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A study to see if a new generic form of primaquine is the same as the one currently on the market

Submission date
22/10/2021

Recruitment status
No longer recruiting

Registration date
11/11/2021

Overall study status
Completed

Last Edited
11/06/2024

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Primaquine (PQ) or PQ phosphate is a drug that was developed in the 1950s by the US army that is used to prevent relapse in Plasmodium vivax and P. ovale malaria and has been recommended for many years by the WHO for blocking the transmission of P. falciparum malaria.
There is now a growing interest in single low-dose PQ for blocking the transmission of Plasmodium falciparum, following the WHO's recommendation in 2012. WHO recommends the use of a single 0.25-mg/kg dose of PQ in combination with standard artemisinin-based combination therapy (ACT) for the treatment of P. falciparum malaria in elimination and resistance containment settings. Several trials have shown that single low-dose primaquine reduced mosquito infectivity.
Children are disproportionally affected by malaria of which vivax malaria affects young children less than 15 years of age, peaking between 2 and 6 years, which carries the highest risk of illness and death. Children under the age of 5 years accounted for 67% of deaths from malaria in the African region in 2019.
However, there are no paediatric PQ formulations that are friendly to children. The availability of paediatric drugs in the right dosage forms with acceptable taste and odour/flavour is critically important for increasing adherence and allowing PQ regimens that do not need tablet fractions or require crushing tablets.
PQ is now considered essential for eliminating malaria but to ensure child-friendly PQ is made available it either has to be WHO prequalified or registered with a stringent drug regulatory authority.
WHO prequalification offers the possibility of a line extension based on demonstrating proportionality with the adult 15 mg tablet. For a generic manufacturer, a bioequivalence study must be performed comparing the generic (test) product with the reference 15 mg of primaquine.
This study is to establish the bioequivalence of a new scored 15 mg generic PQ tablet, produced by IPCA in India. The study will be conducted to international standards, following WHO guidelines and other applicable requirements.

Who can participate?
Healthy volunteers aged 18-45 years old inclusive

What does the study involve?
A single dose of the test and the reference products, both corresponding to primaquine 15 mg, is given to healthy volunteers under fasting conditions in two consecutive periods with a break of at least 10 days. Vitals signs and well-being will be monitored and blood samples will be collected at specific timepoints.

What are the possible benefits and risks of participating?
Participation in this study will yield no direct benefits to the participants. The risks as mentioned below are minimized as only a single dose is given in each period with an appropriate break between treatment periods. The adverse events are nausea, vomiting, epigastric (upper abdomen) distress, abdominal cramps, leukopenia (low white blood cells), hemolytic anemia (low red blood cells) in G6PD-deficient individuals, and methemoglobinemia in NADH methaemoglobin reductase deficient individuals, cardiac arrhythmia (abnormal heart rhythm) and QT interval prolongation, dizziness, rash and pruritus (itching).
Blood taking causes discomfort but this tends to be brief. Rarely, the sampling site may become infected. Full aseptic techniques will be used when taking blood to minimise the infection risk. The volume of blood taken is very small and not a health threat.
There are no direct short term benefits to the community. If the researchers are able to eventually make paediatric primaquine available, people in malaria-endemic countries will benefit.

Where is the study run from?
Cliantha Research Limited (India)

When is the study starting and how long is it expected to run for?
May 2021 to May 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Bob Taylor
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
Protocol No. C1B00842, MORU Ref No. MAL21010

Study information

Scientific Title
Single-dose oral bioequivalence study of primaquine phosphate tablets USP 15 mg (test) and primaquine 15 mg tablet (reference) in healthy adult human subjects under fasting conditions

Acronym
BE_PRIM

Study objectives
Primaquine phosphate tablets USP 15 mg (test) has equivalence bioavailability to primaquine 15 mg tablet (reference).
The objectives of this study are:
1. To compare and evaluate the oral bioavailability of primaquine phosphate tablets USP 15 mg of IPCA with that of primaquine 15 mg tablet of Sanofi in healthy, adult, human subjects under fasting conditions.
2. To monitor the safety and tolerability of the subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 27/04/2022, Oxford Tropical Research Ethics Committee (OxTREC; University of Oxford Research Services, University Offices, Wellington Square, Oxford OX1 2JD, UK; +44 (0) 1865 282585; oxtrec@admin.ox.ac.uk), ref: 40-21
2. Approved 21/10/2022, IBIOME – IEC (B- 01, Krishna Complex, Near Rajpath Club, S. G. Highway, Bodakdev, Ahmedabad – 380 054, Gujarat – India, +91-97244 05402; ibiomeiec@gmail.com), ref: C1B00842

