Clinical trial results:
An exploratory phase II, randomised, double-blind, placebo-controlled, parallel-group study investigating the efficacy and safety of Sepranolone in women with menstrual migraine

Summary

EudraCT number	2019-001081-15
Trial protocol	SE FI
Global end of trial date	06 April 2021

Results information

Result version number	v1 (current)
This version publication date	21 April 2022
First version publication date	21 April 2022

Trial information

Trial identification

Sponsor protocol code	APH204

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Asarina Pharma ApS
Sponsor organisation address	Ole Maaloes Vej 3, Kobenhavn N, Denmark, 2200
Public contact	Peter Nordkild, Asarina Pharma ApS, peter.nordkild@asarinapharma.com
Scientific contact	Peter Nordkild, Asarina Pharma ApS, peter.nordkild@asarinapharma.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	31 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2021
Global end of trial reached?	Yes
Global end of trial date	06 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of two different doses (10 mg and 16 mg) of sepranolone on number of menstrual migraine days compared with placebo in patients with menstrual migraine.

Protection of trial subjects:

The clinical safety of the women was followed throughout their participation in the study with for example physical examinations (including also vital signs and inspection of injection sites), safety blood sampling and AE and concomitant medication reporting. Women received training in IMP self-administration by a qualified health care professional at the clinical site prior to drug dispensing. Due to possible local injection reactions seen in a previous study, women in this study were instructed to aim to inject the IMP at discrete sites using a rotating scheme periumbilically.

Background therapy:

Patients were allowed to take rescue medication and be on stable doses of any allowed chronic or PRN concomitant migraine treatment or other pain medications, including treatments for migraine prophylaxis, at the discretion of the investigator. The rescue medication was the patient’s standard of care symptomatic migraine treatment on an as-needed basis. Hormonal treatments, CGRP-monoclonal antibody treatment and Botulinum toxin for migraine prophylaxis were not allowed.

Evidence for comparator: -

Actual start date of recruitment	27 August 2019
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	Sweden: 62
Country: Number of subjects enrolled	Finland: 24
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	86
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject first visit (FSFV) was 27Aug2019. First subject randomised was 02Dec2019. Last subject last visit (LSLV) was 06Apr2021.

Pre-assignment

Screening details:

A telephone eligibility pre-screening was performed to filter out women that may have the potential to meet the menstrual migraine criteria. Women passing this pre-screening interview were invited to a first study site Visit 1 to provide their informed consent, after which they could be formally screened.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sepranolone 10 mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Sepranolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

25 mg/mL. 0.4 mL in prefilled syringes.

Arm title	Sepranolone 16 mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Sepranolone 16 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use, Solution for injection

Dosage and administration details:

40 mg/mL. 0.4 mL in prefilled syringes.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Intralipid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

0.4 mL(out of which 16µL of Intralipid®) in prefilled syringes.

Number of subjects in period 1	Sepranolone 10 mg	Sepranolone 16 mg	Placebo
Started	28	27	31
Completed	26	26	28
Not completed	2	1	3
Subject choice due to worsening of migraine	-	1	-
Consent withdrawn by subject	-	-	1
did not want to take IMP for the last cycle	-	-	1
last study drug 29APR2020 and decided not to cont	1	-	-
lack of efficacy	-	-	1
AE myom increasing in size. Hysterectomy scheduled	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Sepranolone 10 mg
Reporting group description: -	
Reporting group title	Sepranolone 16 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Sepranolone 10 mg	Sepranolone 16 mg	Placebo
Number of subjects	28	27	31
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	39	39	40
full range (min-max)	24 to 45	28 to 47	23 to 44
Gender categorical Units: Subjects			
Female	28	27	31
Male	0	0	0

Reporting group values	Total		
Number of subjects	86		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years median full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	86		
Male	0		

End points

End points reporting groups

Reporting group title	Sepranolone 10 mg
Reporting group description: -	
Reporting group title	Sepranolone 16 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	modified intention-to-treat analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intention-to-treat (mITT) analysis set includes patients in the FAS who did not substantially deviate from the protocol, have a valid baseline assessment, and have completed at least one confirmed ovulatory treatment cycle with evaluable primary data. Only cycles during which the patient gets at least 4 doses of study drug are considered to have evaluable primary data. Only cycles where the subject has taken the study treatment during the period of Day -14 and Day 1 of the menstrual cycle will be considered as valid cycles. The mITT will be the primary analysis set for efficacy analyses.

Primary: Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5

End point title	Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5[1]

End point description:

T1

End point type	Primary

End point timeframe:

during Day -2 to Day +5 of three menstrual cycles compared to baseline

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: Statistical analyse specified for pooled Sepranolone (10 and 16 mg) versus placebo - see statistical analysis for T2 valid for all three period T1. T2 and T3.

End point values	Sepranolone 10 mg	Sepranolone 16 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	31	
Units: day				
median (full range (min-max))	4.000 (1.00 to 7.00)	2.000 (0.00 to 7.00)	3.000 (0.00 to 7.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5

End point title	Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5

End point description: T2	
End point type	Primary
End point timeframe: during Day -2 to Day +5	

End point values	Sepranolone 10 mg	Sepranolone 16 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	25	27	
Units: day				
median (full range (min-max))	3.000 (0.00 to 7.00)	3.000 (0.00 to 7.00)	2.000 (0.00 to 7.00)	

Statistical analyses

Statistical analysis title	primary endpoint mITT

Statistical analysis description:

Missing data = 5.73090 %. Missing data did not exceed over 15%, no sensitivity analysis was performed. The p-values are one-sided.
A day during which the woman was needed to take rescue treatment will count as a migraine day, whether or not she has reported headache of any intensity.
Data based on modified intention-to-treat analysis set APH204_14_02_08_04_mITT.rtf Primary endpoint: Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5, SAS program

Comparison groups	Sepranolone 10 mg v Sepranolone 16 mg v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8705 [2]
Method	p-value one-sided

Notes:

[2] - p-value Sepranolone (pooled 10 and 16 mg) versus placebo - change from baseline.
Applicable for T1 (subjects included in analysis = 84), T2 (subjects included in analysis = 78) and T3 (subjects included in analysis = 76).

Primary: Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5

End point title	Change from baseline in the mean number of menstrual migraine days during Day -2 to Day +5[3]
End point description: T3	
End point type	Primary
End point timeframe: during Day -2 to Day +5	

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: Statistical analyse specified for pooled Sepranolone (10 and 16 mg) versus placebo - see statistical analysis for T2 valid for all three period T1. T2 and T3.

End point values	Sepranolone 10 mg	Sepranolone 16 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	27	
Units: day				
median (full range (min-max))	3.000 (0.00 to 7.00)	2.900 (0.00 to 7.00)	2.000 (0.00 to 7.00)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs (including SAEs) were collected from the start of IMP administration until the end-of-study visit (Visit 9).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Sepranolone 10 mg
Reporting group description: -	
Reporting group title	Sepranolone 16 mg

Reporting group description: -

Serious adverse events	Placebo	Sepranolone 10 mg	Sepranolone 16 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 28 (0.00%)	0 / 27 (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	Placebo	Sepranolone 10 mg	Sepranolone 16 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 31 (80.65%)	25 / 28 (89.29%)	26 / 27 (96.30%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 31 (3.23%)	1 / 28 (3.57%)	2 / 27 (7.41%)
occurrences (all)	1	2	3
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	0 / 28 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 31 (3.23%)	2 / 28 (7.14%)	0 / 27 (0.00%)
occurrences (all)	1	5	0
Injection site erythema			
subjects affected / exposed	3 / 31 (9.68%)	2 / 28 (7.14%)	10 / 27 (37.04%)
occurrences (all)	4	2	16
Injection site haematoma			
subjects affected / exposed	10 / 31 (32.26%)	11 / 28 (39.29%)	13 / 27 (48.15%)
occurrences (all)	14	12	17
Injection site pain			
subjects affected / exposed	6 / 31 (19.35%)	12 / 28 (42.86%)	14 / 27 (51.85%)
occurrences (all)	8	15	23
Injection site pruritus			
subjects affected / exposed	1 / 31 (3.23%)	1 / 28 (3.57%)	6 / 27 (22.22%)
occurrences (all)	1	1	6
Injection site swelling			
subjects affected / exposed	4 / 31 (12.90%)	6 / 28 (21.43%)	15 / 27 (55.56%)
occurrences (all)	7	8	27
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 31 (6.45%)	0 / 28 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	3 / 28 (10.71%)	0 / 27 (0.00%)
occurrences (all)	1	3	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 31 (0.00%)	2 / 28 (7.14%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 28 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Infections and infestations			
Corona virus infection			

subjects affected / exposed	3 / 31 (9.68%)	2 / 28 (7.14%)	2 / 27 (7.41%)
occurrences (all)	3	2	2
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	5 / 28 (17.86%)	11 / 27 (40.74%)
occurrences (all)	5	6	12
Upper respiratory tract infection			
subjects affected / exposed	3 / 31 (9.68%)	1 / 28 (3.57%)	3 / 27 (11.11%)
occurrences (all)	4	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2019	Addition of endpoints related to reduction in migraine days over a longer time period, changes to recall period of MPFID, adding a depression scale to monitor any mood change, addition of one new laboratory sample, addition or clarification to eligibility criteria, change in signs related to assessment of injection related adverse events.
01 April 2020	Changes to ensure safety of the subjects and site staff, enable secure IMP distribution to subjects as well as adaptation of monitoring in order to maintain data quality due to Covid-19 pandemic.
14 December 2020	IMP shelf-life extension due to expiry date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported