Clinical trial results:
Phase IIa, Double-Blind, Placebo-Controlled, Study of ESN364 Administered for 12 Weeks to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Women Presenting With Polycystic Ovarian Syndrome

Summary

EudraCT number	2014-004409-34
Trial protocol	BE AT NL
Global end of trial date	01 May 2017

Results information

Result version number	v1 (current)
This version publication date	12 May 2018
First version publication date	12 May 2018

Trial information

Trial identification

Sponsor protocol code	ESN364-PCO-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ogeda S.A.
Sponsor organisation address	Rue Adrienne Bolland, Gosselies, Belgium, 6047
Public contact	Clinical Trial Disclosure, Ogeda S.A, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Ogeda S.A, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy of two doses of ESN364 versus placebo when administered for 12 weeks to decrease total testosterone (TT) levels.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) and with applicable local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 2015
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	Netherlands: 10
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Georgia: 7
Worldwide total number of subjects	73
EEA total number of subjects	66

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	73

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Pre-menopausal woman between 18 and 45 years inclusive at screening, diagnosed with PCOS and biochemical hyperandrogenism mandatory. Oligomenorrhea or oligo-ovulation and polycystic ovaries on ultrasound. In total, 105 subjects were screened of which 73 randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding was achieved by the double-dummy method with placebo identical in smell, taste, and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	ESN364 60 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ESN364
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg ESN364 once daily for 12 weeks

Arm title	ESN364 180 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ESN364
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

180 mg ESN364 once daily for 12 weeks

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Placebo oral use once daily for 12 weeks

Number of subjects in period 1	ESN364 60 mg	ESN364 180 mg	Placebo
Started	23	23	27
Completed	21	17	26
Not completed	2	6	1
Consent withdrawn by subject	1	4	1
Adverse event, non-fatal	-	1	-
In and Exclusion criteria not met	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ESN364 60 mg
Reporting group description: -	
Reporting group title	ESN364 180 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	ESN364 60 mg	ESN364 180 mg	Placebo
Number of subjects	23	23	27
Age categorical Units: Subjects			
Adults (18 - 45) years	23	23	27
Age continuous Units: years arithmetic mean full range (min-max)	 27 21 to 41	 26 19 to 34	 27 18 to 44
Gender categorical Units: Subjects			
Female	23	23	27

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			
Adults (18 - 45) years	73		
Age continuous Units: years arithmetic mean full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	73		

End points

End points reporting groups

Reporting group title	ESN364 60 mg
Reporting group description: -	
Reporting group title	ESN364 180 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Efficacy: Change from baseline in Total Testosterone (TT) at Week 12

End point title	Efficacy: Change from baseline in Total Testosterone (TT) at Week 12[1]

End point description:

Change from baseline in Total Testosterone (TT) at Week 12
Total testerone (nmol/L)
Intent-to-treat (ITT) Population: all randomized subjects who received at least one dose of study drug and who have post-baseline efficacy data.

End point type	Primary

End point timeframe:

From baseline through week 12

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: Descriptive only

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[2]	23[3]	27[4]	
Units: nmol/L				
arithmetic mean (standard deviation)	-0.16 (± 0.457)	-0.68 (± 0.561)	-0.04 (± 0.526)	

Notes:

[2] - Actual number of participants used in in the analysis = 17

[3] - Actual number of participants used in in the analysis = 15

[4] - Actual number of participants used in in the analysis = 24

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change in Total Testosterone (TT) from baseline to Week 9 (at trough PK levels)

End point title	Efficacy: Change in Total Testosterone (TT) from baseline to Week 9 (at trough PK levels)

End point description:

Change in Total Testosterone (TT) from baseline to Week 9 (at trough PK levels)
Actual values in Total testosterone (TT)
ITT Population

End point type	Secondary

End point timeframe:

From baseline to Week 9

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	23	27	
Units: Timepoint				
arithmetic mean (standard deviation)				
Baseline	1.65 (± 0.655)	2.16 (± 1.011)	2.01 (± 0.803)	
At Week 6	1.48 (± 0.727)	1.41 (± 0.519)	1.91 (± 0.872)	
At Week 9	1.58 (± 0.635)	1.51 (± 0.405)	1.83 (± 0.732)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change in Menstrual Cycle as Measured by Menses

End point title	Efficacy: Change in Menstrual Cycle as Measured by Menses

End point description:

Change in Menstrual Cycle as Measured by Menses
Change in frequency of menses per treatment arm and per time point
ITT population

End point type	Secondary

End point timeframe:

From treatment (Week 12) to Follow-Up (Week 18)

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[5]	23[6]	27[7]	
Units: Frequency of menses				
arithmetic mean (standard deviation)				
Treatment - Week 12	1.0 (± 0.93)	0.3 (± 0.56)	1.6 (± 1.83)	
Follow-Up - Week 18	0.4 (± 0.60)	0.3 (± 0.45)	0.5 (± 0.58)	

Notes:

[5] - N = 21: Follow-Up - Week 18

[6] - N = 19: Follow-Up - Week 18

[7] - N = 26: Follow-Up - Week 18

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change in Menstrual Cycle as Measured by Spotting

End point title	Efficacy: Change in Menstrual Cycle as Measured by Spotting

End point description:

Change in Menstrual Cycle as Measured by Spotting
Change in frequency of spotting per treatment arm and per time point
ITT population

End point type	Secondary

End point timeframe:

From treatment (Week 12) until Follow-Up (Week 18)

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[8]	23[9]	27[10]	
Units: Frequency of spotting				
arithmetic mean (standard deviation)				
Treatment - Week 12	0.4 (± 0.78)	0.2 (± 0.39)	0.9 (± 1.63)	
Follow-Up - Week 18	0.0 (± 0.00)	0.2 (± 0.50)	0.3 (± 0.67)	

Notes:

[8] - N = 21: Follow-Up - Week 18

[9] - N = 19: Follow-up - Week 18

[10] - N = 26: Follow-Up - Week 18

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change in Menstrual Cycle as Measured by Inter-Menstrual Bleeding

End point title	Efficacy: Change in Menstrual Cycle as Measured by Inter-Menstrual Bleeding

End point description:

Change in Menstrual Cycle as Measured by Inter-Menstrual Bleeding
Changes in frequency of intermenstrual bleeding per treatment arm and time point
ITT population

End point type	Secondary

End point timeframe:

From treatment (Week 12) until Follow-Up (Week 18)

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[11]	23[12]	27[13]	
Units: Frequency of intermenstrual bleeding				
arithmetic mean (standard deviation)				
Treatment - Week 12	0.2 (± 0.39)	0.1 (± 0.29)	0.4 (± 1.01)	
Follow-Up - Week 18	0.3 (± 0.72)	0.0 (± 0.00)	0.1 (± 0.27)	

Notes:

[11] - N = 21: Follow-Up - Week 18

[12] - N = 19: Follow-Up - Week 18

[13] - N = 26: Follow-Up - Week 18

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change from Baseline in Polycystic Ovarian Syndrome questionnaire (PCOSQ) score at Week 6 and Week 12

End point title	Efficacy: Change from Baseline in Polycystic Ovarian Syndrome questionnaire (PCOSQ) score at Week 6 and Week 12

End point description:

Change from Baseline in Polycystic Ovarian Syndrome questionnaire (PCOSQ) score per time point. The questions concern health and health-related issues for women with Polycystic Ovary Syndrome on how they feel related to: Emotions, Body hair, Weight, Infertility problems, Menstrual problems. Polysystic Ovary Syndrome Questionnaire (PCOSQ) was used to measure the health-related quality of life (HRQoL), on a scale from 1 to 7, with 1 representing the greatest possible impairment and 7 representing the least impairment.
ITT population

End point type	Secondary

End point timeframe:

Week 6 and Week 12 (End of Treatment)

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	23	27	
Units: Score				
arithmetic mean (standard deviation)				
Emotions total score Week 6	-0.2 (± 0.73)	-0.2 (± 0.88)	-0.2 (± 0.72)	
Emotions total score Week 12	0.0 (± 0.86)	-0.6 (± 1.15)	-0.1 (± 0.85)	
Body hair total score Week 6	-0.1 (± 0.81)	-0.2 (± 0.64)	-0.5 (± 0.73)	
Body hair total score Week 12	-0.1 (± 0.76)	-0.3 (± 1.06)	-0.3 (± 0.84)	
Weight total score Week 6	-0.2 (± 0.71)	0.1 (± 1.05)	-0.1 (± 1.07)	
Weight total score Week 12	-0.4 (± 0.85)	0.0 (± 1.07)	-0.3 (± 1.09)	
Infertility problems total score Week 6	0.3 (± 1.09)	0.0 (± 0.95)	-0.2 (± 0.99)	
Infertility problems total score Week 12	0.1 (± 1.18)	-0.6 (± 1.39)	0.1 (± 1.22)	
Menstrual problems total score Week 6	0.1 (± 1.07)	0.5 (± 1.71)	0.2 (± 1.06)	
Menstrual problems total score Week 12	0.6 (± 1.17)	0.3 (± 1.21)	0.3 (± 1.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change from Baseline in Sex Hormone Level to Week 6, 12 and 18

End point title	Efficacy: Change from Baseline in Sex Hormone Level to Week 6, 12 and 18

End point description:

Change from Baseline in Sex Hormone Level to Week 6, 12 and 18
Change from Baseline in Sex Hormone Concentrations per Time Point
Estradiol (E2), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Progesterone (P4), LH:FSH ratio, Total Testosterone (TT), Sex Hormone Binding Globulin (SHBG)
ITT Population

End point type	Secondary

End point timeframe:

Week 6, Week 12 and Week 18 (Follow Up Period)

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	23	27	
Units: Time point				
arithmetic mean (standard deviation)				
E2 (pmol/L) Week 6	-134.5 (± 333.38)	-45.3 (± 67.74)	24.8 (± 383.74)	
E2 (pmol/L) Week 12	-106.5 (± 259.44)	-88.8 (± 137.52)	118.8 (± 645.44)	
E2 (pmol/L) Follow-up	-111.7 (± 255.25)	-57.0 (± 150.30)	7.8 (± 163.10)	
FSH (IU/L) Week 6	-0.32 (± 3.598)	-0.95 (± 1.206)	-0.05 (± 2.153)	
FSH (IU/L) Week 12	-1.36 (± 4.078)	-1.29 (± 2.090)	-0.41 (± 2.139)	
FSH (IU/L) Follow-up	-1.33 (± 4.723)	-0.25 (± 2.623)	-0.33 (± 2.123)	
LH (mIU/mL) Week 6	-6.90 (± 17.889)	-8.79 (± 6.976)	0.24 (± 11.819)	
LH (mIU/mL) Week 12	-10.66 (± 16.726)	-9.23 (± 9.694)	-1.78 (± 6.365)	
LH (mIU/mL) Follow-up	-6.82 (± 19.456)	-3.69 (± 10.650)	-1.84 (± 7.731)	
P4 (ng/mL) Week 6	-2.08 (± 4.088)	-0.51 (± 1.301)	-0.66 (± 2.648)	
P4 (ng/mL) Week 12	-1.81 (± 4.719)	-0.69 (± 1.275)	0.77 (± 6.641)	
P4 (ng/mL) Follow-up	-0.98 (± 5.704)	-0.36 (± 1.313)	0.53 (± 5.243)	
LH/FSH ratio Week 6	-1.01 (± 1.699)	-1.36 (± 1.131)	-0.15 (± 1.150)	
LH/FSH ratio Week 12	-1.29 (± 1.754)	-1.39 (± 1.188)	-0.26 (± 0.829)	
LH/FSH ratio Follow-up	-0.50 (± 1.729)	-0.66 (± 1.322)	-0.32 (± 0.935)	
TT (nmol/L) Week 6	-0.15 (± 0.417)	-0.94 (± 0.855)	-0.10 (± 0.541)	
TT (nmol/L) Week 12	-0.16 (± 0.457)	-0.68 (± 0.561)	-0.04 (± 0.526)	
TT (nmol/L) Follow-up	-0.11 (± 0.508)	-0.47 (± 0.970)	-0.10 (± 0.529)	

SHBG (nmol/L) Week 6	-4.73 (± 13.995)	-0.25 (± 6.776)	-6.91 (± 22.136)	
SHBG (nmol/L) Week 12	-3.07 (± 16.282)	-3.56 (± 4.581)	-3.90 (± 27.926)	
SHBG (nmol/L) Follow-up	-3.42 (± 11.667)	14.75 (± 47.950)	-0.17 (± 38.823)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change from Baseline in Endometrium thickness, Ovarian volume, Number of Follicles (cysts), and Dominant Follicle Development (Y/N) as Assessed by Transvaginal Ultrasound (TVU) from Baseline to Week 6 and Week 12 (end-of-treatment)

End point title	Efficacy: Change from Baseline in Endometrium thickness, Ovarian volume, Number of Follicles (cysts), and Dominant Follicle Development (Y/N) as Assessed by Transvaginal Ultrasound (TVU) from Baseline to Week 6 and Week 12 (end-of-treatment)

End point description:

Change from Baseline in Endometrium thickness, Ovarian volume, Number of Follicles (cysts), and Dominant Follicle Development (Y/N) as Assessed by Transvaginal Ultrasound (TVU) from Baseline to Week 6 and Week 12 (end-of-treatment)
Changes from baseline in Transvaginal ultrasound (TVU) Parameters per time point
Ovarian volume, Number of follicles, Dominant follicle development, Endometrial thickness
ITT Population

End point type	Secondary

End point timeframe:

Week 6 and Week 12

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	23	27	
Units: Number				
arithmetic mean (standard deviation)				
Ovary volume (left, cm^3) Week 6	-5.358 (± 12.5094)	-5.139 (± 21.5367)	-0.186 (± 4.5419)	
Ovary volume (left, cm^3) Week 12	-2.034 (± 16.3996)	-5.985 (± 21.3795)	-0.587 (± 4.0751)	
Ovary volume (right, cm^3) Week 6	-0.218 (± 5.6906)	-9.556 (± 20.4629)	-0.542 (± 13.0437)	
Ovary volume (right, cm^3) Week 12	0.757 (± 10.2340)	-10.646 (± 16.3637)	-2.198 (± 7.5347)	
Number of follicles (left ovary) Week 6	0.1 (± 7.26)	-0.4 (± 11.20)	-2.0 (± 8.65)	
Number of follicles (left ovary) Week 12	-1.8 (± 8.15)	3.7 (± 13.12)	-0.7 (± 10.13)	
Number of follicles (right ovary) Week 6	-1.0 (± 4.19)	-2.1 (± 8.56)	-2.1 (± 11.44)	
Number of follicles (right ovary) Week 12	0.6 (± 6.63)	3.1 (± 12.40)	-1.2 (± 9.76)	
Surface of dominant follicle (mm^2) Week 6	-145.755 (± 349.8645)	-19.832 (± 151.2902)	-54.705 (± 113.8735)	

Surface of dominant follicle (mm^2) Week 12	-99.185 (± 311.8806)	15.560 (± 43.7020)	-24.026 (± 153.5590)	
Endometrial thickness (mm) Week 6	0.267 (± 1.8330)	-0.692 (± 1.8615)	0.600 (± 2.9584)	
Endometrial thickness (mm) Week 12	0.042 (± 2.6401)	-0.752 (± 1.6592)	-0.621 (± 2.7920)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment period: From first treatment administration date to last treatment administration date + 6 days with 23.59 added as time part.

