Clinical trial results:
A 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 Uterine Fibroids.

Summary

EudraCT number	2014-004425-41
Trial protocol	BE DE AT
Global end of trial date	04 January 2017

Results information

Result version number	v1 (current)
This version publication date	28 December 2017
First version publication date	28 December 2017

Trial information

Trial identification

Sponsor protocol code	ESN364-UF-02

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	47 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	27 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2017
Was the trial ended prematurely?	Yes

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 reduce excessive uterine bleeding (assessed by Pictorial Blood Loss Assessment Chart [PBAC]).

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 Conference on 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	21 April 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	Belgium: 16
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	23
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

31 subjects were screened. 23 subjects were randomized and all 23 subjects completed the study. Pre-menopausal women between 18 and 55 yrs diagnosed with UF and no surgical intervention for myoma within the last 5 yrs.

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, Data analyst, 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, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of ESN364 60 mg once daily up to 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, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of ESN364 180 mg once daily up to 12 weeks

Arm title	Placebo

Arm description: -

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

Dosage and administration details:
Subjects received an oral dose of Placebo once daily up to 12 weeks

Number of subjects in period 1	ESN364 60 mg	ESN364 180 mg	Placebo
Started	10	6	7
Completed	10	6	7

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	10	6	7
Age categorical Units: Subjects			
Adults (18-64 years)	10	6	7
Gender categorical Units: Subjects			
Female	10	6	7

Reporting group values	Total		
Number of subjects	23		
Age categorical Units: Subjects			
Adults (18-64 years)	23		
Gender categorical Units: Subjects			
Female	23		

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: Change from Baseline in Decreased Uterine Bleeding as Assessed by Pictorial Blood Loss Assessment Chart (PBAC) at Week 12

End point title	Change from Baseline in Decreased Uterine Bleeding as Assessed by Pictorial Blood Loss Assessment Chart (PBAC) at Week 12[1]

End point description:

Uterine bleeding was assessed with the use of PBAC, validated self reporting method to estimate menstrual blood loss. Subjects recorded daily use of tampons and towels and the degree to which they were soiled with blood. Scores ranged from 0 to more than 500 with higher numbers indicating more bleeding. Analysis population was Intent-to-treat (ITT) and it consisted of all randomized subjects who received at least one dose of study drug and who had post-baseline efficacy data.

End point type	Primary

End point timeframe:

From baseline to 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: The study was terminated early due to a low recruitment rate resulting in a lower number of subjects in the analysis. Therefore, the efficacy analysis was limited to descriptive statistics and listings for the primary endpoint.

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	6	7	
Units: PBAC score				
arithmetic mean (standard deviation)	-114.34 (± 223.59)	-90.57 (± 206.96)	20.77 (± 95.09)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Decreased PBAC Score of >30% and >50% from Baseline to Week 12

End point title	Percentage of Subjects with Decreased PBAC Score of >30% and >50% from Baseline to Week 12[2]

End point description:

Percentage of subjects with decreased PBAC score of >30% and >50% per treatment arm. Analysis

population was Intent-to-treat (ITT)

End point type	Primary

End point timeframe:

At week 12

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: The study was terminated early due to a low recruitment rate resulting in a lower number of subjects in the analysis. Therefore, the efficacy analysis was limited to descriptive statistics and listings for the primary endpoint.

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	6	7	
Units: Percentage of Decrease in PBAC score				
number (not applicable)				
>30%	50.0	33.3	28.6	
>50%	40.0	16.7	14.3	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with PBAC Score <75 from Baseline to Week 12

End point title	Percentage of Subjects with PBAC Score <75 from Baseline to Week 12[3]

End point description:

This primary efficacy analysis represents a descriptive statistic of the proportion of patients, per treatment arm, with PBAC scores <75 at week 12, in percentages. Analysis population was Intent-to-treat (ITT)

End point type	Primary

End point timeframe:

At week 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated early due to a low recruitment rate resulting in a lower number of subjects in the analysis. Therefore, the efficacy analysis was limited to descriptive statistics and listings for the primary endpoint.

End point values	ESN364 60 mg	ESN364 180 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	6	7	
Units: PBAC Score in percentages				
number (not applicable)				
PBAC score <75	30.0	0.0	14.3	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacodynamics: Changes from baseline in Hormone Concentrations at week 12

End point title	Pharmacodynamics: Changes from baseline in Hormone Concentrations at week 12

End point description:

Changes from baseline in mean hormone concentrations per timepoint during treatment

End point type	Other pre-specified

End point timeframe:

At 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	10	6	7	
Units: Hormone				
arithmetic mean (standard deviation)				
LH (mIU/mL)	-2.16 (± 3.10)	8.52 (± 15.58)	-0.63 (± 4.87)	
Progesterone (ng/mL)	1.49 (± 2.96)	-0.03 (± 0.41)	3.93 (± 6.51)	
SHBG (nmol/L)	-5.67 (± 13.25)	-5.35 (± 8.32)	10.70 (± 8.91)	
Estradiol (nmol/L)	-0.07 (± 0.21)	-0.08 (± 0.37)	0.32 (± 0.28)	
FSH (IU/L)	0.10 (± 6.88)	19.03 (± 37.43)	-5.69 (± 11.70)	
Cortisol (nmol/L)	33.20 (± 85.19)	59.80 (± 63.64)	-11.70 (± 129.16)	
Androstenedione (nmol/L)	-0.84 (± 2.23)	0.07 (± 1.17)	-0.51 (± 2.53)	
Aldosterone (pmol/L)	-459.00 (± 1313.60)	-42.30 (± 239.55)	118.10 (± 269.11)	
DHEA-S (ug/dL)	11.30 (± 41.56)	6.70 (± 31.26)	11.00 (± 14.21)	
ACTH (pmol/L)	0.54 (± 1.29)	0.48 (± 0.80)	-0.33 (± 0.80)	
Prolactin (ng/mL)	-4.96 (± 6.64)	-2.85 (± 5.29)	-1.41 (± 3.46)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
TEAEs during treatment period. From first treatment administration date time to last treatment administration date + 6 days with 23:59 added as time part.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	ESN364 60 mg
Reporting group description:	
Subjects received an oral dose of ESN364 60 mg once daily up to 12 weeks.	
Reporting group title	ESN364 180 mg
Reporting group description:	
Subjects received an oral dosa of ESN364 180 mg once daily up to 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received an oral dose of Placebo once daily up to 12 weeks.	

Serious adverse events	ESN364 60 mg	ESN364 180 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	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	8 / 10 (80.00%)	6 / 6 (100.00%)	6 / 7 (85.71%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	4 / 6 (66.67%)	1 / 7 (14.29%)
occurrences (all)	0	6	1
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	3 / 6 (50.00%)	2 / 7 (28.57%)
occurrences (all)	0	5	5
Menopausal symptoms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Metrorrhagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pelvic pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Left atrial dilatation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Sinus arrhythmia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 10 (0.00%)	4 / 6 (66.67%)	2 / 7 (28.57%)
occurrences (all)	0	6	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to a low recruitment rate resulting in a lower number of subjects in the analysis. Therefore, the efficacy analysis was limited to descriptive statistics and listings for the primary endpoint.

Notes: