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A phase 1, partially blind, placebo-controlled, ascending single and multiple oral dose, safety, tolerability, pharmacokinetic and pharmacodynamic study in healthy subjects and osteoarthritis patients administered APPA-1

Submission date
29/01/2018

Recruitment status
No longer recruiting

Registration date
30/01/2018

Overall study status
Completed

Last Edited
16/02/2021

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Osteoarthritis (OA) is a condition that affects joints. The surfaces within joints become damaged so the joint doesn't move as smoothly as it should. This causes pain, a grating or grinding sensation and stiffness in the joints. OA is a degenerative disease which affects the articular cartilage which is the cushioning on the ends of our bones. When we mature or finish growing, that cartilage is fairly thick, it is firm and rubbery and smoother than glass. For many reasons people start to lose the cartilage or may suffer an injury which will cause them to lose cartilage. It can affect adults at any age, but most commonly starts between the ages of 40 and 50. About three times as many women as men are affected. There is no cure for OA, but medication can be taken in the long-term to relieve symptoms of the condition. In addition, participants may receive physiotherapy to help with mobility or may need surgery to correct any joint problems that develop. APPA-1 ("the Study Drug") is intended to decrease cartilage destruction, reduce joint inflammation and pain. Therefore it is hoped it may be effective in the treatment of OA, and following further testing could be made available to patients. The Study Drug is an investigational drug which is being developed by AKL Research & Development Ltd, with an aim to help people with Osteoarthritis in the future. Prior to this study, data on the safety of oral apocynin and paeonol which combined make the Study Drug [APPA-1] is limited to a small number of studies in mice and rats. There is anecdotal evidence to support the use of APPA-1 in humans; traditional herbal medicines containing either paeonol or apocynin have been used for centuries and are generally regarded as safe in addition, APPA has been available as an unlicensed herbal supplement, with no adverse safety reactions reported. This is a phase I study, which means that it is the first clinical trial of APPA-1 in humans. The aim of this study is to explore the pharmacokinetic (what the body does to the drug) and (exploratory) pharmacodynamics (what the drug does to the body).

Who can participate?
Adults aged 18 to 75 years old who are healthy or have OA.

What does the study involve?
This study consists of two parts. Those in the first part consist of the health participants. They are allocated to one of five groups. Groups 1,2,3, and 4 consist of male participants only and group 5 consists of female participants only. Those in the part one groups 1, 2, 4, and 5 receive on dose of treatment on day one (after fasting). They reside at the CRU for two nights until 24 hours after the treatment dose. They are required to attend a post study outpatient visit 7 and 10 days after treatment. Those in the part one group 3 receive two doses of treatment. The first dose is administered on day 1 in a fasted state. The second dose is administered at least 7 days after the first dose. The second dose is administered 30 minutes after being fed a high fat breakfast to assess the possible effects of food. Participants who are allocated to the second part of the study receive treatment for 14 days (up to two doses a day) in either a fed or fasting state (as determined by the first part of the study). This involves staying in the CRU for two nights from the evening of day 1 (day before the first treatment dose) until the morning of day 2 (24 hours after the dose). Participants are required to self-dose on days 3,4,5, and 6 and again on days 8,9,10,11 and 12. They receive their day 7 dose at the CRU. On day 13, participants reside in the CRU for a further two nights until day 15 but receive treatment on day 13 and 14. Participants are followed up on day 16 and day 21. The safety and tolerability of the treatment is assessed at each study visit.

What are the possible benefits and risks of participating?
Participants may benefit from the treatment however, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of participants with osteoarthritis. The risks involved in this study have been carefully assessed and the main objective of the staff at the Unit is to maintain safety at all times. Some of the study procedures may cause slight discomfort such as blood sampling and cannula insertion may cause temporary pain, bruising and/or bleeding to the arm and ECG may result in skin rashes and darkening or lightening of skin at electrode sites.

Where is the study run from?
Royal Liverpool University Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2016 to July 2019

Who is funding the study?
AKL Research & Development Limited (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2017-000833-29

Protocol serial number
34619

Study information

Scientific Title
A Phase 1, partially Blind, Placebo-Controlled, Ascending Single and Multiple Oral Dose, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Study in Healthy Subjects and Osteoarthritis Patients administered APPA-1

Acronym
APPA

Study objectives
Significant body of evidence (summarised above) has accrued from use of the individual components of APPA (which includes registration in the UK under the Traditional Herbal Medicinal Products Scheme THMPS) over the centuries, together with consistent preclinical and animal model data suggesting that APPA has the potential to represent an effective drug for the relief of pain in osteoarthritis and that the risk of toxicity will be potentially lower than existing drugs, which currently comprise simple analgesics or non-steroidal anti-inflammatory agents.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central – Oxford A Research Ethics Committee, 02/11/2017, ref: 17/SC/0443

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Drug

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Osteoarthritis

Interventions
The study has been designed in two parts: Part A and Part B. Part A involves 20 healthy participants studied in 5 groups (group A1 to A5), each group consisting of 4 participants. Groups A1 to A4 are male participants only, Group A5 consists of female participants only.

Participants in groups A1, A2, A4 or A5 receive one dose of treatment on day 1 in a fasted state. This involves residing in the CRU for two nights from the evening of Day-1 (day before dosing) until the morning of Day 2 (24 hours after dose). Participants are required to attend a post study outpatient visit at the CRU 7 to 10 days post treatment.

Participants in group A3 receive two doses of treatment. The first dose is administered on day 1 in a fasted state. The second dose is administered at least 7 days after the first dose. The second dose is administered 30 minutes after being fed a high fat breakfast to assess the possible effects of food.

The study (part A and part B) is expected to last a minimum of 34 weeks.

Participants on part B receive treatment for 14 days (up to two doses a day) and depending on the results from Part A, this is either done in a fed or fasted state. This involves residing in the CRU for two nights from the evening of Day-1 (day before first treatment dose) until the morning of Day 2 (24 hours after dose).

Participants are required to self-dose on days 3, 4, 5 and 6 and then again on days 8, 9, 10, 11 and 12.

Day 7 dose is administered at the CRU at an outpatient appointment.

On Day 13, participants reside in the CRU for a further two nights stays until Day 15 but receive treatment on day 13 and 14 only.

An additional outpatient appointment is scheduled for day 16 and a final post study visit on Day 21.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
APPA-1

Primary outcome(s)
Safety and tolerability is measured using discussions with subjects at each study visit.

Key secondary outcome(s)

1. Pain and function outcomes measured using questionnaires at day -1, day 14 and day 21 for group B subjects
2. Single and multiple oral dose pharmacokinetics of APPA-1 constituents (paeonol/apocynin) in healthy subjects and osteoarthritis patients is measured using blood samples taken from subjects at day 1 and day 2 (for group A) and day 1, 2, 7, 14, 15 and 16 for group B subjects
3. The effect of food on the single oral dose pharmacokinetics of APPA-1 constituents (paeonol /apocynin) in healthy subjects is measured using blood samples taken from subjects at day 1 and day 2 (for group A) and day 1, 2, 7, 14, 15 and 16 for group B subjects
4. The effect of gender on the single oral dose pharmacokinetics of APPA-1 constituents (paeonol/apocynin) in healthy subjects is measured using blood samples taken from subjects at days 1 and 2 (for group A) and days 1, 2, 7, 14, 15 and 16 for group B subjects
5. The multiple oral dose pharmacodynamics of APPA-1 in osteoarthritis patients is measured using blood samples taken from subjects at days 1 and 2 (for group A) and days 1, 2, 7, 14, 15 and 16 for group B subjects

Completion date
31/07/2019

Eligibility

Key inclusion criteria
Part A:
1. Written informed consent
2. Between 18 and 75 years of age, inclusive
3. Of any ethnic origin
4. Healthy male subjects (groups A1 to A4)
5. Healthy female subjects (group A5)
6. BMI between 18.0 to 35.0 kg/m2
7. In good health as defined by medical history (including confirmation from GP), physical examination, vital signs assessment, 12 lead ECG and clinical laboratory evaluation.

Part B:
1. Written informed consent
2. Between 18 and 75 years of age inclusive
3. Of any ethnic origin
4. Male or female subjects with a diagnosis of osteoarthritis fulfilling the American College of Rheumatology (ACR) criteria for diagnosis
5. BMI between 18.0 to 35.0 kg/m2

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
28

Key exclusion criteria
Part A & B:
1. Male subjects who do not agree, or whose partners of childbearing potential do not agree, to use appropriate contraception or to refrain from donating sperm from the time of dosing until the Follow Up Visit.
2. Female of childbearing potential not in agreement to use two highly effective methods of contraception, or to refrain from donating ova, from the time of screening until the Follow Up Visit
3. Donated blood in the 3 months prior to screening, plasma in the 7 days prior to screening, platelets in the 6 weeks prior to screening
4. Consume more than 28 units of alcohol per week if male, or 21 units of alcohol per week if female or any significant history of alcohol / substance misuse as determined by the investigator
5. Unwilling to abstain from vigorous exercise for 48 hours prior to any study visit
6. Unwilling to abstain from alcohol for 48 hours prior to any study visit
7. Received any medication, including St John's Wort, known to chronically alter drug absorption or elimination within 30 days prior to first dose administration unless in the opinion of the investigator it will not interfere with study procedures or compromise safety
8. Subjects who have any abnormality of vital signs prior to the first dose administration that, in the opinion of the investigator, would increase the risk of participating in the study
9. Subjects who have any clinically significant abnormal physical examination finding
10. Subjects who have any clinically significant 12 lead ECG abnormality that, in the opinion of the investigator, would increase the risk of participating in the study
11. Subjects who have any clinically significant allergy or allergic condition as determined by the investigator (with the exception of non-active hay fever)
12. Subjects who have any clinically significant abnormal laboratory safety results as determined by the investigator with specific exclusions of any AST or ALT greater than or equal to 1.5 times ULN at screening or day -1; total bilirubin > ULN (Gilbert's syndrome is acceptable)
13. Subjects who have hepatitis B or C or are carriers of HBsAg or are carriers of HCV Ab or are positive for HIV 1/2 antibodies.
14. Subjects who have a positive alcohol breath test or a positive urine drug screen (a repeat assessment is acceptable)
15. Subjects who are still participating in another clinical study or who have participated in a clinical study involving administration of an investigational product in the 3 months (or 5 half-lives, whichever is longer) prior to first dose administration
16. Subjects who have previously received APPA or its constituent parts within 3 months of receiving first dose.
17. Subjects who, in the opinion of the investigator, should not participate in this study.
18. Tobacco smoking within last 30 days, including use of e-cigarettes and not willing to abstain from smoking until after study involvement.

Part A exclusions only:
1. Female subjects who are pregnant or currently lactating
2. Received any prescribed systemic or topical medication within 14 days prior to the first dose administration (with the exception of the OCP)
3. Received any non-prescribed systemic or topical medication, herbal remedy or vitamin /

mineral supplementation within 14 days prior to the first dose administration (with the exception of paracetamol).
4. Subjects who have, or have any history of, any clinically significant cardiovascular, respiratory, gastrointestinal, neurological, psychiatric, metabolic, endocrine, renal, hepatic, haematological or other major disorder as determined by the investigator
5. Subjects with International Normalised Ratio (INR) > 1.3

Part B exclusions only:
1. Received any prescribed systemic or topical medication within 14 days prior to the first dose administration unless in the opinion of the investigator it will not interfere with study procedures or compromise safety and has been at stable dose for at least two weeks prior to screening.
2. Received any non-prescribed systemic or topical medication, herbal remedy or vitamin / mineral supplementation within 14 days prior to the first dose administration unless in the opinion of the investigator it will not interfere with study procedures or compromise safety.
3. Subjects who have any clinically significant medical history in the opinion of the investigator: stable, well controlled conditions such as hypertension, dyslipidaemia, type 2 diabetes (controlled by diet, exercise and/or oral medications), asthma (controlled by inhaled corticosteroids and or beta-2 agonists) etc. are acceptable
4. Subjects who have had recent (< 3 months) surgery or are scheduled to have any surgical procedure in the study period
Predose Exclusion Criteria for Parts A and B
Positive urine drugs of abuse screen/alcohol breath test; Clinically significant vital signs/12-lead ECG findings; Clinically significant abnormal lab findings; Intercurrent illness/clinically significant AE; deviati

Date of first enrolment
01/03/2018

Date of final enrolment
30/06/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Sponsor information

Organisation
Research Support Office

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Industry

Funder Name
AKL Research & Development Limited

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		16/02/2021	16/02/2021	No	No
HRA research summary			28/06/2023	No	No