Primary study design
Interventional

Study design
Open-label randomized two-period two-treatment two-sequence crossover balanced single-dose oral bioequivalence study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bioequivalence study

Interventions
The following visits will be performed:
1. Screening phase: between Day -28 and Day -2
2. Interventional phase:
Period 1: Day -1 to 3
Wash-out interval of at least 10 days
Period 2: Day -1 to 3

A single dose of the test product (primaquine phosphate tablets USP 15 mg [IPCA]) and reference product (primaquine 15 mg tablet [Sanofi]) will be administered orally to the healthy male and female subjects under fasting conditions in two study periods as per the randomization schedule (TR or RT), generated by using SAS® statistical software, with a washout interval of at least 10 days between consecutive administration.

Both test and reference products will be orally administered, swallowed whole with about 240 ml of water at ambient temperature, on the morning of study Day 0. The first subject will be started at approximately 09:00 AM. This activity will be followed by a mouth and hand check of the subjects to assess compliance to dosing.

Vital signs and well-being assessment will be performed and blood samples for pharmacokinetic analysis will be collected at pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours post-dose in each period.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
The bioequivalent rate (Cmax) and extent (AUCt) of absorption of primaquine (plasma concentrations evaluated using LCMS/MS assay) after single dose administration of test and reference products, measured using samples collected at pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours in each period of this cross over study

Key secondary outcome(s)
1. The plasma PK profile of primaquine measured after single-dose administration of the test and reference products, measured using using LCMS/MS on samples collected at pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours in each period of this cross over study
2. The plasma PK profile of carboxyprimaquine after single-dose administration of the test and reference products (supportive data), measured using LCMS/MS on samples collected at pre-dose (0.0 hour) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours in each period of this cross over study
3. Safety and tolerability of subjects after single-dose administration of the test and reference products, assessed by measuring the full blood count and routine biochemistry on the first day of each dosing cycle

Completion date
01/05/2023

Eligibility

Key inclusion criteria
1. Age 18 to 45 years old, both inclusive
2. Male or non-pregnant, non-lactating female
2.1. Female of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test performed within 28 days prior to the first dosing day. They must be using an acceptable form of contraception.
2.2. For females of childbearing potential, acceptable forms of contraception include the following:
2.2.1. Non-hormonal intrauterine device in place for at least 3 months prior to the start of the study and remaining in place during the study period, or
2.2.2. Barrier methods containing or used in conjunction with a spermicidal agent, or
2.2.3. Surgical sterilization or
2.2.4. Practicing sexual abstinence throughout the course of the study
2.3. Females will not be considered of childbearing potential if one of the following is reported and documented on the medical history:
2.3.1. Postmenopausal with spontaneous amenorrhea for at least 1 year, or
2.3.2. Bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or
2.3.3. Total hysterectomy and an absence of bleeding for at least 3 months
3. BMI: 18.5 to 30.0 kg/m², both inclusive; BMI value should be rounded off to one significant digit after decimal point (e.g. 30.04 rounds down to 30.0, while 18.45 rounds up to 18.5)
4. Able to communicate effectively with study personnel
5. Willing to provide written informed consent to participate in the study

6. Non-smokers and non-tobacco users (i.e. having no past history of smoking and tobacco consumption for at least 1 year prior to the study)
7. All volunteers must be judged by the principal or sub-investigator or physician as normal and healthy during a pre-study safety assessment performed within 28 days of the first dose of study medication which will include:
7.1. A physical examination (clinical examination) with no clinically significant finding
7.2. Results within normal limits defined site normal range for the following tests:
7.2.1. Hematology: haemoglobin, total RBC count, total WBC count, platelet count, differential leukocyte count: neutrophils, lymphocytes, eosinophils, monocytes, basophils, blood indices: HCT, glucose-6-phosphate dehydrogenase (G6PD)
7.2.2. Biochemistry: BUN, serum creatinine, random glucose, SGPT & SGOT, alkaline phosphatase, uric acid, serum bilirubin, serum total protein: total proteins, albumin, serum electrolytes: serum sodium, serum chloride, serum potassium, serum phosphorous, serum calcium
7.2.3. Urinalysis: colour, quantity, specific gravity, odour, appearance, reaction, albumin, bilirubin, ketone bodies, sugar, urobilinogen and microscopical examination (performed based on clinical judgment)
7.2.4. Immunological tests: HIV-I & II, HBsAg, syphilis (RPR), anti HCV
7.2.5. Serum (β-HCG) pregnancy test (for females of childbearing potential)
7.2.6. Additional tests and/or examinations (apart from those mentioned in the protocol) may be performed, if necessary, based on the principal investigator's discretion
7.2.7. All results will be assessed against the current laboratory normal ranges at the time of testing and a copy of the normal ranges used will be included in the study documentation

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
All

Total final enrolment
50

Key exclusion criteria
1. History of allergic responses to primaquine or other related drugs, or any of its formulation ingredients
2. Have significant diseases or clinically significant abnormal findings during screening [medical history, physical examination (clinical examination), laboratory evaluations, ECG, chest X-ray recording, and, for females, gynaecological history
3. Any disease or condition like diabetes, psychosis or others, which might compromise the

haemopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system or any other body system
4. History or presence of bronchial asthma
5. Use of any hormone replacement therapy within 3 months prior to the first dose of study medication
6. A depot injection or implant of any drug within 3 months prior to the first dose of study medication
7. Use of CYP enzyme inhibitors or inducers within 30 days prior to the first dose of study medication (see http://medicine.iupui.edu/clinpharm/ddis/main-table)
8. History or evidence of drug dependence or of alcoholism or of moderate alcohol use
9. History of difficulty with donating blood or difficulty with the accessibility of veins
10. A positive hepatitis screen (includes subtypes B & C)
11. A positive test result for HIV antibody and/or syphilis (RPR)
12. Volunteers who have received a known investigational drug within seven elimination half-life of the administered drug prior to the first dose of study medication
13. Volunteers who have donated blood or lost blood: 50 ml to 100 ml within 30 days or 101 ml to 200 ml within 60 days or >200 ml within 90 days (excluding volume drawn at screening for this study) prior to the first dose of study medication, whichever is greater
14. History of difficulty in swallowing or of any gastrointestinal disease, which could affect drug absorption
15. Intolerance to venepuncture
16. Any food allergy, intolerance, restriction or special diet that, in the opinion of the principal investigator or sub-investigator, could contraindicate the volunteer's participation in this study
17. Institutionalized volunteers
18. Use of any prescribed medications within 14 days prior to the first dose of study medication
19. Use of any OTC products, vitamin and herbal products, etc, within 7 days prior to the first dose of study medication
20. Use of grapefruit and grapefruit-containing products within 7 days prior to the first dose of study medication
21. Ingestion of any caffeine or xanthine products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc), recreational drugs, alcohol or other alcohol-containing products within 48 hours prior to the first dose of study medication
22. Ingestion of any unusual diet, for whatever reason (e.g. low sodium) for 3 weeks prior to the first dose of study medication
23. Volunteers with glucose-6-phosphate dehydrogenase (G6PD) deficiency
24. Volunteers with a family or personal history of hemolytic anemia

Date of first enrolment
14/12/2022

Date of final enrolment
30/12/2022

Locations

Countries of recruitment
India

Study participating centre

Cliantha Corporate
TP 86, FP 28/1, Off S.P. Ring Road
Sarkhej
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 03/04/2024:
The data from this study may be available upon receipt of a formal request and submission to

the MORU Data Access Committee. Data cannot be shared until after we have obtained primaquine prequalification.

Previous IPD sharing plan:
Data will be shared according to the MORU data sharing policy on request from datasharing@tropmedres.ac. The data may be available in 2023.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		11/06/2024	11/06/2024	Yes	No
Other unpublished results		23/05/2024	23/05/2024	No	No
Protocol file	version 3.0	04/10/2022	01/03/2024	No	No
Statistical Analysis Plan	version 3.0	04/10/2022	01/03/2024	No	No