Clinical trial results:
Pilot/Phase IIa Trial to Investigate the Effect of ESN364 in Early Postmenopausal Women Suffering From Hot Flashes

Summary

EudraCT number	2015-002578-20
Trial protocol	BE
Global end of trial date	06 October 2016

Results information

Result version number	v1
This version publication date	15 November 2017
First version publication date	15 November 2017

Trial information

Trial identification

Sponsor protocol code	ESN364-HF-204

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	06 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of ESN364 on the severity and frequency of hot flashes (HF) in early postmenopausal women suffering from HF, in terms of changes in weekly Hot Flash Score (HFS) from baseline to Week 12.

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 September 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: 87
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Women between 40-65 yrs with spontaneous amenorrhea for at least 12 consecutive M or at least 6M with biochemical criteria of menopause or had bilateral oophorectomy, who have experienced at least 49 moderate or severe HF or night sweats over a period of 7 consecutive days; with at least 4 of those days with 7 or more moderate or severe HF per day.

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	Investigator, Monitor, Subject, 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

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:

Subjects received 90 mg of ESN364 orally twice a day 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:

Subjects received 90 mg of placebo orally twice a day for 12 weeks.

Number of subjects in period 1	ESN364	Placebo
Started	43	44
Completed	40	40
Not completed	3	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	-
Subject continued to have too many hot flashes	-	1
Personal reason	1	-
Incl/Excl. criteria not met	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ESN364
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	ESN364	Placebo	Total
Number of subjects	43	44	87
Age categorical Units: Subjects			
Adults (18-64 years)	43	44	87
Gender categorical Units: Subjects			
Female	43	44	87

End points

End points reporting groups	
Reporting group title	ESN364
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change from baseline to Week 12 in weekly Hot Flash Score (HFS).	
End point title	Change from baseline to Week 12 in weekly Hot Flash Score (HFS).
End point description:	
The HFS was based on the hot flash severity and frequency which were assessed at a minimum twice a day. The HFS was calculated as the (number of mild HF/day × 1) + (number of moderate HF/day × 2) + (number of severe HF/day × 3). Higher scores indicated worse symptoms. The analysis population was Intent-to-treat (ITT) and it consisted of all randomized subjects who received at least one dose of the study medication and subjects who have had post-baseline efficacy data.	
End point type	Primary
End point timeframe:	
From baseline through week 12	

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Change from baseline to week 12				
arithmetic mean (confidence interval 95%)	-26.51 (-30.83 to -22.18)	-12.19 (-16.55 to -7.83)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-12.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.89
upper limit	-7.79

Notes:

[1] - P-value: < 0.001

Secondary: Change from baseline over time in weekly HF severity score (Method 1).

End point title	Change from baseline over time in weekly HF severity score (Method 1).

End point description:

Method 1 takes into account the number and severity of moderate and severe HF occurred during a given time period. The Hot Flash Severity score (based on severity and frequency) was calculated as follows:
HF Severity score = [(number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]/(#moderate HF + #severe HF)
The weekly hot flash severity was calculated: Mean HF Severity day-score over 1 week
Higher scores indicate worse symptoms. For weekly HF severity score calculated by method 1 the maximum was 3 (the maximum is attained when all HF are severe). The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Change from baseline to week 12				
arithmetic mean (confidence interval 95%)				
Change from baseline to week 12	-1.656 (-1.937 to -1.376)	-0.534 (-0.798 to -0.270)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.504
upper limit	-0.741

Notes:

[2] - P-value: < 0.001

Secondary: Change from baseline over time in weekly HF severity score (Method 2).

End point title	Change from baseline over time in weekly HF severity score (Method 2).

End point description:

Method 2 (as recommended by FDA) takes into account moderate and severe HF during a given time period. The Hot Flash Severity (based on severity and frequency) was calculated as follows:
HF Severity day-score = [(number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]
The weekly hot flash severity was calculated: Mean HF Severity day-score over 1 week
Higher scores indicate worse symptoms. There was no maximum score since the number of HF does not have an upper limit. The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline through week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Change from baseline to week 12				
arithmetic mean (confidence interval 95%)				
Change from baseline to week 12	-26.61 (-31.06 to -22.17)	-12.14 (-16.62 to -7.65)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	Placebo v ESN364
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-12.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	-7.83

Notes:

[3] - P-value: < 0.001

Secondary: Changes from baseline over time in weekly HF severity score and Hot Flash Frequency (all severities).

End point title	Changes from baseline over time in weekly HF severity score and Hot Flash Frequency (all severities).

End point description:

HF frequency for all severities scores were calculated by method 1:
Method 1 takes into account the number and severity of moderate and severe HF occurred during a given time period. The Hot Flash Severity score (based on severity and frequency) was calculated as follows:
HF Severity score = [(number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]/(#moderate HF + #severe HF)
The weekly hot flash severity was calculated: Mean HF Severity day-score over 1 week
Higher scores indicate worse symptoms. For weekly HF severity score calculated by method 1 the maximum was 3. The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline through week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Change from baseline to week 12				
arithmetic mean (confidence interval 95%)				
Change from baseline to week 12	-75.3 (-86.4 to -64.3)	-35.6 (-46.7 to -24.5)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	Placebo v ESN364
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.9
upper limit	-22.1

Notes:

[4] - P-value: < 0.001

Secondary: Changes from baseline over time in weekly HF severity score and Hot Flash Frequency (moderate & severe).

End point title	Changes from baseline over time in weekly HF severity score and Hot Flash Frequency (moderate & severe).

End point description:

HF frequency for moderate and severe scores were calculated by method 2:
Method 2 (as recommended by FDA) takes into account moderate and severe HF during a given time

period. The Hot Flash Severity (based on severity and frequency) was calculated as follows:
HF Severity day-score = [(number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]
The weekly hot flash severity was calculated: Mean HF Severity day-score over 1 week
Higher scores indicate worse symptoms. There was no maximum score since the number of HF does not have an upper limit. The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Change from baseline to week 12				
arithmetic mean (confidence interval 95%)				
Change from baseline to week 12	-76.1 (-87.2 to -0.65)	-35.3 (-46.9 to -23.6)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-35.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.6
upper limit	-22.8

Notes:

[5] - P-value: < 0.001

Secondary: Change in overall mean score from baseline over time in Hot Flash Related daily Interference Scale (HFRDIS).

End point title	Change in overall mean score from baseline over time in Hot Flash Related daily Interference Scale (HFRDIS).

End point description:

The HFRDIS was completed at the clinical site in the ePRO diary, at any time during the visit. The HFRDIS is a 10-item scale which measures a woman's perceptions of the degree to which hot flashes interfere with 9 daily life activities (work, social activities, leisure, sleep, mood, concentration, relations with others, sexuality, enjoying life); the 10th item measures interference with overall quality of life. This scale was modeled after items on the Brief Pain Inventory and Brief Fatigue Inventory, both of which assess the extent to which pain or fatigue interfere with daily life. Subjects were asked to rate the extent to which hot flashes have interfered with each item during the previous 4-week time interval

using a 0 (do not interfere) to 10 (completely interfere) scale. The overall mean score is presented. The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline and week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Overall mean score				
arithmetic mean (confidence interval 95%)				
Baseline	5.29 (4.69 to 5.89)	5.02 (4.46 to 5.58)		
Week 12	1.12 (0.71 to 1.53)	3.03 (2.23 to 3.83)		

Statistical analyses

Statistical analysis title	ANCOVA result Week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.83
upper limit	-1.13

Notes:

[6] - P-value: < 0.001

Secondary: Changes from baseline over time in Leeds Sleep Evaluation Questionnaire (LSEQ).

End point title	Changes from baseline over time in Leeds Sleep Evaluation Questionnaire (LSEQ).

End point description:

The subjects' sleep quality was evaluated every 4 weeks from the start of study drug intake (Visit 2) through the follow-up visit (Visit 6) using the LSEQ. The LSEQ is a visual analogue scale which requires respondents to place marks on a group of 10-cm lines representing the changes they have experienced in a variety of symptoms since the beginning of treatment. The LSEQ is a visual analogue scale which requires respondents to place marks on a group of 10-cm lines representing the changes they have experienced in a variety of symptoms since the beginning of treatment.Lines extend between extremes like "more difficult than usual" and "easier than usual". Responses were measured using a 100-mm scale and are averaged to provide a score for each domain. The analysis population was Intent-to-treat

(ITT).

End point type	Secondary

End point timeframe:

From baseline and week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: LSEQ score				
arithmetic mean (confidence interval 95%)				
Getting to sleep - baseline	3.872 (3.318 to 4.426)	3.869 (3.391 to 4.348)		
Getting to sleep - week 12	6.104 (5.615 to 6.594)	5.197 (4.672 to 5.722)		
Quality of sleep - baseline	2.691 (1.936 to 3.445)	2.390 (1.850 to 2.929)		
Quality of sleep - week 12	6.767 (6.054 to 7.479)	4.332 (3.481 to 5.183)		
Awake following sleep - baseline	3.740 (3.070 to 4.409)	4.273 (3.700 to 4.846)		
Awake following sleep - week 12	6.341 (5.601 to 7.081)	5.256 (4.588 to 5.925)		
Behaviour following wakening - baseline	3.728 (3.093 to 4.363)	4.112 (3.549 to 4.675)		
Behaviour following wakening - week 12	6.162 (5.439 to 6.884)	5.356 (4.699 to 6.013)		

Statistical analyses

Statistical analysis title	Getting to sleep - Ancova result week 12
Comparison groups	Placebo v ESN364
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.895
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.599

Statistical analysis title	Quality of sleep - Ancova result week 12

Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.433
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.334
upper limit	3.532

Notes:

[7] - P-value: < 0.001

Statistical analysis title	Awake following sleep - Ancova result week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	2.12

Statistical analysis title	Behaviour following wakening-Ancova result week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	1.8

Secondary: Changes from baseline over time in Greene Climacteric Scale (GCS).

End point title	Changes from baseline over time in Greene Climacteric Scale (GCS).

End point description:

Changes in climacteric symptoms was evaluated every 4 weeks from the start of study drug intake (Visit 2) through the follow-up visit (Visit 6) using the GCS. The questionnaire was paper-based, administered at the clinical site at any time during the visit. The GCS is a 21-item scale which provides a brief but comprehensive and valid measure of climacteric symptomatology. Each item was rated by the subject according to its severity using a four-point rating scale from 0 (none) to 3 (severe). The first 20 items of the scale combine into three main independent symptom measures: psychological symptoms (items 1 to 11; score 0 to 33), physical symptoms (items 12 to 18; score 0 to 21), and vasomotor symptoms (items 19 to 20; score 0 to 6), by summing up the individual item scores. Item 21 was a probe for sexual dysfunction. The total score range was 0 to 63. Higher scores indicate worse symptoms. The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline and week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: GCS score				
arithmetic mean (confidence interval 95%)				
Total GSC score - baseline	21.9 (18.5 to 25.4)	21.0 (17.8 to 24.2)		
Total GSC score - week 12	8.5 (5.9 to 11.1)	14.6 (11.6 to 17.6)		

Statistical analyses

Statistical analysis title	Total GCS score - Ancova results week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	-2.8

Notes:

[8] - P-value: < 0.001

Secondary: Changes from baseline over time in Sheehan Disability Scale (SDS).

End point title	Changes from baseline over time in Sheehan Disability Scale (SDS).

End point description:

The subjects' functional impairment of life was evaluated every 4 weeks from the start of study drug intake (Visit 2) through the follow-up visit (Visit 6) using the SDS. The questionnaire will be paper-based, administered at the clinical site at any time during the visit. The SDS is a composite of 3 self-rated items designed to measure the extent to which 3 major sectors in a patient's life are impaired by panic, anxiety, phobic, or depressive symptoms. The patient rates the extent to which his/her 1-work/school, 2- social life, and 3- family life are impaired by his/her symptoms on a 10-point visual analog scale. The 3 items may be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). The analysis population was Intent-to-treat (ITT).

End point type	Secondary

End point timeframe:

From baseline and week 12

End point values	ESN364	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: SDS score				
arithmetic mean (confidence interval 95%)				
Global functional impairment - baseline	14.3 (12.2 to 16.3)	11.8 (9.7 to 13.8)		
Global functional impairment - week 12	2.1 (0.9 to 3.2)	6.8 (4.4 to 9.2)		

Statistical analyses

Statistical analysis title	Global functional impairment-Ancova result week 12
Comparison groups	ESN364 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	-2.8

Notes:

[9] - P-value: < 0.001

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment period: week 1 to 12	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	ESN364
Reporting group description:	
Subjects received 90 mg of ESN364 orally twice a day for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 90 mg of placebo orally twice a day for 12 weeks.	

Serious adverse events	ESN364	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ESN364	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 43 (67.44%)	34 / 44 (77.27%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Hypotension			

subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Meniscus operation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Inflammation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Nipple pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Uterine haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

Vaginal discharge			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
Vulvovaginal dryness			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Psychiatric disorders			
Burnout syndrome			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Electrocardiogram QT interval abnormal			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Neutrophil count increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 43 (6.98%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Tachycardia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	7 / 43 (16.28%)	6 / 44 (13.64%)	
occurrences (all)	7	6	
Migraine			

subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 43 (4.65%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Dry mouth			

subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Intestinal obstruction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Paraesthesia oral			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Sensitivity of teeth			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	

Pruritus generalised			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
Arthritis			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Bursitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Fibromyalgia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Muscle rigidity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Myositis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Patellofemoral pain syndrome			

subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 43 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Lung infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 43 (2.33%)	4 / 44 (9.09%)	
occurrences (all)	1	4	
Oral candidiasis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	

Subcutaneous abscess			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Vaginal infection			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	The overall reason for the revision is to liberalize the participant selection criteria to facilitate recruitment, and to allow for a lower number of subjects to be included in the interim analysis. For a detailed overview of the changes, please refer to the Protocol Amendment section of the full CSR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported