Clinical trial results:
A double-blind, placebo controlled, parallel-group, randomised study of safety, tolerability and efficacy of AMAP102 in patients with osteoarthritis.

Summary

EudraCT number	2012-001769-34
Trial protocol	SE DE
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	18 February 2016

Trial information

Trial identification

Sponsor protocol code	102-240-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AnaMar AB
Sponsor organisation address	Medicon Village, Lund, Sweden, SE-223 81
Public contact	Helena Arozenius, AnaMar AB, helena.arozenius@anamar.com
Scientific contact	Helena Arozenius, AnaMar AB, helena.arozenius@anamar.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 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of AMAP102 in patients with pain secondary to osteoarthritis (OA) over 28 days of dosing

Protection of trial subjects:

Rescue medication (paracetamol) was dispensed to the patient by the investigator. Daily use of rescue medication (paracetamol) was limited to 3 g. Rescue medication was replenished at each visit if required.

Background therapy:

No background therapy was used as part of the clinical trial

Evidence for comparator:

There were no active comparators included in the clinical trial.

Actual start date of recruitment	21 January 2013
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: 21
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Poland: 75
Worldwide total number of subjects	116
EEA total number of subjects	116

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)	61

From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicentre study that included 16 sites across Germany, Poland and Sweden.
Studied Period (Years): Approximately 1 year and 6 months
Date of First Enrolment: 21-Jan-2013
Date of Last Completed: 31-Jul-2014

Pre-assignment

Screening details:

Overall, 257 patients were screened and 116 patients were randomised to receive study drug. The number of patients randomised to receive AMAP102 or placebo was similar.
Screening Period: Visit 1 (Days -12 to 1)
The screening criteria included: Discontinuation of all pain medication (as specified in the Inclusion/Exclusion Criteria)

Period 1

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

Blinding implementation details:

This was a randomised, double-blind, placebo-controlled study with limited access to the randomisation code. Investigational medicinal product and placebo capsules were identical in physical appearance. The treatment each patient received was not be disclosed to the investigator, study centre personnel, patient, AnaMar AB, or their representatives. The treatment codes were held according to the interactive voice response system (IVRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	AMAP102

Arm description:

Following the confirmation of eligibility to the study, the patients were randomised in a 1:1 ratio to AMAP102 or placebo.

Arm type	Experimental
Investigational medicinal product name	AMAP102
Investigational medicinal product code	AMAP102
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

For protocol versions 1 to 3, treatment comprised of oral AMAP102 75 mg or placebo b.i.d for 28 days. After the issue of protocol version 4, treatment comprised of oral AMAP102 or placebo b.i.d for 28 days, AMAP102 25 mg b.i.d or placebo b.i.d between Days 1 and 6
and AMAP102 50 mg b.i.d or placebo b.i.d between Days 7 and 28 (for those patients who reported clinically significant AEs or any tolerability issues between Days 7 and 28, the study drug dose could be down-titrated).

Arm title	Placebo

Arm description:

Following the confirmation of eligibility to the study, the patients were randomised in a 1:1 ratio to AMAP102 or placebo.

Arm type	Placebo

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

Dosage and administration details:

For protocol versions 1 to 3, treatment comprised of oral AMAP102 75 mg or placebo b.i.d for 28 days. After the issue of protocol version 4, treatment comprised of oral AMAP102 or placebo b.i.d for 28 days, AMAP102 25 mg b.i.d or placebo b.i.d between Days 1 and 6
and AMAP102 50 mg b.i.d or placebo b.i.d between Days 7 and 28 (for those patients who reported clinically significant AEs or any tolerability issues between Days 7 and 28, the study drug dose could be down-titrated).

Number of subjects in period 1	AMAP102	Placebo
Started	59	57
Completed	42	51
Not completed	17	6
Consent withdrawn by subject	3	4
Physician decision	1	-
not defined	1	-
Adverse event, non-fatal	10	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Randomised Double-blind Treatment Period

Reporting group description: -

Reporting group values	Randomised Double-blind Treatment Period	Total	
Number of subjects	116	116	
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			
arithmetic mean	65.3		
standard deviation	± 8.51	-	
Gender categorical			
Units: Subjects			
Female	84	84	
Male	32	32	
Identification of Target Knee			
Patients who had arthritis flare in either the left or right knee were selected at baseline.			
Units: Subjects			
Left	55	55	
Right	61	61	

Subject analysis sets

Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population (full analysis set) comprised of all patients who were correctly included (implying that they fulfilled all entry criteria), randomised and had taken at least 1 dose of the study drug. The ITT population was used to perform confirmatory analyses of the primary efficacy evaluation only. Missing data were imputed using the Last Observation Carried Forward (LOCF) principle.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all patients who were randomised and received at least 1 dose of study drug. This population was used to assess comparative safety information.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all patients in the ITT population who did not have major deviations from the protocol that could have affected the primary (and secondary) endpoints. The PP population was the main analysis set from which conclusions on efficacy were drawn.

Reporting group values	Intention to Treat	Safety Population	Per Protocol Population
Number of subjects	104	115	88
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			
arithmetic mean	65.5	65.3	65
standard deviation	± 8.52	± 8.51	± 8.44
Gender categorical Units: Subjects			
Female	27	31	25
Male	77	84	63
Identification of Target Knee			
Patients who had arthritis flare in either the left or right knee were selected at baseline.			
Units: Subjects			
Left	51	55	43
Right	53	60	45

End points

End points reporting groups

Reporting group title	AMAP102
Reporting group description:	
Following the confirmation of eligibility to the study, the patients were randomised in a 1:1 ratio to AMAP102 or placebo.	
Reporting group title	Placebo
Reporting group description:	
Following the confirmation of eligibility to the study, the patients were randomised in a 1:1 ratio to AMAP102 or placebo.	
Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent-to-treat (ITT) population (full analysis set) comprised of all patients who were correctly included (implying that they fulfilled all entry criteria), randomised and had taken at least 1 dose of the study drug. The ITT population was used to perform confirmatory analyses of the primary efficacy evaluation only. Missing data were imputed using the Last Observation Carried Forward (LOCF) principle.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all patients who were randomised and received at least 1 dose of study drug. This population was used to assess comparative safety information.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol (PP) population included all patients in the ITT population who did not have major deviations from the protocol that could have affected the primary (and secondary) endpoints. The PP population was the main analysis set from which conclusions on efficacy were drawn.	

Primary: The primary efficacy endpoint was the Western Ontario and McMaster Universities Osteoarthritis Index® (WOMAC®) Pain Subscale Score for the target knee

End point title	The primary efficacy endpoint was the Western Ontario and McMaster Universities Osteoarthritis Index® (WOMAC®) Pain Subscale Score for the target knee
End point description:	
Mean change from Baseline in WOMAC® Pain Subscale Score on the Target Knee at Visits 3 (Day 7), 4 (Day 14) and 5 (Day 28) (PP Population)	
End point type	Primary
End point timeframe:	
Change from Baseline in WOMAC® Pain Subscale Score on the Target Knee at Visits 3 (Day 7), 4 (Day 14) and 5 (Day 28) (PP Population)	

End point values	AMAP102	Placebo	Per Protocol Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	48	88	
Units: Pain Subscale Score				
arithmetic mean (standard deviation)				
Change from baseline to day 7 (mean)	-3.7 (± 6.11)	-4 (± 6.32)	-3.85 (± 6.21)	
Change from baseline to day 14 (mean)	-5.8 (± 7.44)	-7 (± 7.27)	-6.4 (± 7.34)	

Change from baseline to day 28 (mean)	-8.5 (± 7.98)	-8.2 (± 8.53)	-8.35 (± 7.27)	

Statistical analyses

Statistical analysis title	Wilcoxon Rank-Sum test

Statistical analysis description:

Both groups recorded a similar decrease in the mean change from baseline throughout the treatment period.

Comparison groups	Placebo v AMAP102
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.669 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Wilcoxon Rank-Sum test

[2] - The decrease from baseline was not statistically significantly different between the AMAP102 group and the placebo group for Visit 3 (Day 7)

Statistical analysis title	Wilcoxon Rank-Sum test

Statistical analysis description:

Both groups recorded a similar decrease in the mean change from baseline throughout the treatment period.

Comparison groups	Placebo v AMAP102
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.397 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Wilcoxon Rank-Sum test

[4] - The decrease from baseline was not statistically significantly different between the AMAP102 group and the placebo group for Visit 4 (Day 14)

Statistical analysis title	Wilcoxon Rank-Sum test

Statistical analysis description:

Both groups recorded a similar decrease in the mean change from baseline throughout the treatment period.

Comparison groups	Placebo v AMAP102
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.784 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Wilcoxon Rank-Sum test

[6] - The decrease from baseline was not statistically significantly different between the AMAP102 group and the placebo group for Visit 5 (Day 28)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	AMAP102
Reporting group description:	
AMAP102 - dose 25 mg b.i.d. to 75 mg b.i.d.	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	AMAP102	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 59 (1.69%)	1 / 56 (1.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	
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: 0.05 %

Non-serious adverse events	AMAP102	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 59 (52.54%)	19 / 56 (33.93%)	
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 59 (8.47%)	2 / 56 (3.57%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 59 (5.08%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Eye disorders			
Photopsia			
subjects affected / exposed	7 / 59 (11.86%)	0 / 56 (0.00%)	
occurrences (all)	7	0	
Vision blurred			
subjects affected / exposed	3 / 59 (5.08%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 59 (1.69%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	8 / 59 (13.56%)	3 / 56 (5.36%)	
occurrences (all)	8	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 59 (5.08%)	0 / 56 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2012	Protocol Amendment 1, Version 2 (24-Aug-2012) The amendment was issued following objections raised to the submitted protocol version 1.1 (12-Jul-2012) by the Läkemedelsverket/Swedish Medical Products Agency (MPA). In addition, updates were made to improve the clarity of the protocol and the procedures to be used for some assessments.
03 October 2012	Protocol Amendment 2, Version 3 (03-Oct-2012) The amendment was issued following objections raised to the submitted protocol version 2.0 (24-Aug-2012) by the MPA and to the submitted protocol version 1.1 (12-Jul-2012) by the Berlin State Ethics Committee (State Office of Health and Social Affairs). Changes that were made included the exclusion of patients with significant cardiovascular complications and patients who were taking potent inhibitors of CYP3A4 and CYP1A2. Furthermore, updates were made to improve the clarity of the protocol and the procedures to be used for some assessments.
31 October 2012	Non-Substantial Protocol Amendment 3, Version 3.1 (31-Oct-2012) The amendment was issued to ensure consistency between both the protocol and the patient's eDiary.
23 October 2013	Protocol Amendment 4, Version 4 (23-Oct-2013) The amendment was issued to adjust the eligibility criteria for patients entering the study in order to aid recruitment, as it was proving more challenging than anticipated for the study investigators to find patients that met the entry criteria of the protocol. In addition, there had been a higher frequency of anticipated AEs, which had resulted in early discontinuations. For better tolerability to the study drug, the therapeutic dose was reduced from 75 mg b.i.d to 50 mg b.i.d. Specifically, the following changes were made: For a better tolerability to the study drug, AMAP102 dosage was reduced from 75 mg b.i.d to 50 mg b.i.d AMAP102 50 mg b.i.d was selected following the results obtained from the Phase I study that showed 50 mg b.i.d was safe and well tolerated and the observations from the initial blinded safety review on the patients receiving AMAP102 75 mg or placebo b.i.d A titration step was introduced to allow the patient to become accustomed to the study drug prior to administering the proposed therapeutic dose of AMAP102. The brief physical examination on Day 7 was amended to complete physical examination prior to the up-titration of the study drug. The brief physical examination on Day 28 was amended to complete physical examination as this is the Early Discontinuation Visit and in case patients do not return to the follow-up visit on Day 35. The complete physical examination on Day 35 was amended to brief physical examination. The introduction of a blinded interim analysis and a safety review, to be performed in parallel, after the first 60 randomised patients. The blinded interim analysis was to determine the need for a sample size increase and the safety review involved reviewing all reported AEs, SAEs and patient withdrawals due to an AE. The inclusion and exclusion criteria were amended in order to remove the requirement for OA The requirement for the X-rays at screening were clarified.

Notes:

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.

There were no statistical differences on the primary, secondary or exploratory efficacy endpoints between AMAP102 and placebo.

Notes: