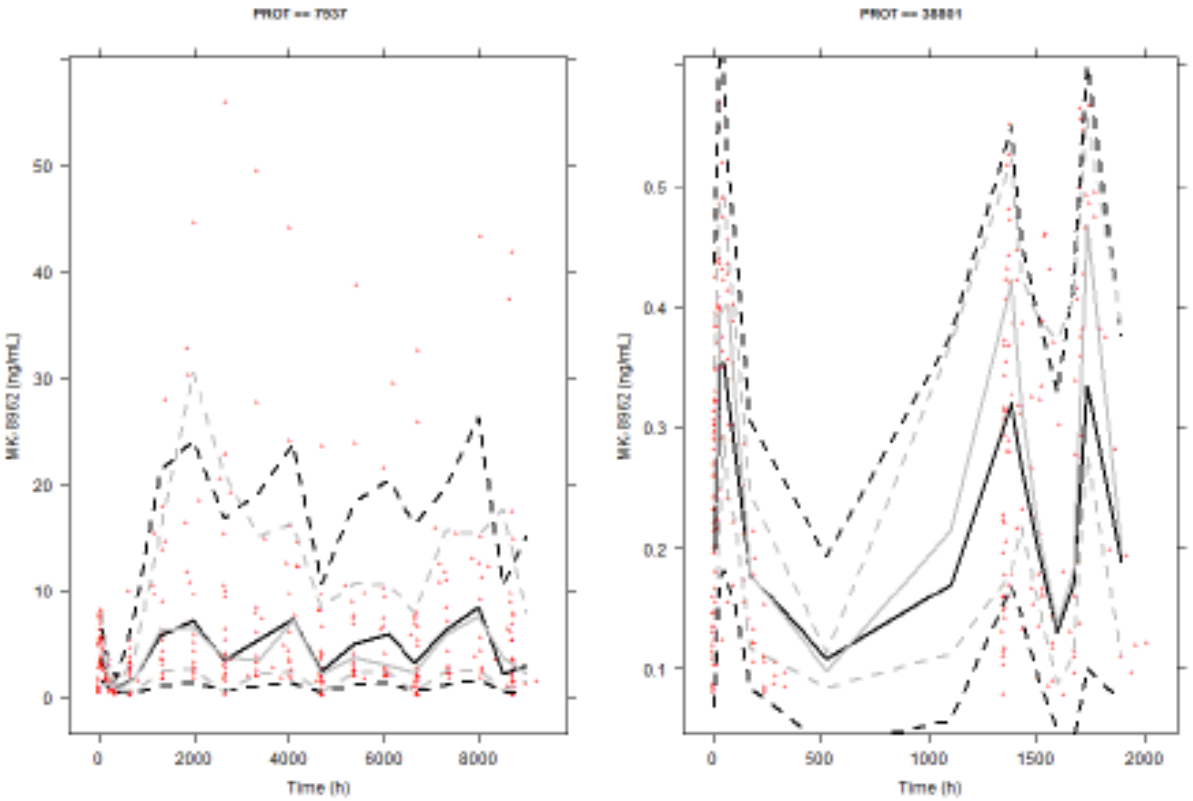
Parameter	Estimate	RSE	Shrinkage
CL (L/h)	0.200	6.2%	
V (L)	35.3	9.5%	
Ka (h^{-1})	0.0739	13.8%	
Relative F	1.26	8.3%	
Scaling factor ng/mL to IU/L	4.5	5.8%	
WT on CL and V	1.28	16.3%	
Random effects			
IIV on CL (Ω)	0.0708	36.9%	3.4%
IIV on V (Ω)	0.136	33.7%	5.8%
IIV on KA (Ω)	0.272	35.4%	18.3%
Proportional error MK-8962	0.272	13.0%	6.1%
Proportional error FSH-IR	0.459	14.1%	1.7%

Figure 2 Goodness of fit plots of CFA concentrations in adult males



Visual predictive check of the model is shown in Figure 3, for both studies separately (left figure study P031, right figure study P022). Red markers represent observed data. Grey lines represent median (solid line) and 10% and 90% quantiles of the observed data. Black lines represent median and 10% and 90% prediction intervals of the simulations. Predicted variability in concentrations is somewhat higher than observed.

Figure 3 Visual predictive check of population PK in adult males



Simulations

In order to obtain a summary of individual MK-8962 exposure estimates, a simulation was conducted in which individual PK profiles for study P031 were predicted on the basis of the individual post-hoc parameter estimates. From these predicted profiles, non-compartmental PK parameter estimates were derived. These are summarized in Table 5.

Table 5 Estimated CFA PK parameters in adult males

	Cmax,ss (ng/mL)	tmax,ss (h)	Cmin,ss (ng/mL)	CL (L/h)	V (L)	AUCss (ng.h/mL)	t1/2 (h)
N	18	18	18	18	18	18	18
Arithmetic mean	5.68	37.2	1.08	0.207	35.4	1013.2	124.7
Standard deviation	1.88	9.74	0.74	0.066	14.9	337.9	56.8
CV%	33.1%	26.2%	69.0%	32.2%	42.0%	33.3%	45.5%
Geometric mean	5.38	36.1	0.90	0.196	32.6	962.2	115.2
Geometic CV%	35.2%	26.4%	65.6%	34.0%	42.8%	34.0%	40.4%
Median	5.32	36.5	0.68	0.192	33.3	986.5	106.4
Min	3.20	24	0.42	0.113	17.4	605.4	71.7
Max	9.27	57	3.14	0.312	70.1	1674.2	256.5

Additional simulations were performed to predict typical CFA AUC, typical FSH-IR trough concentrations as well as FSH-IR PK profiles in adolescent male patients for a range of body weight values and CFA doses. The simulation results are presented in Table 6 and Figure 4 and Figure 5 for a restricted set of body weight values and CFA doses. Results indicate that the majority of the population will achieve CFA exposure near the target AUC of 1200 ng.h/mL.

In high body weight patients (> 100 kg) however, CFA exposure would be predicted to remain below this target value.

Table 6 Predicted CFA AUC for different combinations of dose and weight in adult males

MK-8962 dose		100 µg	150 µg	200 µg
Body weight (kg)	CL (L/h)	AUC_{ss} (ng.h/mL)		
50	0.101	1243	1864	2485
60	0.128	984	1476	1968
70	0.156	808	1212	1615
80	0.185	681	1021	1362
90	0.215	586	878	1171

Figure 4 Simulated distribution of CFA AUCss values for adolescents based on model in adult males

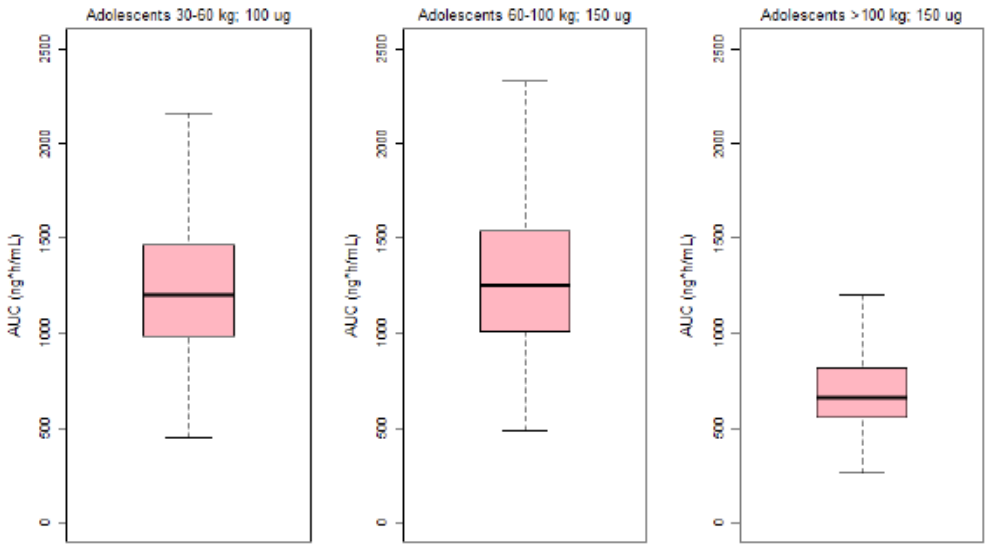
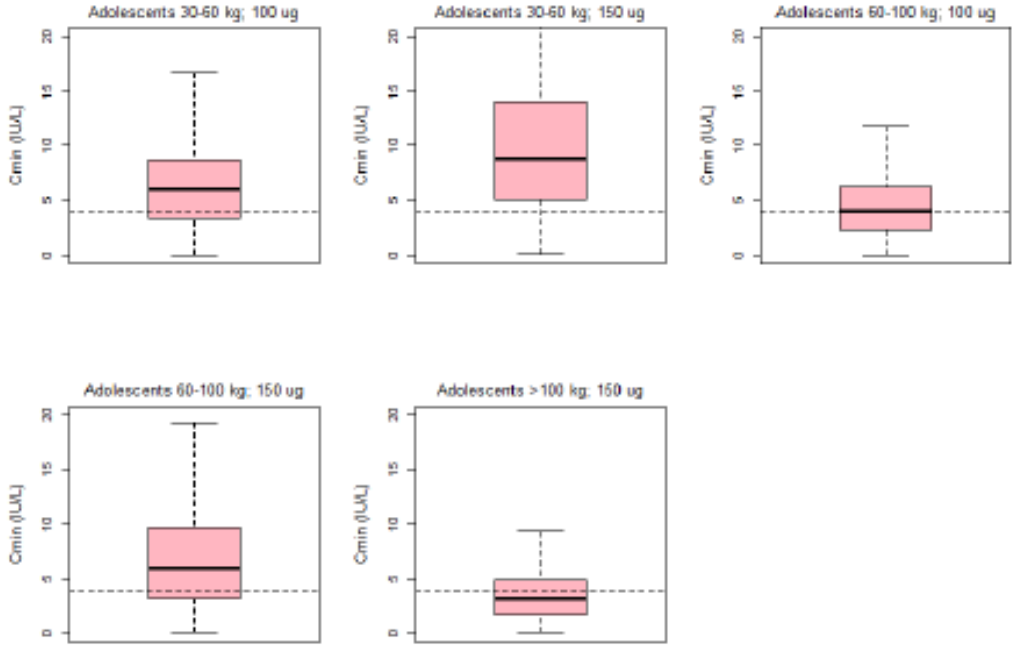


Figure 5 Simulated distribution of predicted FSH-IR C-trough values for doses of 100 or 150 ug MK-8962 in different body weight groups for adolescents (FSH-IR of 4IU/L labeled as a horizontal dashed line) based on model in adult males



Simulations using the population PK model demonstrate that trough serum FSH-IR levels are expected to remain above 4 IU/L when adolescent males are treated once every two weeks with either 100 µg (for a body weight of ≤60 kg) or 150 µg (for a body weight of >60 to 100 kg) of CFA. When treating adolescent males weighing >100 kg, 150 µg CFA every two weeks may result in a trough serum FSH-IR level slightly below 4 IU/L in the majority of subjects. These results were the basis for the dose selected for study P043.

A threshold above which efficacy is expected is mentioned as 4 IU/L for FSH-IR. This is based on the trough concentration to recFSH (Puregon).

Reference was provided describing the model on which the estimation of the exposure to Puregon was based upon (publication Rose et al, 2016). There are some uncertainties with the derivation of the target exposure, such as product differences (recFSH and Puregon vs Elonva), differences between populations (the literature models are based on women instead of men and a different indication), and differences in study conditions (e.g. single dose versus steady state, etc.), which result in uncertainties on the derived target exposure. There are no clinically relevant consequences (e.g. different posology or indication consequences) associated with the proposed target exposure. The data indicated no relationship between exposure and clinical measures. Nonetheless, Elonva was considered to be effective, which indicates that the exposure to Elonva is rather high. Additionally, the current posology did not translate into limiting safety risks.

In the prior model in women, pharmacokinetics were reported to be described using a one-compartment model with first order absorption from the subcutaneous depot and first order elimination. The final model in men was the same basic model with some minor adaptations. It is agreed that endogenous FSH was removed from the model. The situation that no measurable FSH is present prior to treatment, would not account for healthy men, but can be assumed for the patient population.

Clearance, volume of distribution, Ka, relative bioavailability, scaling factor, effect of body weight on CL and V, and proportional error of CFA and FSH-IR were estimated with high precision (RSE 6 – 16%). Interindividual variation in CL, V and Ka was estimated with somewhat higher RSE (34 – 37%). Goodness

of fit plots showed adequate fit. Visual predictive check showed sufficient fit, except that the variability was somewhat higher in the predicted values compared to the observed values.

Comparable exposure is observed in groups weighing 30 – 60 kg receiving 100 µg on the one hand, and groups weighing 60 – 100 kg receiving 150 µg on the other hand. Mean and approximately the 25th and 75th percentile of FSH-IR are expected to remain above the threshold of 4 IU/L. In adolescent males weighing >100 kg, 150 µg CFA every two weeks may result in a trough serum FSH-IR level slightly below 4 IU/L in the majority of subjects. Considering the lack of an exposure-efficacy relationship, this is not expected to be clinically relevant.

2.3.2.3. POP PK- modeling in adolescent males

The population PK in adolescent males is based on the model in adult men, as described above. The data from study P043 were combined with the previously available data in adult men. Pre-dose concentrations above the LLOQ, measurements below the LLOQ and missing values were reported to have been excluded from the analysis.

Objectives of the analyses were:

- Update the prior CFA population PK model, based upon adult male data, to adequately describe the PK of CFA in adolescent males being treated for HH.
- Analyze the effects of intrinsic factors such as body weight, age, and height.
- Characterize the PK parameters Cmax, Cmin, AUC, CL and V of CFA in study P043, a clinical study in adolescent males.

CFA plasma concentration-time data were analyzed using a nonlinear-mixed effects modeling approach. Endogenous FSH levels in males with HH are negligible. In study P043, only adolescent males with FSH < 2 IU/L were enrolled.

Time matched CFA and FSH concentrations were visualized stratified by study. Assessment indicated that the relation was highly significant for study P031, while there was no clear discernible relation in study P043. Based on this observation, it was concluded that it was not scientifically appropriate to use a linear scaling factor to describe CFA concentrations in terms of FSH immunoreactivity as had been done in the adult male HH model. Also, the futility of the FSH/CFA interrelation in study P043 precluded the estimation of separate scaling factors by study. Apparently different FSH assays were used with a different level of cross-reactivity of the FSH assay for CFA in the two HH male patient studies.

The FSH concentrations and scaling factor were therefore removed from the model. Body weight was retained as a covariate. Other potential covariates (age, BMI, height) were investigated using graphical exploration followed by linear regression (continuous covariates) and analysis of variance (ANOVA) testing.

Data programming was conducted in SAS v 9.3. Population PK analysis was conducted in NONMEM 7.4.3. run on a grid of Intel Xeon servers running the CentOS 7 Linux with Open Grid Scheduler, GNU Fortran Compiler (Version 4.8.5), and Perl-speaks-NONMEM (PsN, version 4.8.1). Post processing of population PK analysis results was conducted in R-Studio version 1.3. using R version 4.0.2.

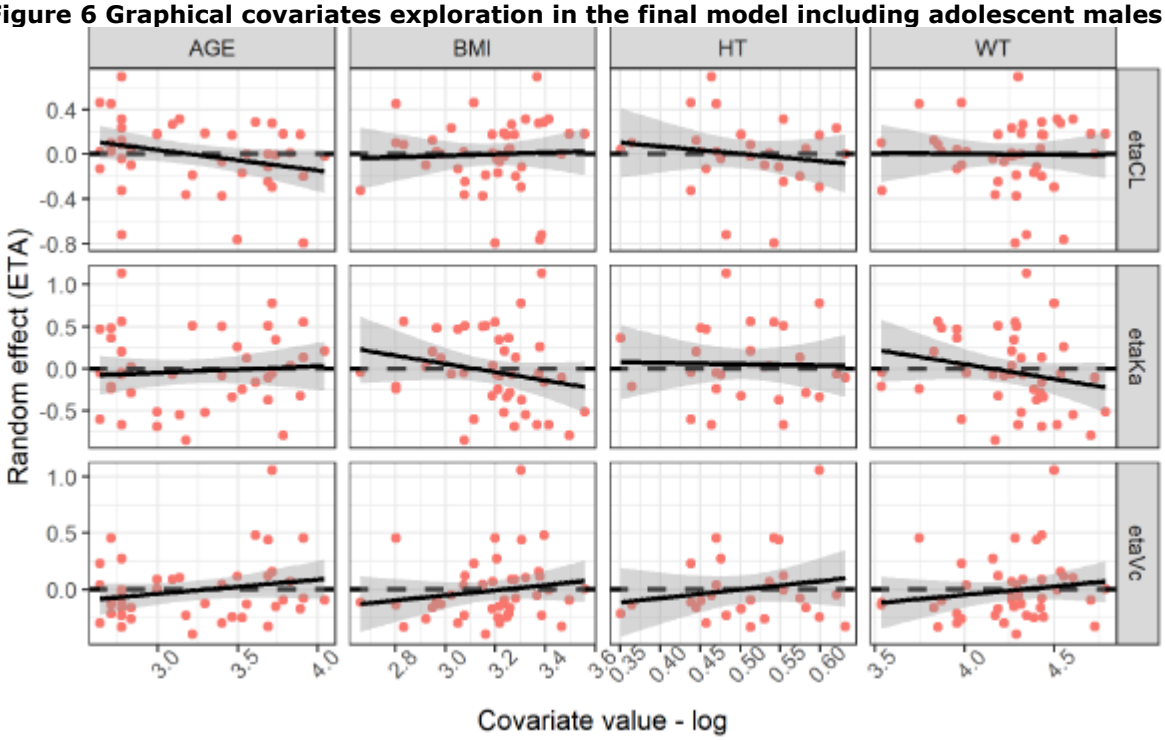
Results

In total, 43 males were included in the population PK dataset, 10 subjects from study P022, 16 subjects from study P031, and 17 subjects from study P043. The final analysis dataset consisted of a total of 565 CFA concentrations, 267 from healthy adult males, 164 from adult males with HH, and 134 from adolescent males with HH. Since in three subjects from study P022, measurable CFA concentrations were present prior to treatment, and these subjects had elevated concentrations throughout the study, these subjects were

excluded from the analysis in agreement with the previous model. Also, samples with measurable pre-dose from trials P031 and P043 were excluded, one from each study.

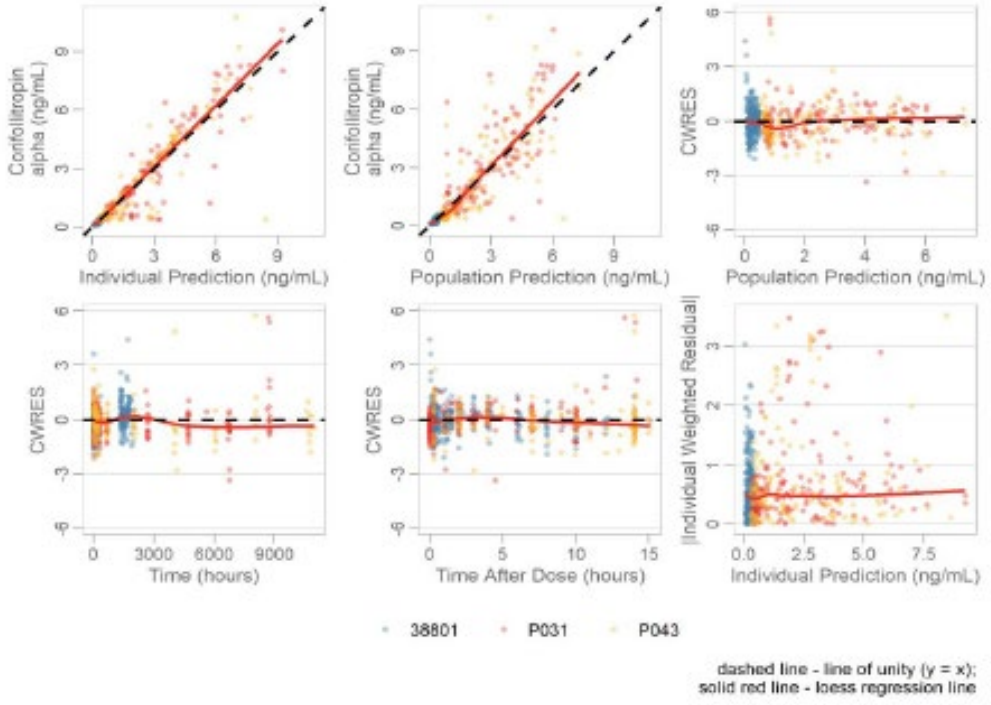
The final model was a one-compartment model with first order absorption. As mentioned above, the scaling factor between CFA and FSH was removed from the model. The relative bioavailability parameter to account for the use of different formulations between the studies P022 (non-protein free formulation) on the one hand and P031 and P043 (protein-free commercial formulation) on the other hand, was retained. Effect of body weight on central volume of distribution and clearance was fixed to 1 and 0.75 respectively (estimates in run215 [run previously to the final run] were 1.2 with RSE 15.3% and 0.76 with RSE 23.2% respectively). This was reported to be in agreement with literature (no reference provided). Graphical exploration of covariates is shown in Figure 6. No additional covariates were included.

Figure 6 Graphical covariates exploration in the final model including adolescent males



Goodness of fit plots are shown in Figure 7.

Figure 7 Final model goodness of fit plots in model including adolescent males



Estimated parameters in the final model are shown in Table 7.

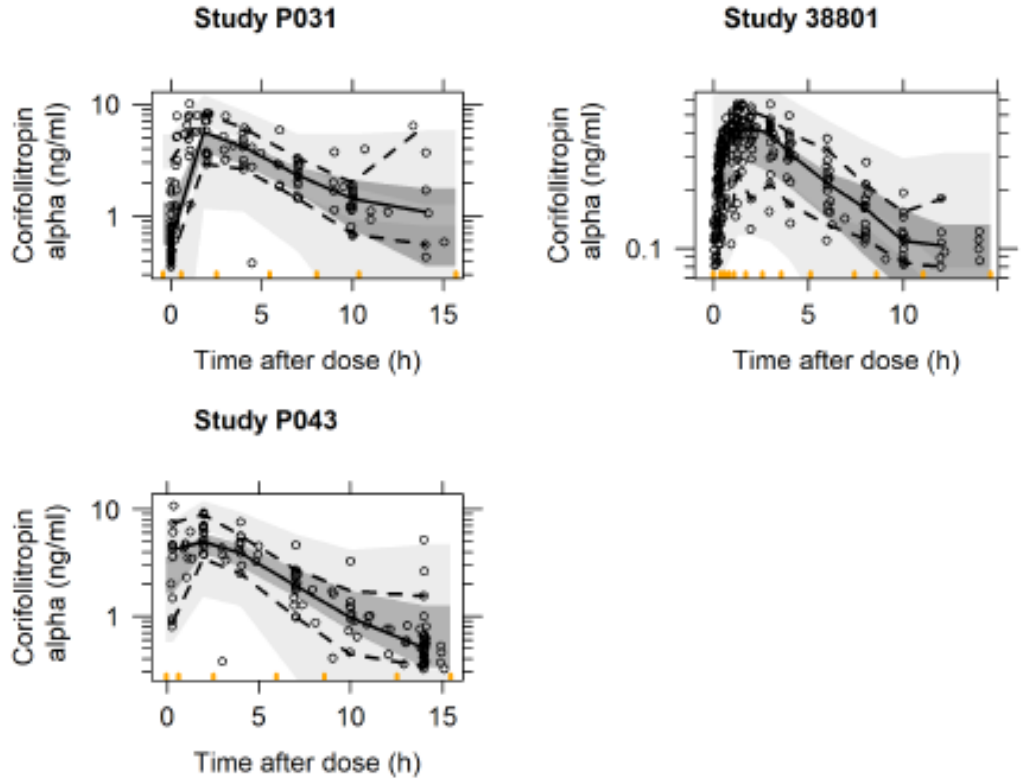
Table 7 Parameter estimates from final population PK model including adolescent males

Parameter	Estimate	RSE (%)	Shrinkage (%)
KA [1/h]	0.0711	11.2	
V [L]	31.8	8.01	
CL [L/h]	0.215	5.18	
Rel F [--]	1.3	7.66	
Random effects			
IIV on KA (Ω)	0.309	28	18.3
IIV on V (Ω)	0.0986	40.8	10.8
IIV on CL (Ω)	0.102	27.6	3.07
Proportional error CFA	0.271	12.3	8.05

CL = apparent clearance; Rel F = describes relative bioavailability between preliminary (P) formulation used in first in human study 38801 and marketed (M) image used in studies P031 and P043 (expressed as $F_{M/P}$).; KA = first-order absorption rate; V = apparent central volume of distribution;

Visual predictive checks are shown in Figure 8 (stratified by study, study 38801 = study P022). Predicted variability in concentrations is somewhat higher than observed, possibly because of the relatively small dataset.

Figure 8 Visual predictive check of the population PK model including adolescents, stratified by study



Source: GOF-PopPK_v3.r, Reference: 8b2e31:9baec5.

Note: Open circles represent observed data. Lines represent median (solid line) and 5th and 95th percentiles of the observed data (dashed lines). Light grey areas represent the 95% confidence interval of the simulated, 5th and 95th percentiles and the dark grey area represents the 95% confidence interval around the simulated median. Orange ticks on x-axis represent the edges of the data bins to visualize which data corresponds to each bin (auto binning option used in PsN)

Simulation

Based on the final model, individual (post-hoc) PK parameters were estimated for all subjects. A summary of the estimated parameters for the subjects in study P043 is shown in Table 8.

Table 8 Estimated (posthoc) CFA PK parameter summary for study P043

Metric	Mean	SD	CV (%)	Geometric mean	Geometric CV (%)	Median	Min	Max
Cmax (ng/mL)	6.45	2.03	31.5	6.15	33.4	6.67	3.44	10.5
Cmin (ng/mL)	0.649	0.65	100	0.474	91.1	0.443	0.0881	2.77
Tmax	33.1	9.22	27.9	31.8	30.9	35.3	16.8	48.7
AUCss (h.ng/mL)	949	380	40.1	891	36.4	864	506	2010
Cavg (ng/mL)	2.82	1.13	40.1	2.65	36.4	2.57	1.51	5.99
CL (L/h)	0.182	0.0785	43	0.169	41.8	0.155	0.0791	0.387
V (L)	20.6	7.15	34.7	19.5	36.9	21.5	11.2	34.2
t½ (h)	83.5	27.8	33.3	80	29.7	76.7	46.9	164

Source: mrk-elonva-146-exposures-20210429-run216.R, Reference: f8e398:ed0837

The resulting distribution of CFA AUC_{ss} values is presented per body weight/dose group and compared to adult males with HH in Figure 9. Results indicate that across weight bands similar CFA exposures were observed, the body weight band specific mean AUC values being 864 ng.h/mL for subjects ≤ 60 kg and 847 ng.h/mL for subjects > 60 kg as compared to 912 ng.h/mL in adult males with HH. Corresponding Cmin values are shown in Figure 10.

Figure 9 Distribution of CFA AUCss values at the recommended dose level for each age group and weight band, based on the model including adolescent males

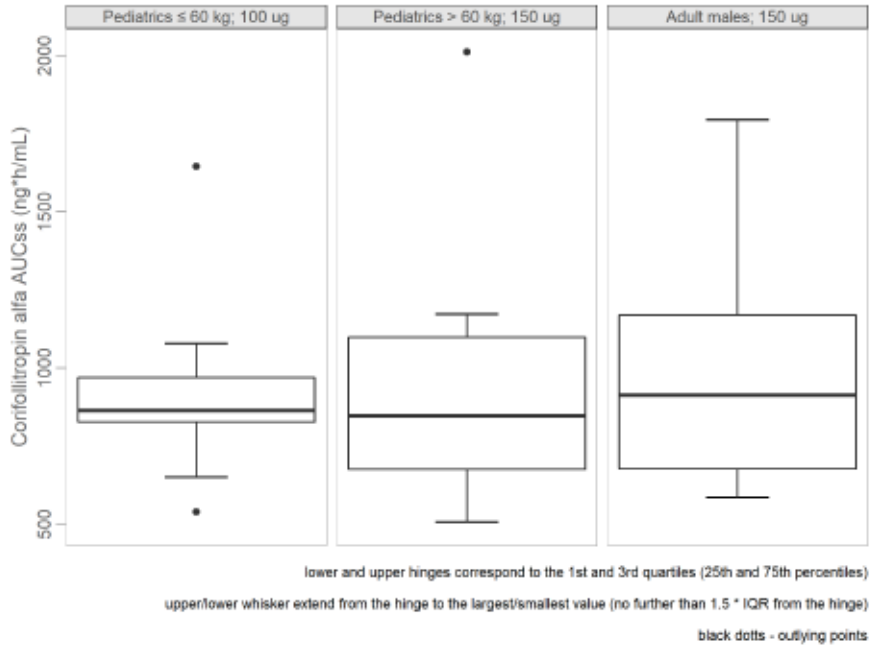
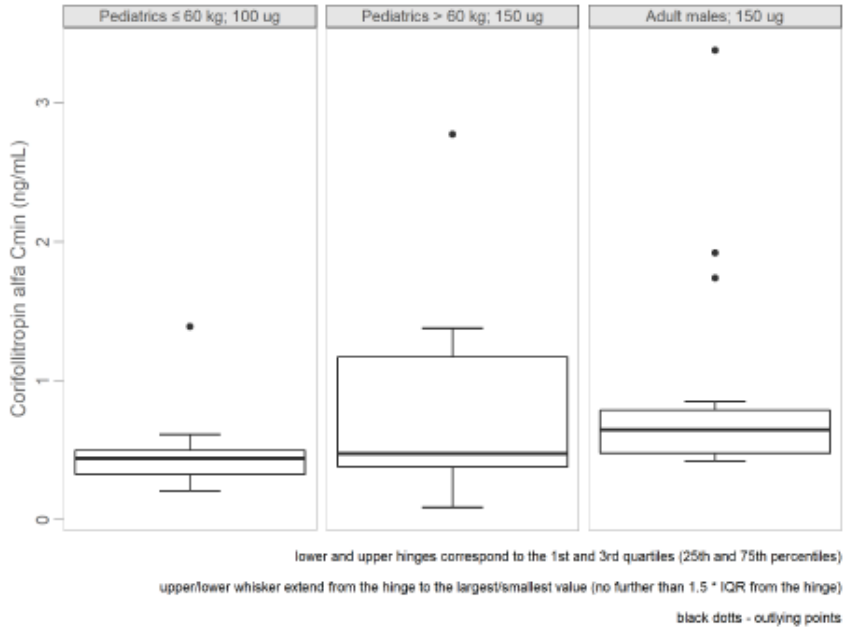


Figure 10 Distribution of CFA Cmin values at the recommended dose level for each age group and weight band, based on the model including adolescent males



Additional simulations were performed to predict typical AUC_{ss} and C_{min} values for CFA for a representative range of body weight values and corresponding CFA doses. The results are shown in Table 9.

Table 9 Predicted CFA AUCss and Cmin values for different combinations of CFA dose and body weight based on model including adolescent males

WT (kg)	CL (L/h)	DOSE (µg)	AUC_{ss} (ng.h/mL)	Cmin (ng/mL)
35	0.11	100	1180	0.708
40	0.122	100	1070	0.681
50	0.144	100	902	0.635
60	0.165	150	1180	0.895
75	0.196	150	999	0.824
90	0.224	150	871	0.768
120	0.278	150	702	0.681

Source: mrk-elonva-146-exposures-20210429-run216.R, Reference: d23d25:030368

The Pop PK model showed a good fit in both adult men and adolescents.

Ka, volume of distribution, clearance, relative bioavailability and proportional error of CFA were estimated with high precision (RSE 5 – 12%). Interindividual variation in CL, V and Ka was estimated with somewhat higher RSE (28 – 41%). Goodness of fit plots and VPC showed good fit except for somewhat higher predicted variability than observed.

Estimated V 32 L and CL 0.22 L/h for the model including adult and adolescent males were similar to those in adult men alone (V 35 L and CL 0.20 L/h).

When simulated PK parameters for adolescents (subjects in study P043) are compared to simulated parameters for adult men (arithmetic mean) (based on studies P022 and P031), Cmax is comparable between adolescents and adult men (6.5 ng/mL vs 5.7 ng/mL), which also goes for AUCss (949 ng.h/mL vs 1013 ng.h/mL). Average estimated Cmin is 40% lower for adolescents than for adult men (0.65 ng/mL vs 1.1 ng/mL). The lack of a relationship between exposure and testicular volume indicates that the difference in Cmin between adolescents and adults (0.65 ng/mL vs 1.1 ng/mL) is not expected to cause a difference in efficacy.

AUCss and Cmin were comparable between both paediatric dose groups. As in adult men, exposure is expected to be lower when body weight exceeds 100 kg. Considering the lack of an exposure-efficacy relationship, this is not expected to be clinically relevant.

No actually measured pharmacokinetic data were provided. No non-compartmental analysis was performed because of the relatively sparse PK sampling that was performed in the studies. The visual predictive check indicates that the Pop PK model has an acceptable fit: in general, all observations were within the predicted area.

Three subjects from study P022 were excluded from the Pop PK analyses of both studies P031 and P043, because they had measurable CFA concentrations prior to treatment. Two subjects from study P031 were removed from the Pop PK analysis based on adult + adolescent subjects, but not from the Pop PK analysis based on adult subjects only. This because in the analysis based on adult + adolescent subjects, only CFA concentrations were used, whereas only FSH-IR concentrations (no CFA concentrations) were available for these subjects, which is agreed.

2.3.3. Pharmacodynamics

Mechanism of action

CFA has been shown to have the same pharmacodynamic profile as (rec)FSH, but with a markedly prolonged duration of FSH activity. In women CFA has been shown to initiate and sustain multiple follicular growth for an entire week, therefore a single subcutaneous injection of the recommended dose of CFA could

replace the first seven injections of any daily (rec)FSH preparation in a controlled ovarian stimulation (COS) treatment cycle. The long duration of FSH activity was achieved by adding the carboxy-terminal peptide of the β-subunit of hCG to the β-chain of human FSH.

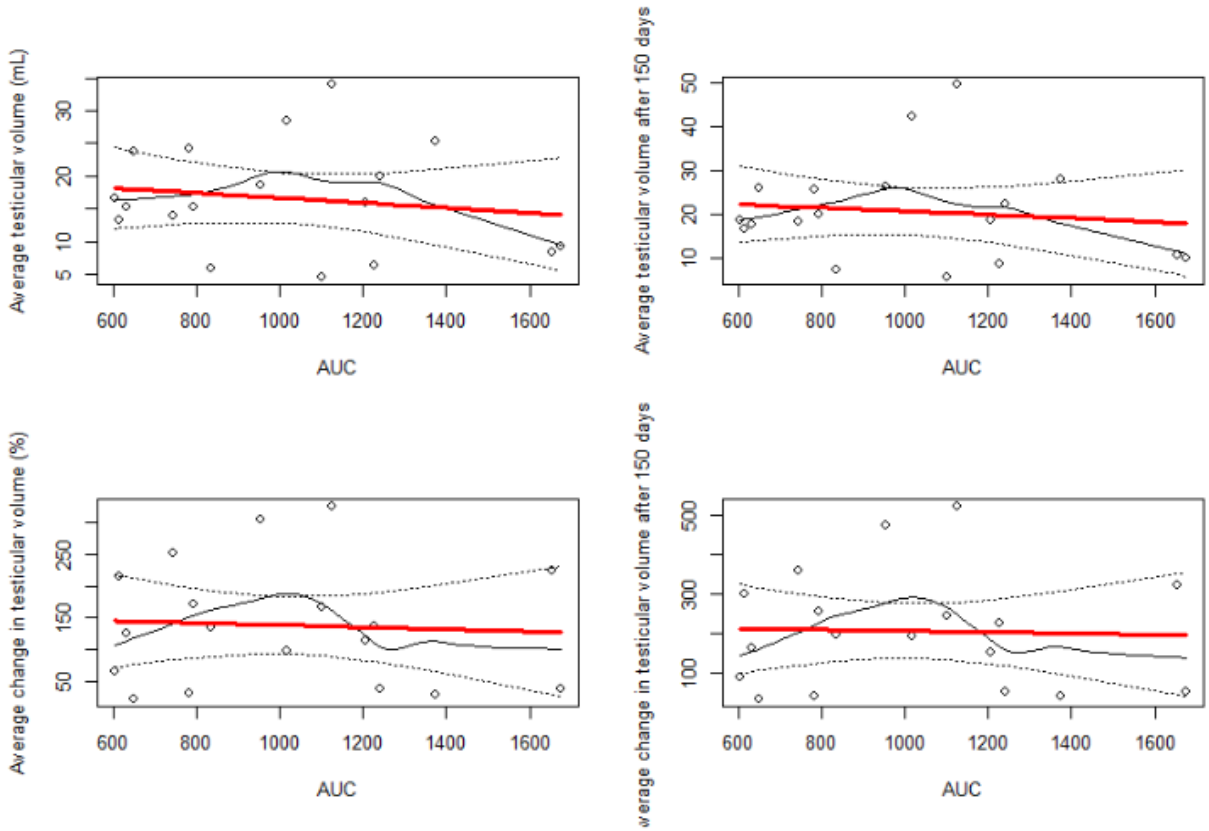
Primary and secondary pharmacology

No separate pharmacodynamic data have been submitted within the dossier.

2.3.4. PK/PD modelling

An exploration of potential PK-PD correlations for testicular volume is presented in Figure 11, based on data from studies P022 and P031. There appear to be no clear relationships between testicular volume and MK-8962 AUC, neither when looking at the average testicular volume (or change from baseline) over the complete treatment period, or after Day 150. Also, as indicated by the confidence intervals of the regression lines including a horizontal (flat) line, no significant linear relationships were identified for any of the four TV measures.

Figure 11 PK-PD correlations for testicular volume

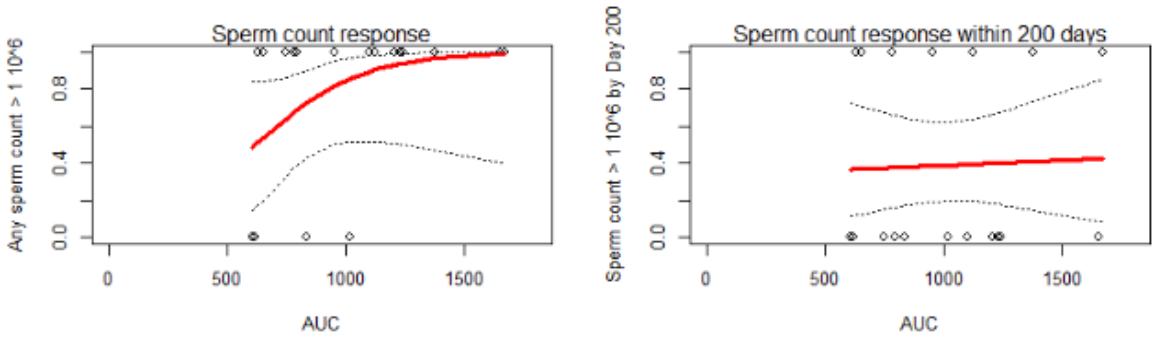


Note: Solid black line represents loess smooth. Solid red line is linear regression, dashed black lines represent associated 95% confidence interval.

Figure 12 presents the results of exploratory logistic regression analyses for sperm count response (defined as any sperm count observation > $1 \cdot 10^6$ in a subject). When based on all data across the complete treatment period, a trend for increased response with increasing AUC is apparent. However, this trend does

not reach statistical significance (p-value 0.132). When restricted to the first 200 days of treatment, no trend for a relationship is seen.

Figure 12 PK-PD correlations for sperm count response



There were insufficient data to establish reliable PK-PD relationships.

2.3.5. Discussion on clinical pharmacology

The Pop PK model showed a good fit in both adult men and adolescents.

A threshold above which efficacy is expected is mentioned as 4 IU/L for FSH-IR. This is based on the trough concentration to recFSH (Puregon). Reference was provided describing the model on which the estimation of the exposure to Puregon was based (publication Rose et al, 2016). There are some uncertainties with the derivation of the target exposure, such as product differences (recFSH and Puregon vs Elonva), differences between populations (the literature models are based on women instead of men and a different indication), and differences in study conditions (e.g. single dose versus steady state, etc.), which result in uncertainties around the derived target exposure. There are no clinically relevant consequences (e.g. different posology or indication consequences) associated with the proposed target exposure. The data indicated no relationship between exposure and clinical measures. Nonetheless, Elonva was considered to be effective, which indicates that the exposure to Elonva is rather high. Additionally, the current posology did not translate into limiting safety risks. Therefore, this issue will not be further pursued.

When simulated PK parameters for adolescents (subjects in study P043) are compared to simulated parameters for adult men (arithmetic mean) (based on studies P022 and P031), C_{max} is comparable between adolescents and adult men (6.5 ng/mL vs 5.7 ng/mL), which also goes for AUC_{ss} (949 ng.h/mL vs 1013 ng.h/mL). Average estimated C_{min} is 40% lower for adolescents than for adult men (0.65 ng/mL vs 1.1 ng/mL). The lack of a relationship between exposure and testicular volume indicates that the difference in Cmin between adolescents and adults (0.65 ng/mL vs 1.1 ng/mL) is not expected to cause a difference in efficacy.

AUCss and Cmin were comparable between both paediatric dose groups. As in adult men, exposure is expected to be lower when body weight exceeds 100 kg. Considering the lack of an exposure-efficacy relationship, this is not expected to be clinically relevant.

No actually measured pharmacokinetic data were provided. No non-compartmental analysis was performed because of the relatively sparse PK sampling that was performed in the studies. The visual predictive check indicates that the Pop PK model has an acceptable fit: in general, all observations were within the predicted area.

2.3.6. Conclusions on clinical pharmacology

The proposed indication can be accepted from a pharmacokinetic point of view.

2.4. Clinical efficacy

Study P043

This clinical overview summarizes results from a global, Phase 3, single-group, open-label efficacy and safety study of corifollitropin alfa (CFA, Elonva®, MK 8962) in combination with hCG for the treatment of HH in adolescent males (14 to less than 18 years of age) (study P043). In this study, CFA was administered alone for the first 12 weeks and in combination with hCG for the following 52 weeks.

Study P031

Additionally, this clinical overview references results from a Phase 3 study (study P031) that assessed PK, PD, efficacy, and safety of CFA in combination with hCG in azoospermic adult men with HH. The PK and PD results from study P031 were used to select the dose of CFA to be used in adolescent males in study P043.

Study P043 was earlier submitted and assessed within the Article 46 procedure EMEA/H/C/ 001106/P46/019.

Data of study 031 has been assessed under the 'Clinical Pharmacology' section of this assessment report.

2.4.1. Dose response study(ies)

See 'Clinical Pharmacology' section of this assessment report.

2.4.2. Main study

Study P043

Study P043 was a phase III, multi-centre, open label, single-group trial to investigate the efficacy and safety of MK-8962 (corifollitropin alfa) in combination with hCG for initiation or restoration of puberty as assessed by increased testicular volume in adolescent males 14 to <18 years old with HH.

The study protocol and study results of P043 were earlier assessed and agreed within the Article 46 procedure EMEA/H/C/ 001106/P46/019.

Further, the protocol of Study P043 has been agreed upon in the PIP for CFA (PIP decision: P/0143/2019).

Methods

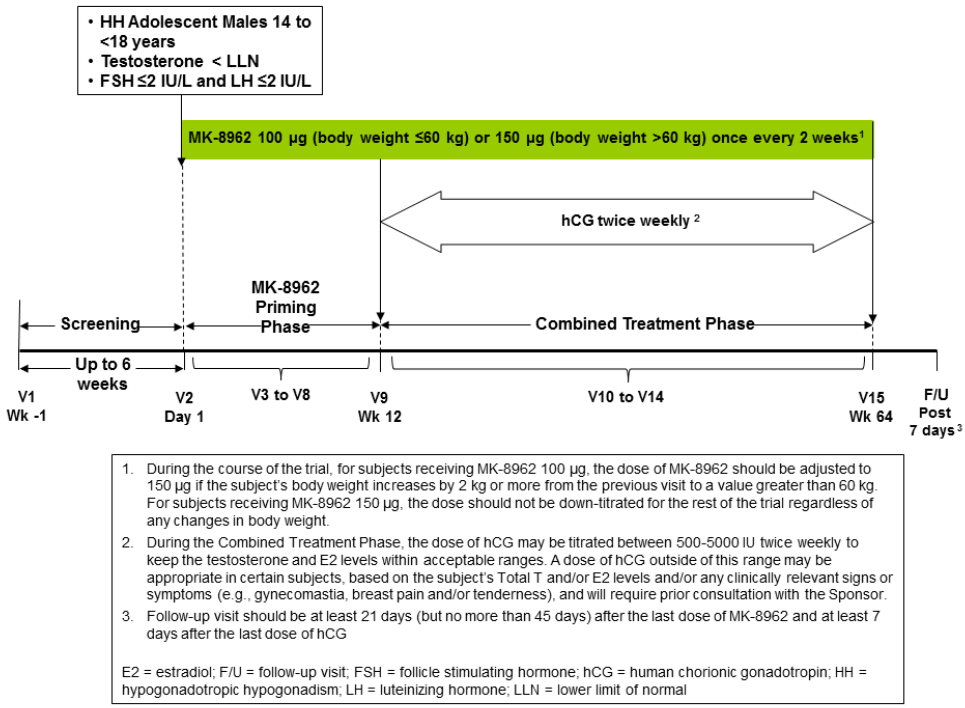
Study design

This was a multi-centre, open-label, single-group study evaluating the treatment of corifollitropin alfa (MK-8962) in combination with hCG (500 to 5000 IU) sc given twice weekly to induce and/or restore puberty and induce and/or restore spermatogenesis in adolescent males with HH.

The study included a screening period, priming period with CFA, combined treatment period with CFA and hCG for 52 weeks, and a follow-up visit. Each subject participated in the trial for approximately 73 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact.

The study design diagram is presented in Figure 13.

Figure 133 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

After a screening phase of up to 6 weeks, each subject was treated for 12 weeks with MK-8962 alone (i.e., priming phase).

The rationale for the priming period with CFA instead of hCG in adolescents with HH was to mimic the gonadotropin pattern of normal puberty, stimulating FSH receptors on Sertoli cells with CFA prior to stimulation of LH receptors on Leydig cells with hCG, to induce testicular growth, masculinization, and preservation of future fertility in these participants. This approach was supported by evidence of successful induction of testicular growth and fertility with recFSH pre-treatment followed by GnRH therapy in men with CHH and prepubertal testes (Dwyer AA et al; J Clin Endocrinol Metab 2013;98:E1790-E1795).

After completion of the Priming Phase, the subject started on combined treatment with both MK-8962 and hCG for 52 weeks. At the end of the combined treatment phase or at premature discontinuation, a post-treatment follow-up visit was scheduled at least 21 days after the last MK-8962 injection (and at least 7 days after the last hCG injection). After the post-treatment follow-up visit, subjects who prematurely discontinued study medication but did not withdraw consent continued to be followed up until they had reached Week 64 after initial treatment allocation.

Subjects discontinued from the treatment due to the presence of neutralizing anti-drug antibodies (ADAs) may continue to be followed until the ADA result becomes negative or until clinically stable for up to 12 months after treatment discontinuation.

Although the study design has been agreed within the Article 46 procedure EMEA/H/C/ 001106/P46/019 the open label design with no randomisation in a small heterogeneous population provides very limited data in support of this sequential treatment regime (CFA + CFA/HCG) in prepubertal adolescents. HH is a rare condition and the challenges to recruitment are acknowledged. Ideally a randomized controlled study

comparing different treatment approaches i.e. sequential vs combined treatment) would have been conducted to properly evaluate the effect of peripubertal priming on future spermatogenesis. The optimality of the treatment paradigm (CFA + CFA/HCG) has been sufficiently discussed with reference to published literature and clinical guidelines.

Duration of treatment

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

Study participants

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.

This study excluded boys who had previously received GnRH, gonadotropins or testosterone treatment. For pubertal induction, testosterone is currently a recommended treatment among paediatric endocrinologists (Boehm 2015).[1] There is limited information regarding the effect of this treatment regimen on patients who have already been commenced on testosterone or any gonadotropin or GnRH treatment. Wording on this effect has been included in the final agreed wording for section 4.4 and 5.1 of the SmPC.

[1] Ref; Boehm et al Nat Rev Endocrinol . 2015 Sep;11(9):547-64 : Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment.

Treatments

The study medications are outlined in the table below.

Drug	Dose	Dose Frequency	Route of Administration	Treatment Period	Use
MK-8962 (CFA)	Body weight ≤60 kg: 100 µg Body weight >60 kg: 150 µg	Once every 2 weeks	SC	Day 1 (Week 0) through Week 64. The last dose was to be administered on the last day of Week 62 (Day 435).	Experimental
hCG[a]	500-5000 IU	Twice a week	SC	The first dose was to be administered on the last day of Week 12 (Day 85), and treatment was to be continued from Week 13 through Week 64.	Standard of care
[a] 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.					

The participant and his legal guardian (or someone designated by the participant's legal guardian such as a caregiver or parent) were instructed at Visit 2 on home-administration of CFA injections. The first 3 doses of CFA were administered by the participant at the trial site on V2/Day 1, Visit 7 (V7)/Week 2 (Day 15), and Visit 8 (V8)/Week 4 (Day 29) as witnessed doses. Later injections were self-administered by the participant or administered by the participant's legal guardian (or the designated person who had been appropriately trained) at home.

At Visit 9 (V9)/Week 12 (Day 85), the subject entered a 52-week MK-8962 and hCG combined treatment phase. The first dose of hCG was self-administered (or administered by an appropriately trained person designated by the subject's legal guardian) at the trial site as a witnessed dose at V9. During the combined treatment phase, the subject had site visits every 8 to 12 weeks from V9 until treatment completion at Visit 15 (V15)/Week 64.

Dose of MK-8962

Subjects with body weight ≤60 kg were given MK-8962 100 µg and subjects with body weight >60 kg were given MK-8962 150 µg. 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.

Dose titration for hCG

The dose of hCG was adjusted between 500 IU and 5,000 IU (inclusive) in order to keep the Total T and E2 levels within the normal ranges as defined in the paragraph below. Blood samples collected at Visit 9/Week 12 and each of the subsequent visits were evaluated for the Total T and E2 levels. Based on the results of these tests, the investigator or qualified designee should log into the Interactive Voice/Web Response System (IVRS/IWRS) between pre-specified visits to request additional medication if hCG up-titration is needed.

The normal range for Total T for this study is defined as the mean ± 2 standard deviation (SD) for a young, healthy male population, and the exact limits are assay-specific. The reference range used by the Sponsor-designated central lab is 240.00 – 950.00 ng/dL (or 8.3 – 33.0 nmol/L).

During hCG treatment, serum E2 levels should also be evaluated to avoid clinically relevant elevations of E2 levels (should be monitored towards maintaining <40% above the upper limit of normal in men [the ULN from the Sponsor-designated central laboratory is 40.00 pg/mL]).

Table 10 MK-8962 and hCG Dosing Schedule

Examples of Dosing Schedule Scenario	MK-8962 100 µg or 150 µg	hCG (can be titrated down to 500 IU or up to 5000 IU)
A	Every other Monday	Every Monday and Thursday
B	Every other Tuesday	Every Tuesday and Friday
C	Every other Wednesday	Every Wednesday and Saturday
D	Every other Thursday	Every Thursday and Monday
E	Every other Friday	Every Friday and Tuesday

Objectives

The primary objectives are:

In adolescent males 14 to <18 years old with HH:

- 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).
- To evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962.

The secondary objectives are:

In adolescent males 14 to <18 years old with HH, to evaluate the following parameters over 64 weeks of treatment with MK-8962 (in combination with hCG for the last 52 weeks):

- Change from baseline in Tanner Stage of pubertal development.
- Growth velocity (height).
- Change from baseline in inhibin B concentrations.
- Change from baseline in levels of endocrine parameters (i.e., LH, calculated free T, Total T, estradiol [E2], SHBG, and AMH).
- Testicular sonographic pattern reflecting pubertal development.
- PK of MK-8962 (based on serum MK-8962 concentrations).

Outcomes/endpoints

Primary efficacy endpoints:

- 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).

Secondary endpoints:

- Tanner Stage of pubertal development at Weeks 12, 36, and 64.
- Growth velocity at Weeks 36 and 64.
- Change from baseline in serum inhibin B concentrations at Week 64.

- Changes from baseline in endocrine parameters LH, Total T, T, E2, SHBG, and AMH at Weeks 12, 36, and 64.
- Characterization of testicular sonographic pattern reflecting pubertal development through 64 weeks of treatment.
- Characterization of MK-8962 PK (based on serum MK-8962 concentrations) through 64 weeks of treatment.

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.

Randomisation

Dispensing of medication and assignment of screening and randomization numbers will be performed via the IVRS/IWRS. After signing informed consent, the investigator or qualified designee should enter the subject in the IVRS/IWRS and the system will assign a screening number. After evaluation of all screening data, indicating that the subject complies with all selection criteria, the subject can be assigned a randomization number to enter the MK -8962 priming phase. No stratification based on age, sex or other characteristics will be used in this trial.

Blinding (masking)

This was an open-label study.

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 randomized 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.

Results

Participant flow

A total of 25 male participants were screened and 17 were allocated across 9 sites in 4 countries. All participants completed the study as per protocol. One participant discontinued study medication due to an SAE. All non-randomized participants were screen failures (Table 11).

Table 11 Disposition of Subjects

	n	%
Not Allocated	8	
Subjects in population	17	
Gender (Age Range in Years)		
Male	17 (14 to 17)	100.0
Protocol Milestone		
Subjects who entered the Priming Period	17	100.0
Subjects who entered the Combined Treatment Period	17	100.0
Subjects who completed the Combined Treatment Period	16	94.1
Trial Disposition		
Completed	17	100.0
Subject Study Medication Disposition		
Started	17	100.0
Completed	16	94.1
Discontinued	1	5.9
Adverse Event	1	5.9
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.		

Recruitment/ Number analysed

The study was conducted in 4 countries, Brazil, Italy, Mexico, and Russian Federation. Seventeen subjects were enrolled in the study.

Only one patient was recruited from Europe, with the rest of the population recruited outside the EU However, since the efficacy and safety analyses are based on a common biological mechanism linking treatment to outcome, there is in general no reason to expect that baseline characteristics and findings in HH patients differ across geographic regions. This is supported by public literature indicating baseline characteristics of the participants in study P043 to be comparable to the baseline characteristics reported for adolescent males with HH from EU countries at the start of treatment (Barrio R et al, Fertil Steril. 1999 Feb;71(2):244-8; Giagulli VA et al, J Sex Med. 2011;8:3471-8; Raivio T et al, Eur J Endocrinol 2007;156:105-11).

Conduct of the study

A total of 8 (47.1%) participants had 1 or more important protocol deviations (PD), and 8 participants had 1 or more PDs considered clinically important. The majority of clinically important PDs were related to

study procedures, with failure to perform significant efficacy evaluations, missing LH, FSH or hCG being the most common procedural deviations, but the deviations identified in this study are not expected to affect the interpretation of safety or efficacy results. A listing of important PDs is presented by participant, study site, and clinical importance in Table 13.

No important protocol deviations were classified as serious GCP compliance issues. The last 3 months of the study were conducted during the COVID-19 pandemic. No protocol deviations associated with the pandemic were reported.

Table 13 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

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 prepubertal levels of FSH, LH, and total T, and Tanner I for genital development (with the exception of 1 participant with Tanner II genitalia) and Tanner I, II or III pubic hair.

The demographic data are summarized in the table below.

Table 14 Subject characteristics

	Corifollitropin Alfa + Corifollitropin Alfa/hCG	
	n	(%)
Subjects in population	17	
Gender		
Male	17	(100.0)
Age (Years)		
14 to 15	7	(41.2)
16 to 17	10	(58.8)
Mean	15.5	
SD	0.9	
Median	16.0	
Range	14 to 17	
Race		
Multiple	1	(5.9)
Black Or African American, White	1	(5.9)
White	16	(94.1)
Ethnicity		
Hispanic Or Latino	4	(23.5)
Not Hispanic Or Latino	13	(76.5)
Tanner Stage - Pubic Hair		
Tanner I	7	(41.2)
Tanner II	9	(52.9)
Tanner III	1	(5.9)
Tanner Stage - Genital Growth		
Tanner I	16	(94.1)
Tanner II	1	(5.9)
Testicular Volume (mL)		
Subjects with data	17	
Mean	2.2	
SD	1.9	
Median	1.5	
Range	0.6 to 7.4	

	Corifollitropin Alfa + Corifollitropin Alfa/hCG	
	n	(%)
Testicular Volume (mL)-Left Testis		
Subjects with data	17	
Mean	1.1	
SD	1.0	
Median	0.7	
Range	0.3 to 4.0	
Testicular Volume (mL)-Right Testis		
Subjects with data	17	
Mean	1.1	
SD	0.9	
Median	0.8	
Range	0.3 to 3.4	
Follicle Stimulating Hormone (IU/L)		
Subjects with data	17	
Mean	0.5	
SD	0.4	
Median	0.3	
Range	0.3 to 1.9	
Luteinizing Hormone (IU/L)		
Subjects with data	17	
Mean	0.2	
SD	0.2	
Median	0.1	
Range	0.1 to 0.9	
Human Chorionic Gonadotropin, Choriogonadotropin Beta (IU/L)		
Subjects with data	16	
Mean	0.3	
SD	0.0	
Median	0.3	
Range	0.3 to 0.3	
Total Testosterone (ug/L)		
Subjects with data	17	
Mean	0.1	

	Corifollitropin Alfa + Corifollitropin Alfa/hCG	
	n	(%)
SD	0.1	
Median	0.1	
Range	0.0 to 0.4	
Estradiol (ng/L)		
Subjects with data	17	
Mean	10.1	
SD	2.4	
Median	9.5	
Range	9.5 to 19.5	
Sex Hormone-Binding Globulin (nmol/L)		
Subjects with data	17	
Mean	55.3	
SD	31.3	
Median	44.9	
Range	15.4 to 124.0	
Inhibin B (ng/L)		
Subjects with data	17	
Mean	44.9	
SD	46.5	
Median	25.0	
Range	11.0 to 155.0	
Antimullerian Hormone (ug/L)		
Subjects with data	17	
Mean	25.7	
SD	12.6	
Median	20.5	
Range	10.9 to 46.0	
Height (cm)		
Subjects with data	17	
Mean	161.4	
SD	11.2	
Median	160.1	
Range	142.0 to 186.1	

	Corifollitropin Alfa + Corifollitropin Alfa/hCG	
	n	(%)
Weight (kg)		
≤ 60	11	(64.7)
> 60	6	(35.3)
Subjects with data	17	
Mean	57.7	
SD	16.6	
Median	53.7	
Range	34.3 to 91.6	
BMI (kg/m^2)		
Subjects with data	17	
Mean	21.9	
SD	4.9	
Median	21.1	
Range	14.3 to 30.4	

At baseline study participants had a mean bilateral testicular volume <4.0 mL for each testicle, Total T less than the LLN of 8.3 nmol/L and FSH ≤2 IU/L and LH ≤2 IU/L all of which complied with the inclusion criteria.

An inhibin B cut-off of 35 pg/mL was also included in the inclusion criteria. Mean Inhibin B levels at baseline were 44.9 ng/L with a median of 25 ng/L but with a range of 11-144. The 2 subjects with a baseline inhibin B level >35 ng/L were diagnosed with CHH based on the same pattern of testicular growth as patients with levels <35 ng/L. The 3rd patient's diagnosis remains unclear based on course on TV growth. CHH is a heterogeneous disorder and variability in biomarker levels is not unusual and that therefore diagnosis might be challenging.

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, 1 had CHARGE syndrome, 1 had KS, and 1 had a HH diagnosis of unknown origin.

Concomitant medications

The most frequent prior medications included levothyroxine (47.1%), somatropin (35.3%), hydrocortisone (29.4%), and desmopressin (23.5%). The most frequent concomitant medications included levothyroxine (52.9%), somatropin (41.2%), hydrocortisone (35.3%), and desmopressin (23.5%). These reported concomitant medications were expected in this subject population, given the underlying etiology of HH in these participants.

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'.

The mean duration of CFA and HCG was 442 days (range 294 to 462 days) and 352 days (range 210 to 371 days), respectively (see Table 15 and 16).

Table 15 Extent of exposure to corifollitropin alfa by dose all subjects as treated (overall treatment period)

Corifollitropin Alfa	≤12 weeks	> 12 weeks to 24 weeks	> 24 weeks to 36 weeks	> 36 weeks to 48 weeks	> 48 weeks to 52 weeks	> 52 weeks to 64 weeks	> 64 weeks	Total Subjects	Duration Range	Mean Duration
Any Dose	0	0	0	1	0	12	4	17	294 to 462 days	442.2 days
Corifollitropin Alfa 100 µg	0	0	1	0	1	7	2	11	252 to 462 days	423.8 days
Corifollitropin Alfa 150 µg	0	1	1	1	0	3	2	8	98 to 462 days	357.0 days

Each subject who received Corifollitropin Alfa is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Corifollitropin Alfa.
Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.
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.
Duration of exposure is calculated assuming one day of dosing = 14 days of exposure.

Table 16 Extent of exposure to HCG by dose all subjects as treated (combined treatment period)

hCG	≤12 weeks	> 12 weeks to 24 weeks	> 24 weeks to 36 weeks	> 36 weeks to 48 weeks	> 48 weeks to 52 weeks	> 52 weeks to 64 weeks	> 64 weeks	Total Subjects	Duration Range	Mean Duration
Any Dose	0	0	1	1	9	6	0	17	210 to 371 days	351.6 days
hCG 500-5000 IU	0	0	1	1	9	6	0	17	210 to 371 days	351.6 days

Each subject who received hCG is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to hCG.
Duration of exposure is calculated assuming one day of hCG dosing = 3.5 days of exposure.

All participants received 6 or 7 doses of CFA every 2 weeks for 12 weeks before starting hCG (priming phase). During the combined treatment period, participants received CFA with 500 to 5000 IU of hCG for 52 weeks. In 2 participants, the dose of CFA was increased per protocol from 100 to 150 µg based on increased body weight.

One patient received CFA for '>36 weeks to 48 weeks', 12 patients received CFA for '>52 to 64 weeks' and four patients were given CFA for '>64 weeks'. The mean duration of CFA and hCG was 442 days (range 294 to 462 days) and 352 days (range 210 to 371 days), respectively.

All subjects received at least 12 weeks of CFA prior to starting hCG. Further, most patients were exposed for a median duration of 64 weeks. One patient suffered from an AE and discontinued treatment at 42 weeks and that two patients had shorter treatment duration due to a switch in dose strength from 100 to 150 µg. It is therefore considered that the duration of CFA was generally 64 weeks and that the divergent doses due to body weight and treatment durations were explainable. Further, the hCG dose was allowed to vary in each subject and dose was titrated based on individual response of the subject so that both testosterone and oestrogen levels were maintained in an acceptable range. This explains that the hCG dose could range from 500 to 5000 IU based on subject response and therefore the overall dose varied substantially.

Numbers analysed

The primary analysis for testicular volume and the analyses for all secondary efficacy endpoints was based on the FAS population.

Two other populations were used for supportive analyses of testicular volume, the completers and MITT populations. The MITT population included all participants who had received at least 36 weeks of treatment (12 weeks of priming with CFA and 24 weeks of combined treatment with CFA and hCG) and had baseline and at least 1 post-baseline measurement of testicular volume at ≥36 weeks of treatment. The completers population included participants who remained on the study medication regimen and completed through Week 64.

Of the total 17 allocated participants, a total of 13 participants were included in the FAS population. A total of 16 participants were included in the MITT population, and 16 participants were included completers population (Table 17).

Table 17 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) Excluded from MITT: • Had no baseline or no post-baseline testicular volume measurement at ≥ 36 weeks of treatment	16 1
Completers Excluded from completers: • Discontinued study medication before completing 64 weeks of treatment	16 1

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 18)).

Table 18 Analysis of testicular volume (mL) change from baseline to week 12

		Baseline				Week 12				Model† Based Geometric Mean Ratio	
	N	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]

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 19). There was a continuous increase in mean testicular volume (measured by ultrasound), 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, three participants had a change of testicular volume of ≥20 mL from baseline.

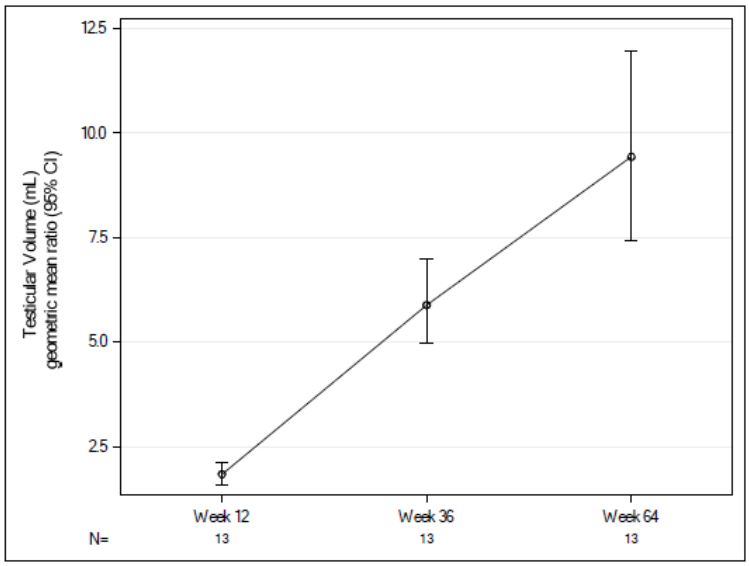
Table 19 Analysis of testicular volume (mL) change from baseline to week 64

	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 14 Analysis of Testicular Volume Change Over Time



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

The primary endpoint for efficacy was shown by an increase in testicular volume, measured as the sum of volumes of left and right testes by ultrasound. In the priming period on CFA alone, with the aim to stimulate FSH receptors on Sertoli cells, 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 at baseline to 12.9 mL, mean fold increase of 9.43 (95% CI of 7.44, 11.97). It was 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 as the testicular volume observed at the end of normally-timed puberty is ≥24 mL (Rohany et al; 2017).

While it may be possible to treat HH adolescents with gonadotropins for a longer duration, the exposure to gonadotropins at the start of puberty is likely to increase the chances of successful induction of spermatogenesis when fertility is desired in the future. Testicular growth and the hormonal profile induced during therapy in study P043 suggest that future fertility is therefore likely to be preserved in these males unlike the situation in HH adolescents treated exclusively with hCG or T to induce masculinization in adolescence. The rationale behind the treatment paradigm and the duration of treatment has further been sufficiently explained by literature data.

Symmetry in testes growth

The increase in mean testicular volume during the overall treatment period was symmetric in both testes, which is shown in the table below (Table 20).

Table 20 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]

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 21).

Table 21 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]

Secondary efficacy endpoint - Tanner Stage of Development

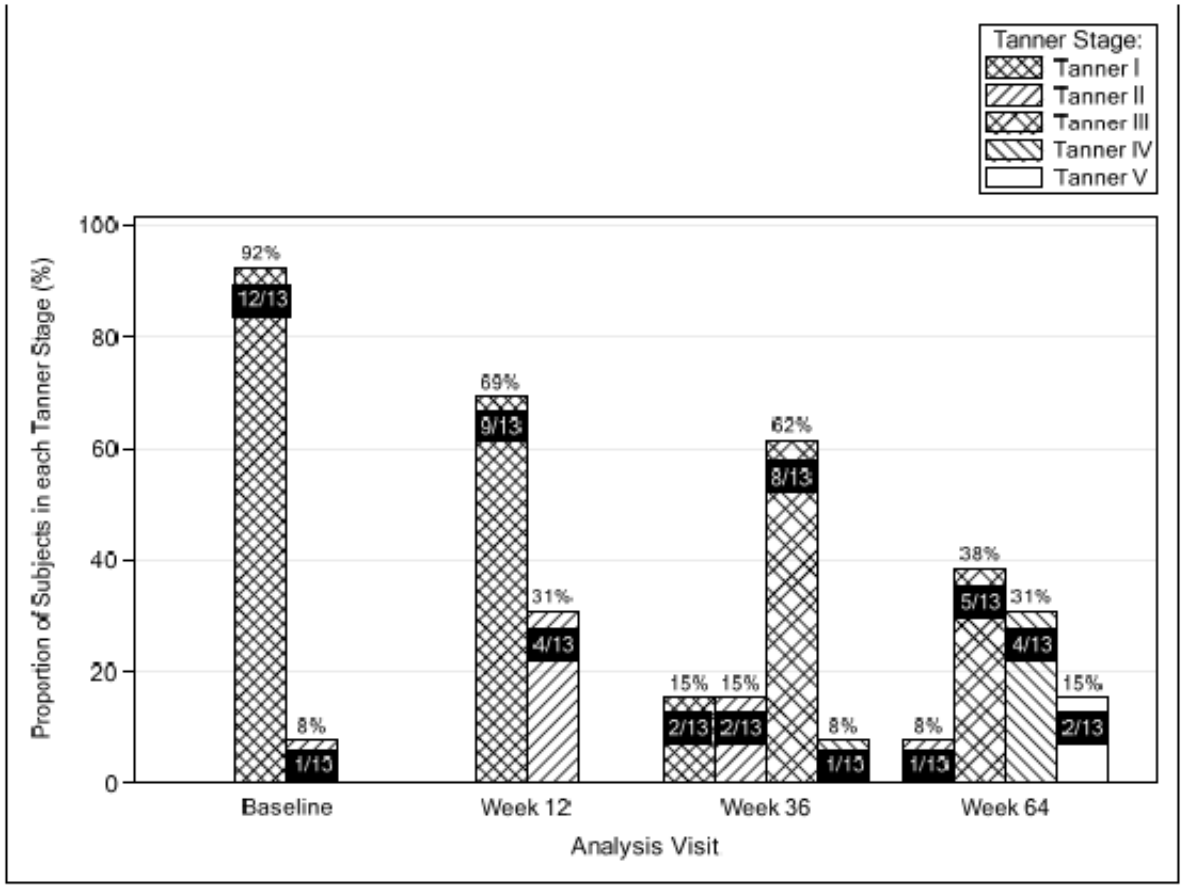
Genital Growth

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 36, most participants had progressed and were in mid puberty (Tanner III). 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 15). One participant had a genital assessment (Tanner staging) collected outside the Week 64 analysis window and was not included in the FAS analysis.

Pubic hair

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

Figure 15 Summary of Tanner stage over time Genital Growth



One participant had a missing value at Week 64.

Source: [P043MK8962: adam-adsl; adtsv]

By week 64 all but one study participant was at Tanner Stage ≥3 and 6 study participants were at Tanner stage IV or V for genital growth

Pubic hair development was similar in the 12 subjects who were Tanner Stage 1 or 2 at baseline. Seven subjects were Tanner Stage IV or V at week 64. Less than half of participants had achieved the final stages of pubertal change further suggesting that treatment duration was too short.

Development of secondary sexual characteristics is often a key outcome for the adolescent patients themselves in order to deal with the psychological distress that can be associated with sexual infantilism. Treatment duration should be adequate to support virilisation.

Secondary endpoint - Growth velocity

Participants demonstrated an increased linear growth in response to hCG, indicative of pubertal changes. Growth velocity at Week 36 (8.2 cm/year) and Week 64 (7.4 cm/year) was as expected in HH boys, who were responding to therapy.

The participants started at a mean pre-treatment height of 160.1 cm ±10.5 cm. At the end of the study, mean height was 169.3 cm ±8.4 cm. Data are summarised in Table 22 below.

It was 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. Changes in height and growth velocities

observed in study participants are generally consistent with the changes observed in boys with normally-timed puberty.

Table 22 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.

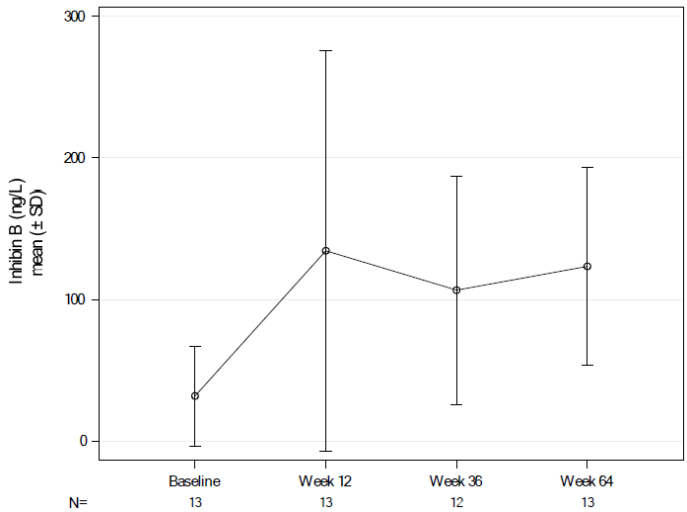
Source: [P043MK8962: adam-adsl; advs]

The study participants demonstrated increased growth velocity, with 8.2 cm/year at week 36 and 7.4 cm/year at week 64, which is generally consistent with the changes observed in boys with normally-timed puberty.

Secondary endpoint - Serum inhibin B concentrations

The inhibin B surge occurs immediately after initiation of CFA suggesting a direct stimulatory effect on the Sertoli cells. Inhibin levels increased from a mean 32 ± 35.3 ng/mL to 134.38 ± 141 ng/mL at week 12. Inhibin levels remain fairly constant over the remainder of the study. The observed increase in inhibin B levels is consistent with proliferation of Sertoli cells in response to CFA. The number of Sertoli cells is associated with sperm-producing capacity. The inhibin B response suggests that the testicles had matured and that the transition from AMH to inhibin B production in the testicles associated with puberty had occurred.

Figure 16 Summary of Inhibin B over time



Source: [P043MK8962: adam-adsl; adeh]

Inhibin levels increased from a mean 32 ± 35.3 ng/mL to 134.38 ± 141 ng/mL at week 12. Inhibin levels remain fairly constant over the remainder of the study. These inhibin values fall short of the inhibin values reported for healthy young men Winters et al 2013 (183-248pg/ml depending on BMI).

Secondary endpoint - Endocrine parameters (LH, Total T, T, E2, SHBG, and AMH)

LH and FSH

There was no evidence of spontaneous puberty (LH ≤3 IU) in any participant during the study (Table 23). Results of FSH levels were consistent with the pattern observed for LH.

Table 23 Summary of LH (IU/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	7 (53.8)	0.19	0.25 (0.24)	0.10	0.10	0.30	[0.10, 0.90]	0.93						
Priming Period															
Week 12	13	9 (69.2)	0.14	0.17 (0.13)	0.10	0.10	0.20	[0.10, 0.50]	0.78	-0.08 (0.15)	-0.10	0.00	0.00	[-0.40, 0.00]	-1.80
Combined Treatment Period															
Week 36	12	11 (91.7)	0.11	0.11 (0.03)	0.10	0.10	0.10	[0.10, 0.20]	0.27	-0.13 (0.25)	-0.20	0.00	0.00	[-0.80, 0.10]	-1.87
Week 64	13	12 (92.3)	0.11	0.12 (0.06)	0.10	0.10	0.10	[0.10, 0.30]	0.48	-0.14 (0.25)	-0.20	0.00	0.00	[-0.80, 0.20]	-1.83

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.

Testosterone (T)

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 (See Table 24; Figure 17 below).

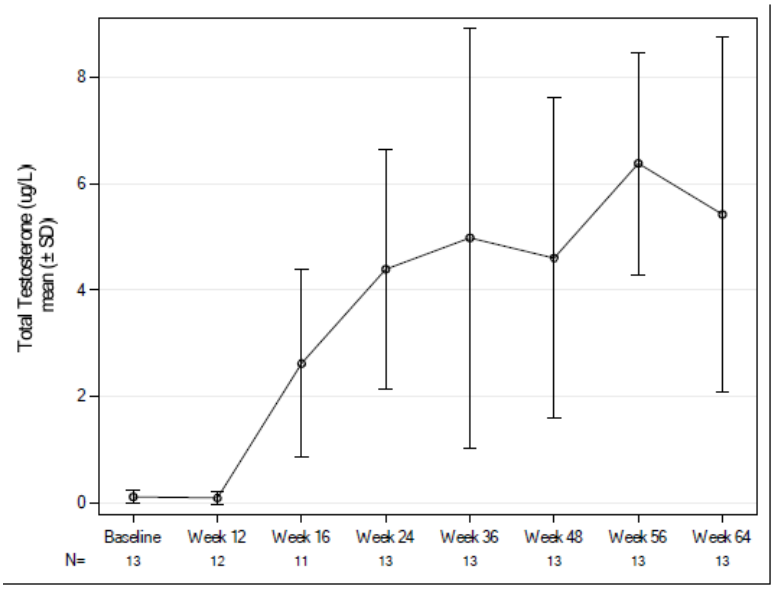
Table 24 Summary of total testosterone (ug/L) change from baseline by time point

			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 17 Summary of total testosterone over time

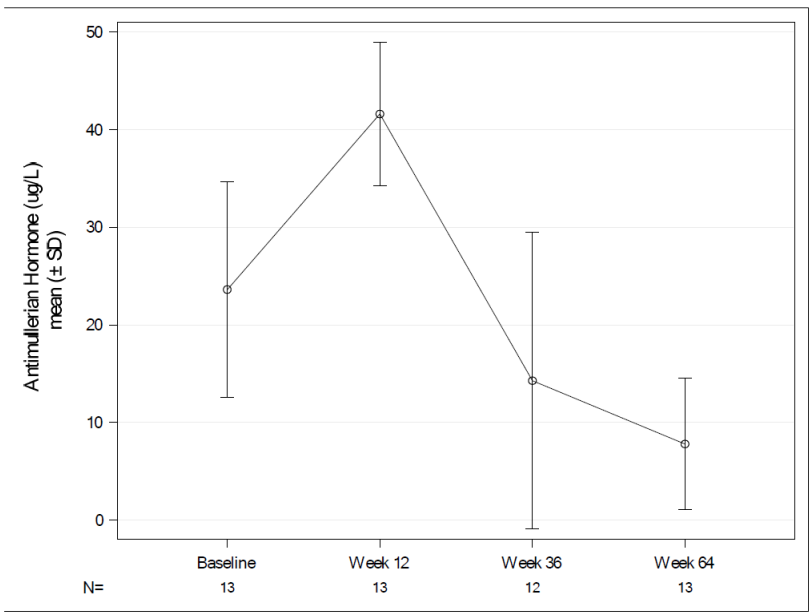


Source: [P043MK8962: adam-adsl; adeh]

Antimullerian Hormone (AMH)

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 18). These results suggest that pubertal progression in response to treatment resulted in further Sertoli cell and testicular maturation. The production of T in response to hCG led to a transition from AMH to inhibin B production in Sertoli cells, a finding associated with puberty.

Figure 18 Summary of AMH over time



Estradiol (E2)

The increased estradiol observed in response to treatment was consistent with the changes in total T levels and reflect peripheral aromatization of T (Table 25). No participant reported an AE of gynecomastia.

Table 25 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]

Sex Hormone-Binding Globulin (SHBG)

The production of SHBG in the liver is regulated by the ratio of T and E2 levels (among others). 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 26).

Table 261 Summary of SHBG (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)	45.63	53.19 (31.68)	34.40	43.10	64.70	[15.4, 124.0]	0.60						
Priming Period															
Week 12	13	0 (0.0)	46.47	54.56 (31.90)	25.10	54.60	75.80	[21.6, 119.0]	0.58	1.37 (15.68)	-9.60	-4.00	11.10	[-21.0, 32.3]	11.45
Combined Treatment Period															
Week 36	12	0 (0.0)	29.28	33.45 (17.09)	16.85	33.10	48.45	[14.4, 61.2]	0.51	-18.45 (25.51)	-17.95	-14.20	-1.15	[-74.6, 4.4]	-1.38
Week 64	13	0 (0.0)	26.29	29.47 (15.11)	17.10	26.00	32.40	[12.3, 58.8]	0.51	-23.72 (26.41)	-26.30	-18.40	-8.70	[-93.8, 12.4]	-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; adehsi]

<u>Secondary endpoint - Testicular sonographic pattern</u>

Participants with HH have a hypoechogenic pattern of the testicular parenchyma, which becomes more normo-echogenic with testicular maturation after gonadotropin treatment.

Changes in echogenicity in testicular sonographic patterns reported in participants were consistent with the testicular maturation observed (Table 27).

Table 27 Summary of testicular sonographic patterns change from baseline by time point

Timepoint	Left Testes n	(%)	Right Testes n	(%)
Subjects in population	13		13	
Priming Period				
Week 12				
Hypoechoic†	2	(15.4)	1	(7.7)
Isoechoic†	10	(76.9)	12	(92.3)
Hyperechoic†	1	(7.7)	0	(0.0)
Combined Treatment Period				
Week 36				
Hypoechoic†	2	(15.4)	1	(7.7)
Isoechoic†	10	(76.9)	9	(69.2)
Hyperechoic†	1	(7.7)	3	(23.1)
Week 64				
Hypoechoic†	2	(15.4)	0	(0.0)
Isoechoic†	8	(61.5)	10	(76.9)
Hyperechoic†	3	(23.1)	3	(23.1)

†in comparison with baseline testicular echogenicity.
% = number of subjects in each Sonographic pattern at timepoint/ number of subjects in population*100.

Ancillary analyses

Supportive analyses of testicular volume change

Supportive analyses of testicular volume change from baseline to Week 64 in the MITT population and completer populations were consistent with the results from the primary analysis (Table 28 and 29 below).

Table 28 Analysis of Testicular Volume (mL) Change from Baseline to Week 64 (Modified Intent-To-Treat Population)

	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	16	1.8	2.3	1.9	1.5	14.5	17.0	11.1	14.6	8.24	(6.19, 10.99)

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.

Table 29 Analysis of Testicular Volume (mL) Change from Baseline to Week 64 (Completers Population)

	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	15	1.6	1.9	1.4	1.5	14.6	17.3	11.4	15.8	9.12	(7.38, 11.26)

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.

Testicular volume changes from Week 12 to Week 64 in the FAS, and completer populations were consistent with the results from the primary analysis (Table 30 and 31).

Table 30 Analysis of Testicular Volume (mL) Change from Week 12 to Week 64 (FAS population)

	N	Week 12				Week 64				Model† Based Geometric Mean Ratio	
		Geometric Mean	Mean	SD	Median	Geometric Mean	Mean	SD	Median	Ratio‡	(95% CI)
Corifollitropin Alfa/hCG	13	2.5	2.8	1.7	2.4	12.9	14.5	6.8	12.7	5.14	(4.23, 6.25)

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.

Table 31 Analysis of Testicular Volume (mL) Change from Week 12 to Week 64 (Completers Population)

	N	Week 12				Week 64				Model† Based Geometric Mean Ratio	
		Geometric Mean	Mean	SD	Median	Geometric Mean	Mean	SD	Median	Ratio‡	(95% CI)
Corifollitropin Alfa/hCG	16	2.9	3.6	3.1	2.4	14.0	16.7	11.3	14.2	4.85	(4.12, 5.70)

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.

The analysis of testicular volume change from baseline to Week 64 by laterality in the FAS analysis populations, and analysis of testicular volume change from baseline to Week 12 and change from Week 12 to Week 64 (Table 32) were consistent with the results from the primary analysis.

Table 32 Analysis of Testicular Volume (mL) Change from Week 12 by Time Point and Laterality (FAS population)

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.

Summary of main study 043

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33 Summary of Efficacy for trial 043

Title: 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)	
Study identifier	P043MK8962

Design	Multi-center, single group, efficacy, pharmacokinetics, safety, open label intervention study evaluating the treatment of corifollitropin alfa (MK-8962; CFA) in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis in adolescent males with HH. The study included a screening period, priming period with CFA, combined treatment period with CFA and hCG for 52 weeks, and a follow-up visit. The primary efficacy objective is 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).		
	Duration of main phase: Screening Priming phase Combined treatment phase Duration of Extension phase:		64 weeks Up to 6 weeks 12 weeks with CFA alone 52 weeks of CFA and hCG not applicable
Hypothesis	Induction and/or restoration of puberty and induction and/or restoration of spermatogenesis in adolescent males with HH.		
Treatments groups	Adolescent males 14 to <18 years of age with HH		64 weeks, 12 weeks CFA alone, 52 weeks of CFA/ hCG, single-arm, n=17
	-		-
	-		-
Endpoints and definitions	Primary endpoint	Change in testicular volume	Mean 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.
	Secondary efficacy endpoint	Tanner Stage	Tanner Stage of pubertal development at Weeks 12, 36 and 64.
	Secondary efficacy endpoint	Growth velocity	Growth velocity at Weeks 36 and 64
	Secondary efficacy endpoint	Change in serum inhibin B	Change from baseline in serum inhibin B concentrations at Week 64
	Secondary efficacy endpoint	Changes in endocrine parameters	Changes from baseline in endocrine parameters LH, Total T, E2, SHBG, and AMH at Weeks 12, 36 and 64
Database lock	08-JUN-2020		
Results and Analysis			

Analysis description	**Primary Analysis - Efficacy**			
Analysis population and time point description	FAS population consisted of all participants, who had a baseline and at least 1 post-baseline measurement of testicular volume, had LH levels ≤3 IU/L during anytime of the study, and had received at least 12 weeks with CFA followed by 24 weeks of CFA and hCG and had no more than 4 weeks from the last dose of CFA when the last (testicular volume) measurement was made.			
Descriptive statistics and estimate variability	Treatment group	Adolescent males 14 to <18 years of age with HH	-	-
	Number of subject	N=17	-	-
	Primary endpoint: Change in testicular volume at week 64 (GM ratio in mL)	9.43 mL	-	-
	95% CI	7.44, 11.97	-	-
	Secondary endpoint: Tanner-Stage at weeks 12, 32, 63 (% in Stage III, IV and V)	0% 70% 84%	-	-
	-	-	-	-
	Secondary endpoint: Growth velocity at weeks 36 and 64 (cm/year)	8.2 cm/year 7.4 cm/year -	- -	- -
	Secondary endpoint: Change in serum inhibin B at week 64 (mean (SD) in ng/L)	91.46 (59.25) ng/L	-	-

	Secondary endpoint: Changes in endocrine parameters at weeks 12, 36 and 64 (mean SD)	LH: -0.08 (0.15); -0.13 (0.25); -0.14 (0.25) IU/L Total T: -0.01 (0.07); 4.87 (3.97); 5.31 (3.31) µg/L E2: 0.81 (2.90); 37.57 (28.73); 45.58 (41.09) ug/L AMH: 17.98 (8.39); 10.23 (15.69); -15.83 (11.58) ug/L SHBG: 0.04 (0.45); -0.53 (0.73); -0.68 (0.76) ug/dL	-	-

Analysis performed across trials (pooled analyses and meta-analysis)

N/A.

Clinical studies in special populations

N/A.

Supportive study(ies)

See 'Clinical Pharmacology' section.

2.4.3. Discussion on clinical efficacy

In the Extension of indication procedure, an additional indication was claimed for Elonva (Corifollitropin alfa; CFA) for treatment of adolescent males (14 to less than 18 years) with hypogonadotropic hypogonadism (HH), in combination with human Chorionic Gonadotropin (hCG). CFA is a recombinant gonadotropin, which has the same mechanism of action as FSH, but different PK properties, i.e. a longer T1/2 which reduces the injection frequency. The dose recommendation is based on body weight, i.e. 100 micrograms for body weight ≤ 60 kg; 150 micrograms for body weight > 60 kg. The dose regimen is Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG. No treatment duration has been recommended.

The rationale for the pre-treatment with CFA in HH adolescents is to mimic the sequential gonadotropin release pattern of normal puberty, i.e. at the initial stage of puberty, FSH secretion induces proliferation of Sertoli cells in the prepubertal testis, leading to an increase in gonadal size. Due to subsequent LH secretion, Leydig cells in the testes start production of T, resulting in cessation of Sertoli cell proliferation, followed by maturation of the Sertoli cells, resulting in the completion of spermatogenesis. This sequential exposure

of the pubertal testes to FSH and LH is thought to be necessary for normal testicular development and subsequent future fertility.

The clinical pharmacology program consisted of two Pop PK studies, on which results the dose to be used in the clinical trial in male adolescents with HH is based.

Pivotal data for efficacy and safety of the selected CFA regimen in this new indication were collected via study P043.

The study protocol of study 043 has been assessed and agreed upon in the paediatric investigation plan (PIP) for CFA (PIP decision: P/0143/2019). Further, the protocol and study results of P043 were assessed and agreed within the Article 46 procedure EMEA/H/C/ 001106/P46/019, submitted earlier this year.

Design and conduct of clinical study P043

P043 was a multi-centre, open-label, single-group study evaluating the treatment of CFA in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis with a total maximum duration of 73 weeks in adolescent males with HH. This single-arm study is considered acceptable, since HH is a rare disease and recruitment of a sufficient number of subjects for both treatment and comparator arm would be unfeasible. The study was performed from February 2017 until June 2020.

Proposed dose strength, which is in relation to weight, is the same as the current posology for women, and combined regimen with hCG were considered adequate, as discussed in the clinical pharmacology section. The proposed sample size and methodology are in line with the assessment of the protocol as agreed in the PIP (PIP-decision P/0143/2019), and therefore acceptable.
To mimic the sequential gonadotropin release pattern of normal puberty, i.e. at the initial stage of puberty, a 2-stage treatment approach proposed to the treatment of HH which is started with CFA treatment (priming period) to stimulate proliferation of immature Sertoli cells and germ cells. This increases testicular size and increases circulating inhibin B levels. Subsequently, a combined treatment of CFA + hCG is given to stimulate Leydig cells in the testes to start production of testosterone for the development of male secondary sexual characteristics, pubertal growth spurt and maturation of Sertoli cells. Although the proposed sample size and methodology are in line with the assessment of the protocol as agreed in the PIP, it is difficult to fully evaluate long-term outcomes of adolescent patients treated with this regimen in this small open label study with no randomisation in a small heterogeneous population. However, HH is a rare condition and the challenges with recruitment are acknowledged. There is no quantitative measure of achievement of spermatogenesis in this study, though increased MTV, decreasing anti-Müllerian hormone levels and increases in Inhibin B levels were suggestive of initiation of spermatogenesis.

Patient management once pubertal development has been achieved, will include long-term treatment with testosterone to maintain secondary sexual characteristics. This has been included in section 4.4 of the SmPC. Transition from paediatric to adult treatment is also addressed in section 4.4 of the SmPC.

Study participants

At least 15 treatment-naïve adolescent male participants of 14 to <18 years of age with the diagnosis of HH, either congenital or acquired with onset before puberty, were to be enrolled in the study. The inclusion and exclusion criteria were acceptable and reflect the pre-puberty HH male population with pre-gonadarche testes.

Efficacy endpoints

The primary and secondary objectives and endpoints were considered adequate for the specific male HH population with appropriate parameters for evaluation of the pubertal development and therefore acceptable and was in line with the agreed PIP (PIP decision: P/0143/2019).

The primary efficacy endpoint is described as the 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).

Key secondary efficacy endpoints concerned the Tanner stage of pubertal development at Weeks 12, 36, and 64, growth velocity at Weeks 36 and 64, change from baseline in serum inhibin B concentrations at Week 64 and changes from baseline in endocrine parameters LH, Total T, T, E2, SHBG, and AMH at Weeks 12, 36, and 64.

Efficacy data and additional analyses

Patient flow

17 patients were enrolled in the study across 9 sites in 4 countries: Mexico (n=1), Brazil (n=4), Russia (n=11) and Italy (n=1). Only one patient was recruited from Europe, with the rest of the population was recruited outside the EU. Since the efficacy and safety analyses are based on a common biological mechanism linking treatment to outcome, there is in general no reason to expect that the findings differ across geographic regions. This is supported by public literature indicating baseline characteristics of the participants in study P043 to be comparable to the baseline characteristics reported for adolescent males with HH from EU countries at the start of treatment (Barrio R et al, Fertil Steril. 1999 Feb;71(2):244-8; Giagulli VA et al, J Sex Med. 2011;8:3471-8; Raivio T et al, Eur J Endocrinol 2007;156:105-11).

The number of patients who completed the study was high with 94% (16/17). One patient discontinued due to the occurrence of an adverse event (see 'safety' section). Almost half of the patients (n=8, 47%) did have protocol deviations, which were mostly related to study procedures and consequently few missing data. None of the deviations were classified as serious and they are not expected to affect the findings.

Demographics and disease characteristics

The 17 participants, who were included in the study, can be considered representative of pre-pubertal HH patients based on Tanner stages and hormone levels. Thirteen patients were included in the full analysis set (FAS). These were subjects who received any dose of CFA and who had a baseline of at least one post-baseline measurement of testicular volume.

Of note, the mean age of the patients was 15.5 years, with a majority over 16 years. The patients, included in the study, were older than adolescent males, who normally start puberty at around the age of 13. However, this is expected given the rationale for selecting the lower age limit of 14 years, as the diagnosis of HH in adolescent males younger than 14 years is difficult to establish, and the likelihood of HH as the diagnosis is higher in males who are 14 years and older. Additionally, delayed puberty is not generally treated (for the induction of secondary sexual characteristics) before the age of 14 years. However, the older age is not expected to have consequences for the outcome of the study.

Treatment of subjects who initiate treatment age 17 may require treatment past age 18 years until the desired induction of puberty and maturation of Sertoli cells has been reached. The wording of the indication in section 4.1 of the SmPC should state adolescent males 14 years and older and this wording was implemented in the Product Information.

Only one study participant was from the EU. Baseline characteristics of the participants in Study P043 were generally comparable to the baseline characteristics of the cohorts of HH adolescents identified in 4 published studies that included European HH adolescents (Rohayem Clinical Endocrinology 2017; 86: 75-87; Barrio Fertility and Sterility 1999;71(2):244-248 and Raivio Eur J Endocrinol 2007; 156:105–11. Giagulli). The underlying aetiology of HH varied across studies and the P043 trial had the fewest patients with diagnosed KS (n=1/17) and the greatest percentage of patients with HH without olfaction deficit (n=14/17). The clinical features of male hypogonadism experienced by KS patients are at the more severe

end of the spectrum and therefore are expected to have a similar response to treatment as subjects in study P043.

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.

Regarding the duration of the use of CFA and hCG, it was noticed that the length of the treatment periods differed among the included patients, although the study was set up for a total treatment period of 64 weeks. The mean duration of combined CFA and hCG was 442 days (range 294 to 462 days) and 352 days (range 210 to 371 days), respectively. Further, the dose of hCG applied varied between patients. All subjects received at least 12 weeks of CFA prior to starting hCG. Further, most patients were exposed for a median total treatment duration of 64 weeks. One patient suffered from an AE and discontinued treatment at 42 weeks and two patients had shorter treatment duration due to a switch in dose strength from 100 to 150 µg. It is therefore considered that the treatment duration of CFA followed by CFA + hCG was generally 64 weeks. Further, the hCG dose was allowed to vary in each subject and dose was titrated based on individual response of the subject so that both testosterone and oestrogen levels were maintained in an acceptable range. This explains that the hCG dose could range from 500 to 5000 IU based on subject response and therefore the overall hCG dose varied substantially.

Efficacy

Primary endpoint

The primary endpoint for efficacy was shown by an increase in testicular volume, measured as the sum of volumes of left and right testes by ultrasound. In the priming period on CFA alone, with the aim to stimulate FSH receptors on Sertoli cells, 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 at baseline to 12.9 mL, mean fold increase of 9.43 (95% CI of 7.44, 11.97) mL. It was 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 as the testicular volume observed at the end of normally-timed puberty is ≥24 mL (Rohany et al; 2017).

While it may be possible to treat HH adolescents with gonadotropins for a longer duration, the exposure to gonadotropins at the start of puberty is likely to increase the chances of successful induction of spermatogenesis when fertility is desired in the future. Testicular growth and the hormonal profile induced during therapy in study P043 suggest that future fertility is therefore likely to be preserved in these males unlike the situation in HH adolescents treated exclusively with hCG or T to induce masculinization in adolescence.

A background discussion with reference to clinical guidelines and recent scientific literature was provided, to support their claim that mimicking the sequential gonadotropin release pattern of normal puberty with the proposed sequential treatment at pubertal age will likely improve the chances of future fertility.

Secondary endpoints

One of the key secondary endpoints concerned the Tanner Stage of pubertal development of the patients. 92% of subjects went to higher Tanner stages (III, IV and V) during the course of the study. Furthermore, all participants had developed pubic hair.

Additionally, growth velocity from baseline to Week 64 was 8.2 cm/year at week 36 and 7.4 cm/year at week 64, which are generally consistent with the changes observed in boys with normally-timed puberty.

Also, the serum inhibin B levels, a surrogate marker of spermatogenesis, increased on the use of CFA alone to week 12. Levels were maintained up to week 64. Levels rose from a mean at Baseline of 51.3 pg/mL(±46.92) to a mean of 98.6 pg/mL (±44.28) at week 52 visit. This suggests that the testicles had matured and that the transition from AMH to inhibin-B production seen in the testicles with puberty has occurred.

Regarding the endocrine parameters, total testosterone levels increased from Week 12 in response to hCG to a 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. The decreased 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. Changes in E2 (increase) and SHBG levels (decrease) were consistent with increased testosterone production. LH and FSH levels remained unchanged, suggesting that spontaneous puberty did not occur.

The results from the secondary objectives can therefore be considered supportive of the primary endpoint.

2.4.4. Conclusions on the clinical efficacy

P043 was a multi-centre, open-label, single-group study evaluating the treatment of CFA in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis with a total maximum duration of 73 weeks in adolescent males with HH.

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

The wording of the indication has been amended as previously requested to allow subjects who have started treatment at the age of 17 to be treated past the age of 18 years. Moreover, the amended dose recommendations, including the treatment duration, for Elonva in adolescent males have been amended in the SmPC.

2.5. Clinical safety

Introduction

One of the primary safety objectives was to evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962, and adverse events, laboratory assessments, and vital sign measurements.

Safety analyses were performed in the ASaT population of the P043 study which included all 17 participants who received at least 1 dose of study medication. AEs were collected from the time of informed consent until the follow-up visit (21 to 45 days after the last day of administration of CFA).

Patient exposure

See section 'extent of exposure'. The mean duration of CFA and hCG was 442 days (range 294 to 462 days) and 352 days (range 210 to 371 days), respectively.

Adverse events

Overall 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. Summary table during the priming period and combined treatment period is presented below in Table 34.

Table 34 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 (88.2)	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 rhinorrhoea (n=2, 8%) (Table 35).

Table 35 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)**
Craniopharyngioma		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)

Sixteen of the 17 participants experienced at least one AE. The most commonly reported AEs were from the SOCs Investigations (52.9%), Infections and infestations (41.2%) and Reproductive system and breast disorders (41.2%). 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. This overdose case is further discussed below. In the priming period, the most frequently reported AEs (>10%) were headache (n=3) and rhinorrhoea (n=2). This seems to be in line with what is been expected for CFA.

Drug-related adverse events

In the overall treatment period, drug-related AEs (as determined by the investigator) were reported for 9 participants (Table 36). 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).

Table 36 Drug-related adverse events

	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)

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).

The most commonly reported drug-related AEs were generally from similar SOCs as observed in all commonly reported AEs, except for spermatocele, see discussion above. This seems to be in line with what is been expected for CFA and hCG. The AEs are in general sufficiently addressed in section 4.8 of the SmPC and presented in a separate ADR table.

Intensity

- All AEs were mild to moderate in intensity. AEs reported with moderate intensity included acne, allergic rhinitis, back pain, craniopharyngioma, 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 event/deaths/other significant events

Deaths

There were no deaths reported in this study.

Serious adverse events

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

The narrative of this patients is as follows:

Event Type	AE Preferred Term	Severity	Study Day (relative to treatment)
SAE	Craniopharyngioma	Moderate	Day 282
Discontinuation Due to AE	Craniopharyngioma	Moderate	Day 282

Age	Sex	Race	Ethnicity
16 years	Male		

Primary Diagnosis	Participant was diagnosed with hypogonadotropic hypogonadism approximately 2 years prior to first dose of study medication.

Medical History	Craniopharyngioma, Optic atrophy, Hemianopia, Postoperative hypopituitarism, Secondary hypogonadism, Testicular microlithiasis, Varicocele
History of Medical/ Surgical Procedures	None
Prior Medications	desmopressin, hydrocortisone, levothyroxine sodium, somatropin
Concomitant Medications	desmopressin, hydrocortisone, levothyroxine sodium, somatropin

MK-8962 150 µg once every 2 weeks was started on Day 1 for the treatment of HH and was continued for 12 weeks, followed by combined treatment with MK-8962 150 µg once every 2 weeks and hCG starting at 1500 IU twice a week on Day 86.

The participant had a medical history of craniopharyngioma approximately 12 years before study entry. On Day 113 the nonserious AE of increased blood testosterone was reported. The dose of hCG was reduced from 1500 IU to 1000 IU on Day 128. On Day 113 the laboratory result for testosterone was 59.4997 nmol/L (NR: 3.47- 41.64 nmol/L); on Day 1 the laboratory result for testosterone was 0.0999 nmol/L. Increased blood testosterone resolved on Day 170 (14.7998 nmol/L).

On Day 282 the participant experienced headache, and on Day 292, a brain MRI showed craniopharyngioma (SAE, recurrence of craniopharyngioma, moderate intensity, onset Day 282). On Day 296 the participant experienced moderate vision impairment compared with the basal level. A neurological examination confirmed the diagnosis of recurrence of craniopharyngioma. Study medication was discontinued on Day 298 in response to recurrence of craniopharyngioma, with the last dose of MK-8962 administered on Day 282 and the last dose of hCG administered on Day 292, and the participant entered posttreatment follow-up. The participant had received 21 doses of MK-8962. An ophthalmologist examination on Day 299 showed worsening of optic nerve atrophy in the right eye. The participant underwent transsphenoidal endoscopic resection of the craniopharyngioma on Day 348. Recurrence of craniopharyngioma resolved on Day 351. Headache had resolved and vision had recovered to the basal level. Results from an MRI performed on Day 403 showed residual tissue of craniopharyngioma.

The participant completed the study on Day 450, with the last contact on the same day.

In the opinion of the investigator, recurrence of craniopharyngioma was considered not related to MK-8962 or hCG and increased blood testosterone was considered related to hCG and not related to MK-8962.

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.

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.

The case narrative is as follows:

Event Type	AE Preferred Term	Severity	Study Day (relative to treatment)
Accidental overdose	Accidental overdose	Mild	Day 373

Age	Sex	Race	Ethnicity
16 years	Male		

Primary Diagnosis	Participant was diagnosed with hypogonadotropic hypogonadism approximately 3 years prior to first dose of study medication.

Medical History	Asthma, Rhinitis allergic, Hypopituitarism, Obesity, Secondary hypogonadism, Myopia
History of Medical/ Surgical Procedures	None
Prior Medications	levothyroxine sodium, somatropin
Concomitant Medications	levothyroxine sodium, somatropin, azithromycin, hexetidine, ambroxol hydrochloride

MK-8962 150 µg once every 2 weeks was started on Day 1 for the treatment of HH and was continued for 12 weeks, followed by combined treatment with MK-8962 150 µg once every 2 weeks and hCG starting at 1000 IU twice a week starting on Day 86 and then hCG dose was increased to 1500 IU twice a week starting on Day 135.

On Day 358 the investigator increased the dose of hCG to 2000 IU twice a week. On Day 370 hCG 5000-IU vials were dispensed to the participant at an unscheduled visit. On Day 373 accidental overdose (nonserious AE, accidental overdose with adverse effect, mild intensity) was reported when the participant was administered the entire 5000-IU vial of hCG per dose (5000 IU hCG twice a week) from Days 373 to 390. Retraining of the participant and the participant's guardians was performed, accidental overdose resolved on Day 390, and hCG 2000 IU twice a week was administered starting on Day 394. On Day 394 laboratory test results showed increased E2 (nonserious AE, mild intensity), which occurred due to overdose, and testosterone was within the normal range.

The participant completed treatment, with the last dose of MK-8962 and hCG administered on Day 450. Increased E2 resolved on Day 474 (Table). The participant completed the study on Day 474, with the last contact on the same day.

In the opinion of the investigator, accidental overdose was considered not related to MK-8962 or hCG and increased E2 was considered related to hCG and not related to MK-8962.

Hepatic Safety

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

Cerebrovascular disorder

One participant with underlying hypopituitarism underwent a routine endocrine evaluation and was discovered to have elevated prolactin levels and 'cerebral discirculation' on Day 295. Upon further inquiry, this AE term meant 'a minimal disorder of cerebral blood flow that often has no clinical signs and is not a sign of a stroke or a cerebrovascular accident'. An MRI on Day 349 reported no changes or other symptoms from previous examinations. The AE of 'cerebral discirculation' was ongoing and stable at the final visit. The investigator assessed the AE as not related to study medication. The verbatim term of 'cerebral discirculation' was mapped to the PT of cerebrovascular disorder.

Laboratory findings

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.

Vital signs

Vital signs (including blood pressure, heart rate, and body weight), and clinical laboratory parameters (serum haematology and chemistry) were measured at visits during the overall treatment period and at the follow-up visit. No notable changes from baseline in systolic or diastolic blood pressure or heart rate were observed through Week 64. The only notable change was in height, which is expected in adolescent

males undergoing puberty. Expected increases in weight with no notable changes in BMI were observed through Week 64. Data are summarised in the Table 37 below.

Table 37 Summary of Change from Baseline in Vital Signs by Time Point

Timepoint	N	Baseline Value			Observed Value			Change from Baseline		
		Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]
Participants in population	17									
Systolic Blood Pressure (mmHg)										
Priming Period										
Week 12	17	107.5 (14.2)	114.0	[84.0, 122.0]	111.7 (10.5)	113.0	[90.0, 123.0]	4.2 (9.5)	1.0	[-12.0, 25.0]
Combined Treatment Period										
Week 36	17	107.5 (14.2)	114.0	[84.0, 122.0]	112.8 (12.1)	117.0	[87.0, 127.0]	5.2 (9.2)	2.0	[-5.0, 30.0]
Week 64	16	106.7 (14.2)	112.0	[84.0, 122.0]	112.2 (10.8)	114.0	[90.0, 124.0]	5.5 (10.2)	3.0	[-12.0, 25.0]
Diastolic Blood Pressure (mmHg)										
Priming Period										
Week 12	17	65.5 (6.9)	65.0	[50.0, 78.0]	67.5 (7.1)	69.0	[60.0, 86.0]	2.0 (6.0)	0.0	[-7.0, 15.0]
Combined Treatment Period										
Week 36	17	65.5 (6.9)	65.0	[50.0, 78.0]	66.5 (7.8)	63.0	[60.0, 87.0]	1.1 (6.1)	0.0	[-8.0, 12.0]

Timepoint	N	Baseline Value			Observed Value			Change from Baseline		
		Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]
Diastolic Blood Pressure (mmHg) (Continues)										
Week 64	16	65.8 (7.0)	66.0	[50.0, 78.0]	68.1 (8.1)	69.0	[50.0, 81.0]	2.3 (6.8)	1.0	[-10.0, 18.0]
Heart Rate (beats/min)										
Priming Period										
Week 12	17	75.6 (9.0)	75.0	[64.0, 92.0]	77.5 (8.8)	79.0	[63.0, 94.0]	1.8 (4.1)	1.0	[-4.0, 11.0]
Combined Treatment Period										
Week 36	17	75.6 (9.0)	75.0	[64.0, 92.0]	74.2 (8.8)	72.0	[61.0, 88.0]	-1.5 (6.8)	0.0	[-19.0, 7.0]
Week 64	16	76.4 (8.8)	75.5	[65.0, 92.0]	76.8 (8.7)	78.0	[60.0, 91.0]	0.4 (7.0)	0.5	[-10.0, 16.0]
N = number of subjects with baseline and postbaseline test results. SD = standard deviation.										

Timepoint	N	Baseline Value			Observed Value			Change from Baseline		
		Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]
Participants in population	13									
Weight (kg)										
Priming Period										
Week 2	13	59.6 (17.2)	53.8	[34.3, 91.6]	59.9 (17.1)	53.9	[34.5, 91.7]	0.3 (0.5)	0.2	[-0.4, 1.4]
Week 4	13	59.6 (17.2)	53.8	[34.3, 91.6]	60.2 (17.0)	54.2	[34.5, 90.5]	0.6 (0.9)	0.5	[-1.1, 2.0]
Week 12	13	59.6 (17.2)	53.8	[34.3, 91.6]	61.1 (17.8)	54.9	[34.5, 90.2]	1.5 (2.3)	1.2	[-1.4, 6.6]
Combined Treatment Period										
Week 16	13	59.6 (17.2)	53.8	[34.3, 91.6]	62.1 (18.0)	54.7	[37.5, 89.3]	2.5 (3.5)	2.0	[-2.3, 11.8]
Week 24	13	59.6 (17.2)	53.8	[34.3, 91.6]	64.1 (18.3)	58.5	[41.8, 92.3]	4.5 (4.4)	4.0	[-0.2, 16.5]

Timepoint	N	Baseline Value			Observed Value			Change from Baseline		
		Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]
Weight (kg) (Continues)										
Week 36	13	59.6 (17.2)	53.8	[34.3, 91.6]	68.3 (19.8)	59.2	[48.4, 101.4]	8.7 (6.6)	7.8	[0.6, 23.7]
Week 48	13	59.6 (17.2)	53.8	[34.3, 91.6]	69.9 (19.2)	60.0	[49.8, 101.6]	10.3 (7.2)	11.0	[-0.3, 28.0]
Week 64	12	60.7 (17.5)	54.5	[34.3, 91.6]	73.6 (20.6)	62.5	[52.0, 106.3]	13.0 (8.0)	12.8	[1.4, 32.7]
Height (cm)										
Priming Period										
Week 12	13	160.6 (10.5)	160.1	[142.0, 179.4]	162.1 (10.3)	162.5	[143.3, 179.5]	1.5 (1.0)	1.5	[0.1, 4.2]
Combined Treatment Period										
Week 36	13	160.6 (10.5)	160.1	[142.0, 179.4]	166.2 (8.8)	167.0	[148.8, 178.8]	5.7 (2.8)	5.5	[-0.6, 10.8]
Week 64	12	160.1 (10.8)	160.1	[142.0, 179.4]	169.3 (8.4)	169.8	[153.3, 179.2]	9.2 (4.6)	9.3	[-0.2, 18.3]

Timepoint	N	Baseline Value			Observed Value			Change from Baseline		
		Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]	Mean (SD)	Median	[Min,Max]
Body Mass Index (kg/m2)										
Priming Period										
Week 12	13	22.9 (5.1)	22.5	[16.5, 30.4]	23.0 (5.3)	23.0	[16.2, 30.1]	0.1 (0.8)	0.1	[-1.0, 1.4]
Combined Treatment Period										
Week 36	13	22.9 (5.1)	22.5	[16.5, 30.4]	24.5 (5.5)	21.7	[18.7, 33.7]	1.6 (2.2)	1.6	[-2.0, 5.7]
Week 64	12	23.4 (5.0)	23.6	[16.5, 30.4]	25.4 (5.5)	23.3	[18.5, 33.7]	2.1 (2.2)	2.3	[-1.7, 4.9]
N = number of subjects with baseline and postbaseline test results. SD = standard deviation.										

Safety in special populations

The current submission provides information in support of the existing CFA safety profile with respect to adolescent boys (14 to 17 years old). It does not provide new safety information on use in pregnancy or when lactating, overdose, drug interactions, drug abuse, withdrawal or rebound, effects on ability to drive machinery, or on impairment of mental ability.

Based on the cumulative data in the clinical development program, no safety signal has been identified. In the 1 participant who discontinued study medication due to a SAE of recurrent craniopharyngioma, testicular volume decreased after discontinuation.

The number of participants in study P043 is low. Despite the small group size, baseline and end-of-treatment characteristics are generally similar to males with HH presenting to endocrinology clinics. These findings suggest that the results from study P043 will be applicable to the general population of adolescents with HH N/A.

Discontinuation due to adverse events

One participant discontinued study medication due to an SAE of craniopharyngioma, but continued in the study. The investigator considered this SAE not related to study medication.

Post marketing experience

Safety of CFA in Female Population

Elonva (CFA) is approved in the female population for COS.

In post-marketing reports, hypersensitivity reactions, both local and generalized including bruising, pain, redness, swelling, itching, and rash, were reported, the majority of which were mild and transient in nature. Very rarely, generalized reactions including erythema and rash have been observed.

Thromboembolic events, both in association with and separate from OHSS, have been reported following fertility treatment with gonadotropins, including Elonva. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities.

Safety of CFA in Adult Male Population

In adult males with HH (P031), AEs that were reported included headache, acne, rash, increased blood testosterone, increased blood estradiol, epididymal cyst, gynecomastia, and injection site reaction.

Safety of CFA PK studies

Safety information collected in the PK studies, that have been discussed earlier in the AR, is in line with the findings in the P043 trial.

2.5.1. Discussion on clinical safety

One of the primary objectives was to evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962, and adverse events, laboratory assessments, and vital sign measurements.

Safety analyses were performed in the ASaT population of the P043 study which included all 17 participants who received at least 1 dose of study medication. AEs were collected from the time of informed consent until the follow-up visit (21 to 45 days after the last day of administration of CFA). Safety information from the adult study (P031) and the PK studies are in line with safety data from the main trial. No safety concerns have been identified.

Adverse events

Sixteen of the 17 participants experienced at least one AE. The most commonly reported AEs were from the SOCs Investigations (52.9%), Infections and infestations (41.2%) and Reproductive system and breast disorders (41.2%). 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).

The cases of spermatocele, were not considered as drug-related, although the number of reported cases was relatively high with 5 out of 17 patients (29%). However, the incidence rate of spermatocele is consistent with the background incidence in published studies in patients with HH. Based on the cumulative review of the 5 cases, in one case the event was resolved during treatment and therefore a clear association of the use of CFA and the occurrence of the event of spermatocele within this case is considered unlikely. The other 4 cases had not resolved at the conclusion of the study. It can be agreed that the initiated increase in testicular volume during this study can be considered an important confounding factor, which may have made these testicular cysts more apparent on imaging as the study progressed. Considering also the high prevalence of spermatocele in the general population, the suggested contribution of congenital anomalies in this area, and the lack of a mechanism of action, it is acceptable to not consider spermatocele an ADR.

Drug-related adverse events

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). The most commonly reported drug-related AEs were generally from similar SOCs as observed in all commonly reported AEs, except for spermatocele. This seems to be in line with what is been expected for CFA and hCG. The AEs are sufficiently addressed in section 4.8 of the SmPC and presented in a separate table.

Serious adverse events

All AEs were mild to moderate in intensity.

There were no deaths reported in this study. Only one SAE has been reported. This SAE concerned a recurrent craniopharyngioma. The patient discontinued study medication, but remained in the study. Based on the information of the narrative, it can be agreed that CFA of hCG has not contributed to the SAE, as the participant had a medical history of craniopharyngioma approximately 12 years before study entry. Craniopharyngiomas are generally benign but are known to recur after resection. Although it is unknown whether this concerns a malignant form, it is known that malignant craniopharyngiomas are very rare, but are associated with poor prognosis. The reported SAE seems therefore not to be related to the trial medication.

Adverse events of special interest

AEs of special interest for CFA were anti-MK-8962 antibodies (i.e., anti-drug antibodies; ADA), and hypersensitivity reactions.

Anti-MK-8962 antibodies

No cases of confirmed anti-MK-8962 antibodies were reported.

Hypersensitivity

There were 3 participants with hypersensitivity AEs: gingival oedema and rhinitis allergic (n=1), dermatitis contact (n=1) and pruritus (n=1). These AEs were considered not related to study medication and resolved while the participant was still on study medication.

One accidental overdose case of hCG has been reported and not with CFA. Consequently, E2 became increased and was thus considered related to hCG, but the AE was resolved at the end of the study.

Also one AE of 'cerebral discirculation' was observed. The AE was ongoing and stable at the final visit. The investigator assessed the AE as not related to study medication, which can be agreed.

Of note, no clinical studies have been performed in elderly, patients with hepatic and/or renal impairment and younger children (< 14 years of age), but this has been sufficiently described in the SmPC.

Clinical laboratory data

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

Vital signs

No notable changes from baseline in systolic or diastolic blood pressure or heart rate were observed through Week 64. Expected increases in weight and height with no notable changes in BMI were observed through Week 64.

Long-term safety

Long term safety data in adolescent males who had received this sequential treatment of CFA priming followed by combined CFA + hCG treatment at pubertal age for hypogonadotropic hypogonadism will be monitored via routine pharmacovigilance (see RMP assessment). However, according to current guidelines, after completion of this treatment, these patients will receive long-term treatment with testosterone to maintain secondary sexual characteristics.

2.5.2. Conclusions on clinical safety

Based on the study data of Study P043, CFA in combination with hCG indicated for male adolescents suffering from HH was generally well tolerated. There were no severe AEs and no SAEs, except one SAE of recurrence of pre-existing craniopharyngioma leading to discontinuation, but was considered not-related to the study medication. Further, no cases of confirmed anti-MK-8962 antibodies were reported. Clinical laboratory data did not show unexpected values or changes due to study medication and no notable changes from baseline through week 64 were observed in the vitals sign assessments.

The main drug-related adverse events were increased E2 and increased blood T. The distribution appears to be in line with what has been expected for this type of medication and the use of hCG. The current safety profile of CFA does not suggest any safety concerns.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

2.6. Risk management plan

The MAH was requested to submit an updated RMP version 10 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10 is acceptable.

The CHMP endorsed the Risk Management Plan version 10 with the following content:

Safety concerns

Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to implement some minor editorial and formatting changes throughout the Product Information.

Please refer to the attached Product Information, which includes all changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

It is agreed with the MAH that the few changes to the package leaflet proposed in this variation are limited to the information in section 1 ("What Elonva is and what it is used for), section 3 ("How to use Elonva") and section 4 ("Possible side effects") to add information on the use of Elonva in adolescent males.

There are no other proposed changes to the content of the package leaflet; in particular the key messages for the safe use of the medicinal product are not impacted. There are no proposed changes to the content

of the Instructions for Use. Just replacement of one picture to a more gender friendly picture is proposed. Furthermore, the design, layout and format of the package leaflet and the Instructions for Use are not be affected by the proposed revisions.

It is therefore agreed with the MAH that the proposed revisions in the Package leaflet do not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Elonva (Corifollitropin alfa; CFA) is a recombinant gonadotropin and is designed as a sustained follicle stimulant with the same pharmacodynamic profile as (rec) follicle stimulating hormone (FSH), but with a markedly prolonged duration of FSH activity. The medicinal product is currently indicated for Controlled Ovarian Stimulation (COS) in combination with a Gonadotropin Releasing Hormone (GnRH) antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program.

The following additional indication was approved: *Elonva is indicated for the treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG).*

Hypogonadotropic hypogonadism (HH) is lack of, or inadequate, production of gonadotropins, i.e. 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 GnRH secretion by the hypothalamus. This results in insufficient testicular function and deficiencies in endogenous testosterone production and spermatogenesis. When gonadotropin deficiency occurs before puberty (prepubertal), puberty is delayed or absent.

3.1.2. Available therapies and unmet medical need

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, to be initiated before hCG treatment.

It is noted that to compensate for the lack of LH, hCG is given instead of LH. LH and hCG share the same alfa subunit and bind to the Leydig cell receptors, but hCG has a half-life of 36 hours, while the half live of LH is only 30 minutes.

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.

The rationale for the pre-treatment with FSH in HH adolescents is to mimic the sequential gonadotropin release pattern of normal puberty, i.e. at the initial stage of puberty, FSH secretion induces proliferation of Sertoli cells in the prepubertal testis, leading to an increase in gonadal size. Due to subsequent LH secretion, Leydig cells in the testes start production of T, resulting in cessation of Sertoli cell proliferation, followed by maturation of the Sertoli cells, leading to the completion of spermatogenesis. This sequential exposure of the pubertal testes to FSH and LH is thought to be necessary for normal testicular development and subsequent future fertility.

Elonva (Corifollitropin alfa; CFA) is a recombinant gonadotropin, which has the same mechanism of action as FSH, but different PK properties, since it has a markedly prolonged duration of FSH activity due to a longer T1/2. A single injection of corifollitropin alfa replaces 7 days of daily recombinant FSH. The Applicant claimed that since treatment of HH in males usually requires long-term treatment, the use of CFA may result in fewer medication errors and improved compliance. The dose recommendation is, based on body weight, 100 or 150 micrograms of Elonva once every two weeks for 12 weeks, followed by concomitant administration of Elonva (once every 2 weeks) with hCG.

3.1.3. Main clinical studies

In line with the approved PIP (PIP-decision: P/0143/2019), one clinical, multi-centre, open-label, single-group trial (P043) was submitted to evaluate the treatment of CFA in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis with a total maximum duration of 73 weeks in 17 adolescent males from 14 to 18 years of age with HH enrolled from 9 study sites in 4 countries in Mexico, Brazil, Russia and Italy. The trial consisted of a prime period of 12 weeks with CFA alone and a combined treatment period of 52 weeks with CFA in combination with the use of hCG. The protocol and study results of P043 were assessed and agreed within the Article 46 procedure EMEA/H/C/ 001106/P46/019, submitted in October 2020.

3.2. Favourable effects

Increase in testicular volume

The primary endpoint for efficacy was shown by an increase in testicular volume, measured as the sum of volumes of left and right testes by ultrasound. In the priming period on CFA alone, with the aim to stimulate FSH receptors on Sertoli cells, 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).

It was 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).

Supportive secondary endpoints

One of the key secondary endpoints concerned the Tanner Stage of pubertal development of the patients. 92% of subjects went to higher Tanner stages (III, IV and V) during the course of the study. Furthermore, all participants had developed pubic hair. Additionally, growth velocity from baseline to Week 64 was 8.2 cm/year at week 36 and 7.4 cm/year at week 64, which is generally consistent with the changes observed in boys with normally-timed puberty. Also, the serum inhibin B levels, a surrogate marker of spermatogenesis, increased on the use of CFA alone to week 12. Levels were maintained through week 64. Regarding the endocrine parameters, levels (T, E2, AMH, SHBG) reached normal ranges as observed in adolescent boys and were maintained through week 64. The results from the secondary objectives can therefore be considered supportive of the primary endpoint.

Study design

Regarding the duration of the use of CFA and hCG, from the data provided, it is clear that all subjects received at least 12 weeks of CFA prior to starting hCG. Further, most patients were exposed for a median total duration of 64 weeks. Further, the hCG dose was allowed to vary in each subject as the dose was titrated based on individual response of the subject so that both testosterone and oestrogen levels were maintained in an acceptable range. Therefore, the hCG dose could range from 500 to 5000 IU based on subject response and therefore the overall dose varied significantly. The hCG dose applied (500-5000 IU) also is added to section 4.2 of the SmPC.

Baseline data

One subject from Europe was included in this study. Since the efficacy and safety analyses are based on a common biological mechanism linking treatment to outcome, there is in general no reason to expect that baseline characteristics and findings in HH patients differ across geographic regions. Further, compared to other published studies conducted in adolescents in the EU, Study P043 trial had the fewest patients with diagnosed KS and the greatest percentage of patients with HH without olfactory impairment. The Applicant adequately justified with background literature that the clinical features of male hypogonadism experienced by KS patients can be expected to have a similar response to treatment as subjects in study P043.

3.3. Uncertainties and limitations about favourable effects

The open label uncontrolled nature of this study makes it difficult to fully evaluate the treatment effect of the combination of CFA and hCG.

Although pubertal development (induced with hCG treatment) was apparent in all study participants by week 64, only 6 study participants were at Tanner stage IV or V for genital growth and 7 were Tanner Stage IV or V at week 64 for pubic growth. Development of secondary sexual characteristics is often a key outcome for the adolescent patients themselves. Treatment duration should be long enough to ensure adequate virilisation. This aspect is reflected in section 4.2.

After achieving adult gonadal development to a satisfactory level, long-term treatment with testosterone is required in these patients to maintain these and refers to a number of literature reports that outline the need to also manage the side effects of testosterone treatment and address psychosocial aspects of CHH along with the long-term health effects of treatment in terms of cardiovascular health, and bone metabolism. The statements are included in section 4.4 of the SmPC regarding the need and the purpose for long-term treatment of patients with HH with testosterone and that no follow-up efficacy or safety data are available once the combined treatment with CFA and hCG at pubertal age has been completed.

A baseline inhibin B cut-off of 35 pg/mL was included in the inclusion criteria. Mean Inhibin B levels at baseline were 44.9 ng/L with a median of 25 ng/L but with a range of 11-144. For the 2 subjects with a

baseline inhibin B level >35 ng/L it can be concluded that they nevertheless were correctly diagnosed. The diagnosis of the 3rd patient remains unclear based on course of TV growth. However, CHH is a heterogeneous disorder and variability in biomarker levels is not unusual.

Regarding the primary endpoint, it was 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, although this is as expected considering the exposure to gonadotropins for 64 weeks, while normal puberty lasts for 2 to 3 years.

The SmPC indicates that duration of treatment may be necessary for 52 weeks or longer. In the absence of follow-up data after the treatment has ended, no conclusions can be drawn whether this treatment also increases future fertility chances. However, on theoretical grounds and published data, an association between degree of testicular volume and initiation of spermatogenesis may increase future success with fertility-inducing treatments in adult males and therefore, the induction of testicular growth and spermatogenesis in adolescent males with HH is likely to increase future fertility chances.

The treatment of subjects who initiate treatment at age 17 may require treatment past age 18 years until the desired induction of puberty and maturation of Sertoli cells has been reached. The wording of the indication in section 4.1 of the SmPC states that the treatment is indicated in adolescent males aged 14 years and older. Section 4.4 has been updated to indicate that after completed pubertal transition with the current treatment regimen, long-term treatment with testosterone is required in these patients to maintain secondary sexual characteristics, but that follow-up treatments have not been evaluated.

3.4. Unfavourable effects

One of the primary objectives was to evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962, and adverse events, laboratory assessments, and vital sign measurements, in the ASaT population of the P043 study, which included all 17 participants who received at least 1 dose of study medication. Based on the study data of Study P043, CFA in combination with hCG indicated for male adolescents suffering from HH was generally well tolerated.

Sixteen of the 17 participants experienced at least one AE. The most commonly reported AEs were from the SOCs Investigations (52.9%), Infections and infestations (41.2%) and Reproductive system and breast disorders (41.2%). Overall, the most common AEs (>20%) were spermatocele (n=5), increased E2 (n=5), increased blood T (n=4), and headache (n=4). Nine participants had drug-related AEs. All AEs were mild to moderate in intensity.

The number of cases of spermatocele were relatively high with 5 out of 17 patients (29%). Considering also the high prevalence of spermatocele in the general population, the suggested contribution of congenital anomalies in this area of disease, and the lack of a mechanism of action, spermatocele is not considered an ADR.

There were no deaths reported in this study. Only one SAE has been reported, which concerned a recurrence of pre-existing craniopharyngioma leading to discontinuation and was considered not-related to the study medication.

Further, no cases of confirmed anti-MK-8962 antibodies were reported. Clinical laboratory data did not show unexpected values or changes due to study medication and no notable changes from baseline through week 64 were observed in the vitals sign assessments.

Long term safety data in adolescent males with HH who have received CFA at pubertal age for induction of gonadal development and initiation of secondary sexual characteristics will be monitored via routine pharmacovigilance.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 38 Effects Table for Elonva (Corifollitropin alfa; CFA) (data cut-off: JUNE2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Population			N=17	-		P043
Primary endpoint*	Change in testicular volume (baseline to week 12)	GM ratio (95% CI) in mL	1.83 (1.58, 2.13) mL (*increase from 1.4 mL to 2.5 mL*)	-	Consistent effect seen in additional sub-analyses.	P043
Primary endpoint*	Change in testicular volume (baseline to week 64)	GM ratio (95% CI) in mL	9.43 (7.44, 11.97) mL (*increase from 1.4 mL to 12.9 mL*)	-	Consistent effect seen in additional sub-analyses.	P043
Secondary endpoint	Tanner Stage of pubertal development at Weeks 12, 36 and 64.	% in Stage III, IV and V	0% 70% 84%	-	Supportive for efficacy hCG	P043
Secondary endpoint	Growth velocity at Weeks 36 and 64.	cm/year	8.2 cm/year 7.4 cm/year	-	Supportive for efficacy hCG	P043
Secondary endpoint	Change from baseline in serum inhibin B concentrations at Week 64.	mean (SD) in ng/L	- 91.46 (59.25) ng/L	-	Supportive for primary efficacy endpoint	P043
Secondary endpoint	Changes from baseline in endocrine parameters LH, Total T, E2, SHBG, and AMH at Weeks 12, 36 and 64	Mean (SD)	**LH**: -0.08 (0.15); -0.13 (0.25); -0.14 (0.25) IU/L **Total T**: -0.01 (0.07); 4.87 (3.97); 5.31 (3.31) µg/L **E2**: 0.81 (2.90); 37.57 (28.73); 45.58 (41.09) ug/L **AMH**: 17.98 (8.39); 10.23 (15.69); -15.83 (11.58) ug/L **SHBG**: 0.04 (0.45); -0.53 (0.73); -0.68 (0.76) ug/dL	-	Supportive for primary efficacy endpoint and efficacy hCG	P043
Unfavourable Effects						
	Most common AEs (>20%) - spermatocele - increased E2 - increased blood T - headache	N (%)	5 (29.4) 5 (29.4) 4 (23.5) 4 (23.5)	-	Expected event, inherent to mechanism of action, some already reported as 'very common' in PI.	P043
	Confirmed cases with anti-MK-8962 antibodies	N (%)	0 (0)	-	No immunogenicity reported in the 17 study participants.	P043

*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).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applied regimen of 12 weeks of pre-treatment with CFA and subsequently 52 weeks of CFA combined with hCG is proposed for the new indication of treatment of adolescent males (14 years and older) with HH. The single uncontrolled study in 17 patients with HH had a generally appropriate study design and included a sufficient number of subjects (n=17) representative for the rare target population. The results showed a clinically relevant increase in testicular volume accompanied by appropriate evidence of pubertal progression as assessed by Tanner stage, growth velocity and other pubertal developmental parameters.

Regarding the other pubertal developmental parameters, increased testosterone levels, growth velocity and progression of puberty (Tanner III, IV and V) indicated appropriate responses to CFA priming followed by combined treatment with CFA + hCG. Decreasing anti-müllerian hormone levels and increases in Inhibin B levels were suggestive of initiation of spermatogenesis. These findings are highly relevant for future fertility in these males unlike the situation in HH adolescents treated exclusively with hCG or T to induce masculinization in adolescence and might even be of benefit for a better quality of life in terms of an improved body image and potentially future fertility prospects.

Regarding safety, in general, the clinical safety profile appeared to be well tolerated by the target population in terms of the frequency, nature and severity of adverse events. Only one SAE has been reported, not-related to the study medication. Further, no ADAs were detected and there were no clinically meaningful changes in clinical laboratory data or vitals sign assessments. Longer-term safety data beyond completion of this CFA + hCG treatment at pubertal age will be monitored via routine pharmacovigilance.

3.7.2. Balance of benefits and risks

In terms of benefit, the applied regimen of 12 weeks of pre-treatment with CFA and subsequently 52 weeks of CFA combined with hCG showed adequate induction of testicular development, measured by a significant and clinically relevant increase in testicular volume from prepubertal to mid pubertal size, in adolescent males with HH. Important findings on development of secondary sexual characteristics by increased Tanner Stage, growth velocity and endocrine parameters were supportive of an induction of pubertal development and induction of spermatogenesis. The use of CFA appeared to be well-tolerated with an acceptable safety profile and without unexpected safety signals over a treatment period of 64 weeks. Long term safety data in adolescent males with HH who have received CFA followed by CFA + hCG for gonadal development and induction of secondary sexual characteristics at pubertal age will be monitored via routine pharmacovigilance.

While it is recognised that HH is considered a rare disease and the number of adolescent patients in the pivotal study is limited, the natural history of HH is well-characterised, the mechanism of action/role of the product in the development of puberty is well-established and the safety profile of the product is well-characterised as it is has been marketed since 2010. Based on these considerations, the data in the dossier at hand is considered sufficiently comprehensive to support a positive conclusion on the balance of benefits and risks of CFA.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Elonva is positive in the treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adolescent males (14 years and older) with hypogonadotropic hypogonadism, in combination with human Chorionic Gonadotropin (hCG) for Elonva, based on final results of the paediatric study P043. Study P043 was an open-label, non-comparative, multi-center safety and efficacy study of corifollitropin alfa in association with hCG in male adolescents with hypogonadotropic hypogonadism, part of the paediatric investigation plan; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement some minor editorial and formatting changes throughout the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0143/2019 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.