Adverse event reporting additional description:

Treatment-Emergent Adverse Events
Safety population: all subjects who were randomized into the study and who used the trial medication at least once were considered evaluable for the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	ESN364 60 mg

Reporting group description:

60 mg ESN364 once daily for 12 weeks

Reporting group title	ESN364 180 mg

Reporting group description:

180 mg ESN364 once daily for 12 weeks

Reporting group title	Placebo

Reporting group description:

Placebo oral use once daily for 12 weeks

Serious adverse events	ESN364 60 mg	ESN364 180 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	2 / 23 (8.70%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis superficial			

subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ESN364 60 mg	ESN364 180 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 23 (73.91%)	21 / 23 (91.30%)	20 / 27 (74.07%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Fibroadenoma of breast			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	2 / 23 (8.70%)	0 / 23 (0.00%)	3 / 27 (11.11%)
occurrences (all)	2	0	3
Impaired healing			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1

Pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast discharge			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Breast discomfort			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Libido decreased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

Nervousness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Weight increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Bundle branch block right			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Tachycardia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 23 (8.70%)	2 / 23 (8.70%)	1 / 27 (3.70%)
occurrences (all)	2	2	1
Headache			
subjects affected / exposed	5 / 23 (21.74%)	9 / 23 (39.13%)	7 / 27 (25.93%)
occurrences (all)	5	9	7
Migraine			
subjects affected / exposed	2 / 23 (8.70%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Paraesthesia			
subjects affected / exposed	0 / 23 (0.00%)	5 / 23 (21.74%)	0 / 27 (0.00%)
occurrences (all)	0	5	0
Tension headache			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Tinnitus			

subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Eye disorders			
Myopia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Abdominal pain lower			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Cheilitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	2	1	1
Dyspepsia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Hypoaesthesia oral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 23 (13.04%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	3	0	1
Oesophagitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Alopecia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Dandruff			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Erythema annulare			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1

Hair growth abnormal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Hirsutism			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	2
Hyperhidrosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 23 (0.00%)	3 / 23 (13.04%)	1 / 27 (3.70%)
occurrences (all)	0	3	1
Skin irritation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Joint swelling			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1

Folliculitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Infected bite			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Nasopharyngitis			
subjects affected / exposed	3 / 23 (13.04%)	2 / 23 (8.70%)	5 / 27 (18.52%)
occurrences (all)	3	2	5
Paronychia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	2 / 23 (8.70%)	0 / 23 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2

Urinary tract infection subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 23 (4.35%) 1	1 / 27 (3.70%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2015	Correction of errors and inconsistencies in the protocol. - Section: 1.3 Clinical Studies: After finalization, errors were found in the CPK-101 CSR. Data taken from the CSR and included in the introduction of this protocol were corrected. - Sections: 7.1.1 Screening Period; 7.1.2 Treatment Period; 7.1.3 Follow-up Period: The subjects need to fast for 8 hours before the screening visit (Visit 1) and before Visits 2, 5, and 7. This was not consistently described throughout the protocol. - Sections: Synopsis, 4.1 Inclusion Criteria; 4.2 Exclusion Criteria: - Sections: 6.2 Prohibited Concomitant Therapies: Clarification of prohibited therapy. - Sections: 5.1 Physical Description of the Study Drug: The protocol stated that certificates of analysis (CoA) would accompany the study drug to the site. This statement was deleted since CoA are not provided to the sites because this is a blinded study and based on the CoA assumptions could be made about the nature of medication kits. - Sections: Time and Events Schedule, 7.1.1 Screening, 7.1.2 Treatment Period, 7.4.1.3 Transvaginal Ultrasound: To allow independent assessment of transvaginal ultrasound (TVU) measurements, TVU images should be transmitted to the independent radiologist (Biomedical Systems) without any measurements that might have been made at the site. This was already described in the Biomedical Systems manual but has now been added to the protocol for clarification. In addition, use of historical TVU at screening will no longer be allowed. TVU will be mandatory at screening (Visit 1) but will only be performed at Visit 2 if the image quality of the screening TVU was insufficient (as judged by the central reader).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported