Clinical trial results:
A phase III, multi-center, open label, uncontrolled trial to investigate the efficacy and safety of MK-8962 (corifollitropin alfa) in combination with human Chorionic Gonadotropin (hCG) in inducing increased testicular volume and spermatogenesis in adult men with hypogonadotropic hypogonadism who remain azoospermic when treated with hCG alone (Phase III; Protocol No. MK-8962-031-00 [also known as SCH 900962, P07937])

Summary

EudraCT number	2012-001258-25
Trial protocol	DE ES IT GB PL Outside EU/EEA
Global end of trial date	08 April 2015

Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	20 April 2016

Trial information

Trial identification

Sponsor protocol code	P07937

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709331
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: MK-8962-031

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000306-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2015
Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will assess if corifollitropin alfa (MK-8962), when administered in combination with human chorionic gonadotropin (hCG), will increase testicular volume in men with HH who remain azoospermic after treatment with hCG alone.

Hypothesis: The lower limit of the 95% confidence interval for the geometric mean increase in testicular volume from Day 1 to Week 52 is greater than one.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	18
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Twenty-three participants entered the 16-week pretreatment phase with hCG. At the end of the pretreatment phase, 18 participants were enrolled in the 52-week combined treatment phase.

Period 1

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

Arms

Arm title	Corifollitropin alfa 150 µg + hCG

Arm description:

During a 16-week pretreatment phase, participants received twice-weekly subcutaneous (SC) injections of human chorionic gonadotropin (hCG) 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Arm type	Experimental
Investigational medicinal product name	Corifollitropin alfa
Investigational medicinal product code	
Other name	MK-8962
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Corifollitropin alfa 150 µg by SC injection, once every 2 weeks for 52 weeks

Investigational medicinal product name	human chorionic gonadotropin (hCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

hCG 1500 or 3000 international units (IU) by SC injection twice a week; administered alone for 16 weeks (pretreatment phase) and then in combination with corifollitropin alfa for 52 weeks (combined treatment phase)

Number of subjects in period 1	Corifollitropin alfa 150 µg + hCG
Started	18
Completed	17
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Corifollitropin alfa 150 µg + hCG

Reporting group description:

During a 16-week pretreatment phase, participants received twice-weekly subcutaneous (SC) injections of human chorionic gonadotropin (hCG) 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Reporting group values	Corifollitropin alfa 150 µg + hCG	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
Age Continuous | Units: years arithmetic mean standard deviation	 31.5 ± 8.8	 -	
Gender, Male/Female Units: Participants			
Female	0	0	
Male	18	18	

Subject analysis sets

Subject analysis set title	Corifollitropin alfa 150 µg + hCG
Subject analysis set type	Safety analysis

Subject analysis set description:

During a 16-week pretreatment phase, participants received twice-weekly SC injections of hCG 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Subject analysis set title	Corifollitropin alfa 150 µg + hCG
Subject analysis set type	Full analysis

Subject analysis set description:

During a 16-week pretreatment phase, participants received twice-weekly SC injections of hCG 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Reporting group values	Corifollitropin alfa 150 µg + hCG	Corifollitropin alfa 150 µg + hCG	
Number of subjects	18	17	
Age categorical Units: Subjects			

Age Continuous | Units: years arithmetic mean standard deviation	± 	± 	
Gender, Male/Female Units: Participants			
Female	0		
Male	18		

End points

End points reporting groups

Reporting group title	Corifollitropin alfa 150 µg + hCG

Reporting group description:

During a 16-week pretreatment phase, participants received twice-weekly subcutaneous (SC) injections of human chorionic gonadotropin (hCG) 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Subject analysis set title	Corifollitropin alfa 150 µg + hCG
Subject analysis set type	Safety analysis

Subject analysis set description:

During a 16-week pretreatment phase, participants received twice-weekly SC injections of hCG 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Subject analysis set title	Corifollitropin alfa 150 µg + hCG
Subject analysis set type	Full analysis

Subject analysis set description:

During a 16-week pretreatment phase, participants received twice-weekly SC injections of hCG 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.

Primary: Change from Baseline in Log-Transformed Testicular Volume at Week 52

End point title	Change from Baseline in Log-Transformed Testicular Volume at Week 52[1]

End point description:

Participants underwent testicular ultrasound in the pretreatment phase at Weeks -16, -8, -1; and during the combined treatment phase at Baseline (predose, Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. The testicular volume was measured as the sum of volumes of left and right testes. The mean change from Day 1 in log-transformed testicular volume was analyzed using a mixed model with a fixed effect for time point and a random effect for the participant. For each time point, the mean change from Day 1 to that time point and the associated 95% confidence interval (CI) was calculated. The geometric mean fold change in testicular volume and its 95% CI was obtained by exponentiation. This endpoint was based on the Full Analysis Set (FAS) population, which consisted of all participants who received any dose of corifollitropin alfa and who had a baseline and at least one post-baseline measurement of testicular volume.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single-arm study and only within-arm statistical analysis was performed. Therefore no between-group statistical analysis was conducted for the primary end point Change from Baseline in Log-Transformed Testicular Volume at Week 52.

End point values	Corifollitropin alfa 150 µg + hCG			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Fold change				
geometric mean (confidence interval	2.3 (2.03 to			

95%)	2.62)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Anti-Corifollitropin Alfa Antibodies

End point title	Percentage of Participants with Anti-Corifollitropin Alfa Antibodies[2]

End point description:

Blood samples were collected for assessment of anti-corifollitropin alfa antibodies in the pretreatment phase at Week -16 and Week -1; during the combined treatment phase at Weeks 4, 16, 28, 50, and 52; and at Week 53 at the post-treatment follow-up visit. This endpoint was based on the All-Subjects-as-Treated (ASaT) population, which consisted of all participants who received any dose of corifollitropin alfa.

End point type	Primary

End point timeframe:

Up to Week 57

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single-arm study. Therefore no between-group statistical analysis was conducted for the primary end point Percentage of Participants with Anti-Corifollitropin Alfa Antibodies.

End point values	Corifollitropin alfa 150 µg + hCG			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Induced Spermatogenesis Resulting in a Sperm Count ≥1x10^6/mL at or before Week 52

End point title	Percentage of Participants with Induced Spermatogenesis Resulting in a Sperm Count ≥1x10^6/mL at or before Week 52

End point description:

Semen samples were produced by masturbation after at least 48 hours of sexual abstinence and collected for evaluation in the pretreatment phase at Week -1, and during the combined treatment phase at Weeks 16, 28, 40, and 52. This endpoint was based on the FAS population, which consisted of all participants who received any dose of corifollitropin alfa and who had a baseline and at least one post-baseline measurement of testicular volume.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Corifollitropin alfa 150 µg + hCG			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 0%)	77.8 (52.4 to 93.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 57 weeks	
Adverse event reporting additional description:	
The Safety Analysis was based on the ASaT population, which consisted of all participants who received any dose of corifollitropin alfa.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Corifollitropin alfa 150 µg + hCG
Reporting group description:	
During a 16-week pretreatment phase, participants received twice-weekly SC injections of hCG 1500 or 3000 IU. Eligible participants were then enrolled in the combined treatment phase in which they received a single dose of corifollitropin alfa 150 µg by SC injection once every 2 weeks for 52 weeks. In addition, eligible participants continued to receive twice-weekly hCG injections on the same schedule begun during the pretreatment phase.	

Serious adverse events	Corifollitropin alfa 150 µg + hCG		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Corifollitropin alfa 150 µg + hCG		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)		
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood testosterone increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Oestradiol increased			

subjects affected / exposed occurrences (all) Testicular scan abnormal subjects affected / exposed occurrences (all) Blood testosterone decreased subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 4 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 3 / 18 (16.67%) 4		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Reproductive system and breast disorders Breast tenderness subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders			

Acne subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Alopecia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2013	The primary reason for the amendment was the addition of text to describe describe the interim analysis (IA) of pharmacokinetic (PK) data after 6 participants completed 6 months of corifollitropin alfa and hCG combined-treatment. The purpose of the IA was to provide data to support preparations for a study in adolescent hypogonadotropic hypogonadism (HH) males (including dose-selection) and development of a PK-model, if necessary, to predict corifollitropin alfa exposure in adolescents. No efficacy or safety analyses were performed in the IA, except that the number of participants with anti-corifollitropin alfa antibodies (Tier-1 Safety Endpoint) was determined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported