Clinical trial results:
A placebo-controlled, double-blinded, randomized, trial using a combination of apocynin and paeonol (APPA) for the treatment of knee osteoarthritis

Summary

EudraCT number	2020-000249-14
Trial protocol	DK
Global end of trial date	16 April 2021

Results information

Result version number	v1 (current)
This version publication date	07 July 2022
First version publication date	07 July 2022

Trial information

Trial identification

Sponsor protocol code	APPA-P2-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04657926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AKL Research and Development Ltd
Sponsor organisation address	Stevenage Bioscience Catalyst, Gunnels Wood Road Stevenage Herts, Stevenage, United Kingdom, SG1 2FX
Public contact	Research and Development, AKL Research and Development Ltd, +44 (1438) 906906,
Scientific contact	Research and Development, AKL Research and Development Ltd, +44 (1438) 906906,

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	16 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2021
Global end of trial reached?	Yes
Global end of trial date	16 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the change in pain, in terms of the WOMAC pain score of the target knee.

Protection of trial subjects:

Patient protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.
To manage pain, subject were provided with rescue pain medication in the form of paracetamol tablets 500 mg. The dosage of paracetamol that the subjects was allowed to take per day was defined according to the standard of care in the countries where the trial was carried out; however, the maximum dose should not exceed 1 gram per dose and 4 grams per day.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	16 September 2020
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	Denmark: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	95
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Subject First Visit was on 16 September 2020
Last Subject Fist Visit was on 05 March 2021

Pre-assignment

Screening details:

Overall 334 subjects were screened in this study. Out of which 152 subjects were randomized and received the study treatment into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	APPA

Arm description: -

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

Dosage and administration details:

27.5 days of treatment with two capsules of IMP twice daily

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:

27.5 days of treatment with two capsules of IMP twice daily

Number of subjects in period 1	APPA	Placebo
Started	75	77
Completed	73	76
Not completed	2	1
Physician decision	-	1
Adverse event, non-fatal	1	-

Lost to follow-up	1	-

Baseline characteristics

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

Reporting group values	APPA	Placebo	Total
Number of subjects	75	77	152
Age categorical Units: Subjects			
Adults (18-64 years)	42	53	95
From 65-84 years	33	24	57
Gender categorical Units: Subjects			
Female	30	45	75
Male	45	32	77
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	73	77	150
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or latino	0	1	1
Not hispanic or latino	74	76	150
Not reported	0	0	0
Unknown	1	0	1

End points

End points reporting groups

Reporting group title	APPA
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	PainDETECT-subgroup APPA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A pre-defined subgroup analysis with a baseline PainDETECT score >12.	
Subject analysis set title	PainDETECT-subgroup Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A pre-defined subgroup analysis with a baseline PainDETECT score >12.	

Primary: Change from baseline in WOMAC pain sub-score (questions 1 to 5) in the target knee as evaluated at week 4.

End point title	Change from baseline in WOMAC pain sub-score (questions 1 to 5) in the target knee as evaluated at week 4.
End point description:	
The primary endpoint of this trial was the change from baseline in WOMAC pain sub-score (questions 1 to 5) in the target knee as evaluated at week 4.	
End point type	Primary
End point timeframe:	
From baseline to week 4.	

End point values	APPA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Score				
least squares mean (confidence interval 95%)	-16.40 (-19.74 to -13.05)	-15.51 (-18.80 to -12.21)		

Statistical analyses

Statistical analysis title	Change in WOMAC pain sub-score at week 4
Statistical analysis description:	
The treatment effect on the primary endpoint was assessed using a repeated measurement analysis of variance (MMRM) on absolute change from baseline, including baseline value, the treatment group, the time point, sex, country, the subject characteristic of unilateral/bilateral knee OA at baseline as factors, and including treatment by time as interaction.	
Comparison groups	Placebo v APPA

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - For the treatment effect testing of APPA versus placebo, the null and the alternative hypothesis was:
H0: Mean(Placebo) = Mean(APPA)
H1: Mean(Placebo) ≠ Mean(APPA),
If the null hypothesis was rejected, the alternative hypothesis was accepted, and it was concluded that the treatment effect of APPA differs from placebo.
The primary endpoint was analyzed in one step thus no adjustment for multiplicity was performed in the primary endpoint analysis.

Secondary: Changes from baseline in WOMAC total score at week 4

End point title	Changes from baseline in WOMAC total score at week 4

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks

End point values	APPA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: points				
least squares mean (confidence interval 95%)	-13.89 (-17.20 to -10.58)	-11.61 (-14.87 to -8.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in WOMAC function scores at week 4

End point title	Changes from baseline in WOMAC function scores at week 4

End point description:

End point type	Secondary

End point timeframe:

From baseline to 4 weeks.

End point values	APPA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Points				
least squares mean (confidence interval 95%)	-13.19 (-16.69 to -9.69)	-10.19 (-13.64 to -6.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in total OA pain assessed by ICOAP scores at week 4

End point title	Changes from baseline in total OA pain assessed by ICOAP scores at week 4

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 4

End point values	APPA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: points				
least squares mean (confidence interval 95%)	-14.36 (-17.92 to -10.79)	-11.70 (-15.21 to -8.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the weekly mean of the average daily pain intensity at Week 4

End point title	Change from baseline in the weekly mean of the average daily pain intensity at Week 4

End point description:

End point type	Secondary

End point timeframe:

From baseline to Week 4.

End point values	APPA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Points				
least squares mean (confidence interval 95%)	-1.2118 (-1.5512 to -0.8724)	-1.0397 (-1.3573 to -0.7221)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in WOMAC pain score in PainDETECT >12 subgroup

End point title	Change from baseline in WOMAC pain score in PainDETECT >12 subgroup

End point description:

Change from baseline in WOMAC pain score in PainDETECT >12 subgroup

End point type	Secondary

End point timeframe:

from baseline to week 4.

End point values	PainDETECT-subgroup APPA	PainDETECT-subgroup Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	25		
Units: points				
least squares mean (confidence interval 95%)	-25.48 (-32.07 to -18.89)	-14.28 (-20.15 to -8.42)		

Statistical analyses

Statistical analysis title	Subgroup analysis

Statistical analysis description:

Difference in change from baseline in WOMAC pain score in PainDETECT >12 subgroup.

Comparison groups	PainDETECT-subgroup APPA v PainDETECT-subgroup Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Subgroup analysis

Statistical analysis description:

Difference in change from baseline in WOMAC pain score in PainDETECT >12 subgroup.

Comparison groups	PainDETECT-subgroup APPA v PainDETECT-subgroup Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until the up to 14-day follow-up phone

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	APPA
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	APPA	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	1 / 77 (1.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 75 (0.00%)	1 / 77 (1.30%)	
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: 4 %

Non-serious adverse events	APPA	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 75 (17.33%)	2 / 77 (2.60%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 75 (4.00%)	2 / 77 (2.60%)	
occurrences (all)	4	2	
General disorders and administration site conditions			

Feeling hot			
subjects affected / exposed	3 / 75 (4.00%)	0 / 77 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 75 (4.00%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 75 (5.33%)	0 / 77 (0.00%)	
occurrences (all)	4	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.

None

Notes: