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A comparison of two different formulations of Ibuprofen in healthy volunteers

Submission date 06/10/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/11/2022	**Overall study status** Completed	
Last Edited 29/01/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aim
Ibuprofen is a commonly used anti-inflammatory drug. Many companies manufacture and sell Ibuprofen. In this study, the sponsor is trying to compare their Ibuprofen formulation (called the Test formulation) with the Ibuprofen formulation made by another company (called the reference formulation).

Who can participate?
Healthy volunteering adults

What does the study involve?
The dose of the Ibuprofen that will be studied in this trial is 2 X 200 mg of each formulation. The study drug will be given orally in the fasting state.
Approximately 28 subjects (Male and female) will be recruited for the study. Each study participant will be screened 28 days in advance of the trial and only those meeting the study inclusion/exclusion criteria will be enrolled. The study will involve two treatment periods - Periods 1 and 2. The study participant will receive one type of formulation at a given treatment period and at the next treatment period will receive the other formulation. In effect, each participant would have received the two different Ibuprofen formulations and this type of study design is called a cross-over study design. This allows the minimisation or elimination of inter-individual differences in drug absorption and metabolism. The amount of Ibuprofen absorbed will be reflected in the blood concentration of Ibuprofen which is called pharmacokinetics (PK). This will be a major objective of the trial to see how the drug concentration builds up in the bloodstream over time after the dosing. The safety of the participants who took the study medications will also be monitored. Frequent blood draws will be carried out to measure drug concentrations as well as do safety laboratory tests. There will be a five-day gap between the two treatment periods. All study participants will be provided with as much information about the study as possible to enable them to sign the informed consent.

What are the possible benefits and risks of participating?
There are no personal benefits to the participants from taking part in the study; however, they are participating in clinical research which may develop new medicines to help others. The potential risks to participants taking part in the present study are anticipated to be acceptable.

The study is being conducted with healthy participants who are not expected to derive any direct benefit from participation in the study. This bioequivalence study will only enroll healthy participants. Only a single dose of the investigational medicinal product will be administered per period. The investigation site will have adequate set-up, experience and safety measures that would be expected of a centre able to perform a PK study. Therefore, it is considered that the risk related to study procedures is low and limited to common AEs related to blood sampling, and discomfort from vital sign measurements. Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

Procedures will be done during the study at assigned times. Participants will be given a schedule of when all the study procedures will take place. The procedures are being performed to monitor their health, assess the safety of the study drug, and learn about how much of the study drug is absorbed systemically.

If the study doctor detects that there may be something wrong with their health, based on the results from any of the study procedures or measurements, he/she will discuss this with the participant. If medical follow-up is needed, the Study Doctor may either contact their GP directly after informing the participant, or refer them to their GP, and where appropriate, may provide the participant with a letter to take to their GP. If urgent treatment is necessary, the study staff are equipped to provide some types of treatment, and if necessary, they will send participants to the hospital by ambulance.

Subjects will be closely monitored while participating in the study for any side effects, will have frequent blood tests to monitor their health and will be provided with emergency contact cards to use during those periods when they are not confined in the clinic between dosing periods. 24-hour continuous medical doctor cover is in place.

Adverse Effects of Study Procedures:
Blood sampling: It is possible that subjects may experience some discomfort when the blood samples are being taken. Taking blood with a needle can cause bleeding and/or soreness around the area of the needle and bruised arms, but these usually clear up within a few days. Having a cannula (a tube for taking the blood) in the arm can cause soreness, bruising, blockage of veins, and (rarely) infection. These problems usually clear up within a few weeks. Blood tests can also make subjects feel faint, so we'll ask subjects to sit or lie down when we take blood. Staff taking blood are trained and experienced in the technique.

ECG: The pads that we stick to the chest to monitor heart rhythm may irritate the skin, and cause itching and redness

Other possible/predictable side effects of participation include:
Possible discovery of latent illness (e.g. viral infection) or condition by screening investigations /examination.
Inconvenience from participation in screening and study-related procedures.
Inconvenience related to changes in lifestyle (exercise, diet, alcohol, concomitant medications, confinement in study centre) required as per study protocol.

COVID-19:
The trial site has a series of policies and operating procedures to follow during the COVID pandemic to reduce the risk of transmission of this infection to staff and study participants. This includes regular testing of staff and study participants to ensure that only those with negative recent COVID tests can be admitted into the clinic site.

Procedures are also in place to deal with the eventuality of positive COVID tests arising in either staff or participants during study confinement.

Where is the study run from?
Reckitt Benckiser (UK)

When is the study starting and how long is it expected to run for?
September 2022 to January 2023

Who is funding the study?
Reckitt Benckiser (UK)

Who is the main contact?
Study mailbox, 5054301@reckitt.com

Contact information

Type(s)
Scientific

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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006326

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
5054301, IRAS 1006326

Study information

Scientific Title
A pivotal, open-label, randomised, balanced, two-way crossover bioequivalence study of a single oral dose of 2 x 200 mg Ibuprofen Formulation A (reference) and 2 x 200 mg Ibuprofen Formulation B (test) in healthy, adult, human (male and female) participants under fasting conditions.

Study objectives
The primary objective of this study is to assess bioequivalence based on a comparison of the PK of the 2 x 200 mg Ibuprofen Formulation A (reference) and 2 x 200 mg Ibuprofen Formulation B (test) in healthy adults in the fasted state.

The secondary objectives are:
1. To characterise the PK profile for both reference product, 2 x 200 mg Ibuprofen Formulation A, and test product, 2 x 200 mg Ibuprofen Formulation B, in healthy adults in the fasted state.
2. To assess the safety and tolerability profile for both reference product, 2 x 200 mg Ibuprofen Formulation A, and test product, 2 x 200 mg Ibuprofen Formulation B, in healthy adults in the fasted state.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/12/2022, Wales Research Ethics Committee 1 Cardiff (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, Wales, UK; +44 (0)2920 785738; Wales.REC1@wales.nhs.uk), ref: 22/WA/0314

Study design
Randomized active-control open-label cross-over study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Healthy volunteer trial

Interventions
The study has a pivotal, open-label, randomised, balanced, two-treatment, two-period, two-sequence, single oral dose, and two-way crossover bioequivalence study design. The Test Formulation is: 2 x 200 mg Ibuprofen Formulation B soft gelatine capsules for oral administration and the Reference Formulation: 2 x 200 mg Ibuprofen Formulation A soft gelatine capsules for oral administration. The study will comprise a pre-study screening, followed by 2 treatment periods (1 and 2) with a minimum of 5 days (+ 2 days) washout between the last dose of treatment period 1 and the first dose of treatment period 2, to allow the complete elimination of the drug before subsequent dosing and avoid carry-over effects, based on 5 elimination half-lives of ibuprofen, which is sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all participants at the beginning of the second period. All participants will attend a post-study follow-up visit 5 days (+/-2 days) after the last dose. Drug administration will be unblinded due to the difference in capsule appearance. Although drug administration will be unblinded, bioavailability and PK analysis of

the samples will be conducted without information on treatment, therefore the laboratory staff responsible for drug concentration analysis will be blinded to treatment.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ibuprofen

Primary outcome measure
The following pharmacokinetic (PK) profile of the 2 x 200 mg Ibuprofen Formulation A (reference) and 2 x 200 mg Ibuprofen Formulation B (test) in healthy adults in the fasted state will be assessed on day 1 of treatment period 1 and day 1 of treatment period 2:
1. AUC0-t
2. Cmax
3. Tmax
The endpoints will be measured using blood samples collected pre-dose (within an hour prior to dosing) and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 240, 360, 480 and 720 minutes for determination of ibuprofen plasma concentrations

Secondary outcome measures
The following PK endpoints will be assessed for test and reference products on day 1 of treatment period 1 and day 1 of treatment period 2:
1. T1/2
2. Kel
3. AUC (0-inf)
4. AUCEX (%) ([AUC0-inf - AUC0-t/AUC0-inf] * 100)
The endpoints will be measured using blood samples collected pre-dose (within an hour prior to dosing) and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 240, 360, 480 and 720 minutes for determination of ibuprofen plasma concentrations.

Safety and tolerability endpoints will be assessed for test and reference products:
1. Overall proportion of participants with adverse events (AEs), i.e. the occurrence of one or more AEs per participant.
2. The absolute value and change from baseline in each vital sign.
3. The absolute value and change from baseline in each haematology, biochemistry and urinary test.
AEs will be measured using non-leading questions throughout the study on day -28 to day -1, day -1 (periods 1 and 2), day 1 (periods 1 and 2), and follow-up

Overall study start date
30/09/2022

Completion date
14/01/2023

Eligibility

Key inclusion criteria
1. Participant has provided written informed consent
2. Comprehension of the nature and purpose of the study and willingness to comply with the requirements of the entire study
3. Healthy, adult, human volunteers of any race within the age range of 18 to 55 years (both inclusive)
4. Body Mass Index (BMI) ≥ 18.5 kg/m2 to ≤ 30 kg/m2
5. Haemoglobin: ≥12.0 gm% for male and ≥11.5 gm% for female
6. Electrocardiogram (ECG) (normal standard ECG in 12 leads after 10 minutes of rest in the supine position should meet the following parameters: 120 ms<PR<220 ms, QRS<120 ms, QTcF≤430 msec (males), QTcF≤450 msec (females))
7. Female participants of childbearing potential willing to use a highly effective method of contraception throughout the study and for one menstrual cycle after last drug administration
8. Negative serum β-Human Chorionic Gonadotrophin (HCG) at the time of screening (for females only)
9. Female participants who are post-menopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy). These subjects are not required to use contraception
10. Male participant who is willing to use contraception with their partner throughout the study (unless anatomically sterile) and agree to inform the Investigator if their partner becomes pregnant during this time. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy
11. Absence of disease markers of human immunodeficiency viruses (HIV I & II), Hepatitis B surface Antibody (HBsAg), Hepatitis C surface Antibody (HCVAb) and P24 antigen test
12. The investigator confirmed that within the last 12 months there is nothing in their medical history that would preclude their enrolment into the study

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
28

Key exclusion criteria
1. Female participant who is pregnant as confirmed by a positive pregnancy test (serum at screening and urine test at day -1 of each treatment period) or is lactating
2. History of undiagnosed vaginal bleeding (for females only)
3. In the opinion of the investigator, the participant has a clinically significant history of asthma or a documented intolerance to NSAIDs resulting in exacerbation of symptoms
4. In the opinion of the investigator, any participant with a clinically relevant history of peptic or

duodenal ulcers, gastrointestinal bleeding or perforation, frequent dyspepsia, migraine headaches, heart failure, renal or hepatic failure, uncontrolled hypertension, nasal polyps, or chronic rhinitis
5. History of chronic diarrhea or vomiting
6. Currently have or history of systemic lupus erythematosus and mixed connective tissue disease
7. History / evidence of allergy or hypersensitivity to Ibuprofen, aspirin, other NSAID, Paracetamol or to any components of the formulations or other allergy that, in the opinion of the investigator contraindicates their participation
8. Participant has a current and previous clinically significant medical history as deemed by the Investigator including but not limited to cardiovascular, respiratory, gastrointestinal, neurological, metabolic, or psychiatric disorders
9. Any major illness in last 12 months or any significant ongoing chronic medical illness, significant history of disease or metabolism disorder.
10. Participant has any condition that may currently interfere with the absorption, distribution, metabolism or excretion of drugs
11. Participant has a history of drug or alcohol abuse, in the opinion of the Investigator, in the two years prior to screening or a positive test for drugs of abuse and alcohol at screening
12. Participant has received an investigational product, or participated in another trial involving a marketed or investigational drug in the 90 days prior to first drug administration
13. Participant has previously been enrolled (randomised) into the current study
14. Participant who is an employee at the site or a partner or first-degree relative of the Investigator
15. Participant has used prescription drugs or vitamins, herbal and dietary supplements, including St. John's Wort, consumption of large quantities of methylxanthine-containing beverages (>5 cups of coffee/day or equivalent), grapefruit, cranberry or juices of these fruits at any time in the 14 days prior to drug administration until the collection of the last PK sample in treatment period 2 or OTC drugs at any time in the 7 days before first drug administration
16. Participant is a current smoker or ex-smoker who has smoked or used nicotine replacement products during the 45 days before screening
17. Participant has a known human immunodeficiency virus (HIV) positive status, or a positive viral serology screen
18. Participant has donated 450 mL or more of blood or blood products or had significant loss of blood in the 90 days prior to first drug administration
19. Haemoglobin level is below 11 gm/dL or for whom it drops >2gm/dL (compared to screening) during the study
20. Participant fails to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
23/11/2022

Date of final enrolment
03/01/2023

Locations

Countries of recruitment
Northern Ireland

United Kingdom

Study participating centre
Celerion GB Limited
22-24 Lisburn Road
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Sponsor information

Organisation
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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Reckitt Benckiser Pharmaceuticals

Alternative Name(s)
Reckitt Benckiser Pharmaceuticals, Inc., Reckitt Benckiser Pharmaceuticals Inc, Reckitt Benckiser Pharmaceuticals Limited, RBP

Funding Body Type

Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Internal report
2. Submission to regulatory authorities
3. Other

The Sponsor company will provide a Clinical Study Report (CSR) and/or associated results will be submitted to regulatory authorities where required for the study, for relevant safety updates to regulatory bodies (e.g. DSUR). The CSR will also be sent to the Investigator. Results from the study will be incorporated into the investigator brochure and be included in submissions for future studies.

Intention to publish date
14/01/2024

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?
HRA research summary			28/06/2023	No	No