A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemoprophylactic Activity of M5717 in a Controlled Plasmodium falciparum Sporozoite Challenge Model in Healthy Participants

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Primary Objectives:- To assess chemoprophylactic activity of single oral doses of M5717 administered after DVI of Plasmodium falciparum sporozoites (PfSPZ) challenge in healthy participants. - To explore the dose-exposure-response relationship of a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ectoparasitic disorders
Study type	Interventional

Summary

ID

NL-OMON49971

Source
ToetsingOnline

Brief title
Chemoprophylactic Activity of M5717 in PfSPZ Challenge Model

Condition

- Ectoparasitic disorders

Synonym
malaria

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: opdrachtgever onderzoek (bedrijf)

Intervention

Keyword: controlled human malaria infection, malaria, plasmodium falciparum, prevention

Outcome measures

Primary outcome

Response endpoints:

- Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge

- Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days)

- Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI

- Clinical symptoms of malaria using the Malaria Clinical Score.

Dose-exposure-response relationship:

- Selected pharmacokinetic (PK) endpoints/concentrations (e.g. AUC0-24, AUC0-144, C24, C144) and pharmacodynamic (PD) endpoints (cured/not-cured) will

be used for PK/PD modeling approaches.

Secondary outcome

- Nature, incidence, frequency, severity of adverse events (AEs)/ serious adverse events (SAEs), and relationship to the study intervention
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin (total)], and urinalysis)
- Incidence of clinically significant changes and abnormalities in vital signs and 12 lead electrocardiogram (ECG).

Exposure endpoints:

- Concentration-time curve for M5717 after single-dose administration
- Pharmacokinetic parameters of M5717 such as AUC0-*, AUC0-t, AUC0-24, AUC0-144, Cmax, C24, C144, tmax, t1/2, *Z, CL/f and Vz/f to be specified in the Integrated Analysis Plan.

Study description

Background summary

Human malaria is an acute febrile illness caused by five Plasmodium parasite species (P falciparum, P vivax, P malariae, P ovale and P knowlesi). According to the latest estimates, released on 19 November 2018 by the World Health Organization (WHO), there were about 219 million cases of malaria and an estimated 435,000 deaths due to malaria worldwide in 2017 (WHO Malaria report , 2018). Most deaths (60%) occur among children below 5 years of age, most of whom live in Africa. In a non-immune individual, symptoms appear about 7 days after the infective mosquito bite and the subsequent asymptomatic liver stages.

Although atovaquone-proguanil (Malarone®) and recently tafenoquine (ArakodaTM, 60 Degrees Pharmaceuticals, Washington, DC, USA) have been registered for chemoprophylaxis in the traveler population, there are limited preventive chemotherapy options available for extended use by the populations in endemic areas and migrants. Chemoprophylactic agents are mainly based on the repurposing of drugs used for treatment and all of these agents are facing emerging or established resistance.
The development of new treatments in malaria targeting prophylaxis and transmission is becoming increasingly important. Target Product Profiles have been defined in the malaria drug development field to address future cure and chemoprophylaxis compound profiles, consistent with the strong recommendation from WHO to develop only combination therapies, to minimize the risk of emerging resistance (Burrows JN et al., 2013).
M5717 is a first-in-class compound with a new mode of action (i.e., inhibition of plasmodial protein synthesis by targeting the Plasmodium eukaryotic translation Elongation Factor 2 [PeEF2]) and shows excellent activity against malaria blood-stages (including clinical isolates and drug-resistant strains), liver-stages, and in transmission blocking assays in preclinical investigations. M5717 displayed a long half-life and an effective exposure with high potency against all forms of the parasite. This allows for administration of a single oral dose and maintaining protection over an extended period of time.
In the view of accelerating the development of new antimalarial medications, CHMI studies have been established, involving infection of participants with low numbers of malaria parasites, either through injection of sporozoites and allowing the development of pre-erythrocytic stages, or injection of malaria-infected erythrocytes (blood stage). These models are well-accepted, their safety profile is well understood, and their overall benefit was demonstrated in terms of reduction of development times and limiting the number of participants in Phase II dose-finding studies.
The DVI of P falciparum sporozoites (PfSPZ) is a validated and standardized model for 100% induction of malaria infection in healthy participants (Mordmüller et al., 2015). DVI of 3200 PfSPZ has been implemented for testing efficacy of malaria vaccines (Jongo et al., 2018; Mordmüller et al., 2017) and more recently for evaluating efficacy of antimalarial drugs (Murphy et al., 2018; Sulyok et al., 2017).
The aim of this study is to assess the chemoprophylactic activity and to explore the dose-exposure-response relationship of single oral doses of M5717 administered immediately (early liver stage) or few days after (late liver stage) DVI of PfSPZ Challenge in malaria-naïve, healthy participants in the CHMI model.

Study objective

Primary Objectives:
- To assess chemoprophylactic activity of single oral doses of M5717 administered after DVI of Plasmodium falciparum sporozoites (PfSPZ) challenge

in healthy participants.
- To explore the dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge in healthy participants.

Secondary Objectives:
- To evaluate the safety and tolerability of single, oral doses of M5717 in healthy participants following infection with PfSPZ challenge.
- To investigate the PK of M5717 after administration of single, oral doses in healthy participants following infection with PfSPZ.

Exploratory Objectives:
- To determine the incidence of resistance generation following M5717 administration.
- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of M5717 (optional).

Study design

Double-blind, randomized, placebo-controlled study.

Intervention

4 to 5 cohorts are planned with different doses. The number of participants will be 4 to 12 participants per cohort with an active to placebo ratio of 3:1. This means that of every 4 participants, 3 will receive an active treatment with M5717 and 1 will receive a placebo.
Participants will receive M5717 or placebo capsules dissolved in water once. The starting dose of M5717 of the first cohort is 200 mg.

The dosage of consecutive cohorts depends on the assessment of safety and PK / PD by the Safety Monitoring Committee (SMC).

This study targets the early stage since for prophylaxis this will give an indication about the concentrations that are needed to have an effect on the parasite in the liver. This is the concentration that needs to be attained over a certain period of e.g.7 days (if dosing is weekly) to be able to prevent the parasite to develop in a human as the human can be infected at all days in this time period. By investigating the effect on the early stage it is thought that this concentration can then be extrapolated to a dose that will ensure high enough blood concentrations needed for prophylaxis for a certain time period (e.g 7 days in our example). It will also help to determine whether dosing every 2 or 3 weeks for prophylaxis is feasible (i.e. if the effective dose needed to sustain certain levels over a certain period does not give safety concerns).

It might be possible that a subject starts with malaria prophylaxis in the

clinical situation when already being infected with the parasite but not yet having progressed to the erythrocyte stage. Thus the malaria infection cannot be detected in the blood of the subject. The second part of the study would like to investigate whether the concentrations that have been established to be effective on the early liver stage, are still effective when the parasite has already multiplied and progressed to the late liver stage.

The concentrations and doses that will be identified in the current study will substantially reduce the number of doses to be investigated in a clinical study in the target population.

Study burden and risks

Burden:
- Admission to the hospital / study site:
- Visits to the doctor / researcher: max 30;
- Daily contact (on site or by telephone / by email) with the doctor / researcher;
- Intravenous injection (inoculation): once;
- Blood tests: 26 times, 12 ml per time;
- Urine examination: 15 times;
- Alcohol breath test: 3 times;
- Physical examination: 4 times;
- Vital signs: 13 times;
- ECG measurement: 5 times;
- Diary: daily from the time of discharge;
- Fasting: from 8 hours prior to 4 hours after dosing. Water is allowed up to 2 hours before the dose and again after 2 hours after the dose.
- Nutritional restrictions: starting 14 days prior to the study until the end of the study.
- Restrictions in the use of medication: see In / Exclusion criteria for details regarding duration.
- Use of contraception: during the study intervention period up to a minimum of 120 days for male and 62 days for female after receiving study medication.
- Travel restrictions: for the entire duration of the study.
- Smoking restrictions: the use of tobacco products is not permitted for the entire duration of participation in the study.
- Alcohol restrictions: abstention from alcohol consumption for 1 week prior to study treatment. After the end of the admission to the research location, no more than 1 drink (2 units) of alcohol per day until the end of the study visit.
- Exercise restrictions: abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Refrain from taking up any new unaccustomed exercise from Screening until the End of Study visit.
- Availability of contact person with whom test subject cohabits: daily during the entire study.

Risks:

- Possible side effects of the study medication: headache, tachycardia, upper respiratory tract infection, sunburn, lymphopenia, myalgia, dizziness, contusion, oropharyngeal pain, rhinorrhea, abdominal discomfort, arthralgia, blurred vision, abdominal distension, increased ALT, increased AST, diarrhea, increased creatine phosphokinase in the blood, oral hypoaesthesia, neutropenia, pyrexia and flushing.
- Possibility of malaria infection.
- Possible side effects of Malarone or Riamet rescue medication.
- Possibility of a positive HIV or Hepatis test result.
- Possibility of a positive pregnancy test.
- Possible damage to an unborn child.
- Possible abrasions in places where electrodes are placed for the ECG metig.
- Possible discomfort and side effects associated with blood sampling: bruising, infection of the puncture site, dizziness, nausea and fainting.

Justification for research:
The risk for the subjects in this study has been minimized by adequate inclusion and exclusion criteria, extensive medical monitoring, and a well-considered dosing schedule. All this makes the risk acceptable to the subjects in light of the "unmet need" of medication against malaria.

Contacts

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Scientific
Merck

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age
1. Are between 18 and 45 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Are overtly healthy as determined by medical evaluation, including no clinically significant abnormality identified on physical examination or laboratory evaluation and no active clinically significant disorder, condition, infection or disease that would pose a risk to participant safety or interfere with the study evaluation, procedures or completion.
Weight
3. Have a body weight within 50 to 100 kg and body mass index within the range 19.0 to 29.9 kg/m2 (inclusive).
Sex
4. Are male or female
Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.
* Male Participants:
Agree to the following during the study intervention period and for at least 120 days after the day of the study intervention dose (covering a full sperm cycle of 90 days starting after 5 half-lives of last dose of study intervention:
* Refrain from donating sperm
PLUS, either:
* Abstain from intercourse with a woman of childbearing potential
OR
* Use a male condom:
* When having sexual intercourse with a woman of childbearing potential, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3 Contraception, since a condom may break or leak.
* Female Participants:
* Have a negative serum test at Screening and a highly sensitive urine pregnancy test within 24 hours before the first study intervention (DVI) and within 24 hours before the second study intervention (M5717) administration, as required by local regulations. [If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive].

* Are not pregnant or breastfeeding, and at least one of the following conditions applies:
* Not a woman of childbearing potential
* At least 1 year post-menopausal (amenorrhea * 12 months and follicle-stimulating hormone (FSH) * 40 mIU/mL) at Screening;
* Surgically sterile (bilateral oophorectomy, hysterectomy or bilateral salpingectomy; tubal ligation alone is not sufficient).
OR
* If a woman of childbearing potential, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
* Before the first dose of the study intervention(s), if using hormonal contraception:
* Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses
OR
* Has used a depot contraceptive or extended-cycle oral contraceptive for at least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
* During the intervention period
* After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 62 days, corresponding to the time needed to eliminate any study intervention(s) (5 times terminal half-live of 155 hours) plus 30 days (a menstrual cycle) after the last dose of study intervention (and agree not to donate eggs (ova, oocytes) for reproduction during this period).
* Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.
* The investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.
Informed Consent
5. Capable of giving signed informed consent, as indicated in Appendix 2 Study Governance, which includes compliance with the requirements (including mandatory intake of rescue medication to participants who have been administered the investigational P. falciparum sporozoite challenge) and restrictions listed in the informed consent form (ICF) and this protocol.
Other Inclusions
6. A non-smoker or ex-smoker for more than 90 days prior to Screening, or a smoker of no more than 5 cigarettes per day or nicotine products (spray, patch, e-cigarette, etc.) equivalent of no more than 5 cigarettes per day. Participants must agree to abstain from smoking while in the study.
7. Willing to adhere to the prohibitions and restrictions (see Section 6.5.3) specified in this protocol, including willingness to stay confined to the inpatient unit for the required duration and willingness to avoid extensive travelling during the study period.
8. Different ways of being reachable 24 hours per day, 7 days per week (e.g.,

by mobile phone, regular phone or electronic mail) during the whole study period.
9. Does not live alone (from start of DVI with malaria sporozoites until at least the end of the antimalarial drug treatment), willing to provide contact details of a person living with him/her who is contactable and available for the duration of the study.

Exclusion criteria

Medical Conditions
1. 12-Lead electrocardiogram (ECG) outside normal range (QTcF > 450 ms, PR interval > 215 ms, or QRS > 120 ms) and deemed clinically relevant by the Investigator.
2. Supine systolic blood pressure > 140 or < 90 mmHg, diastolic blood pressure > 90 or < 50 mmHg, and pulse rate > 90 or < 50 beats per minute (min) at Screening and at Admission on Day -1 (Any abnormal blood pressure or pulse rate results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion).
3. Seropositive for human immunodeficiency virus (HIV) I and II antibody or antigen), hepatitis B virus (HBV; hepatitis B surface antigen [HBsAg]), or hepatitis C virus (HCV; antibody) tests.
4. Liver function tests (see Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments) above the upper limit of normal (ULN) (> 3xULN) (as specified in the Laboratory Manual) the day before DVI / study intervention administration (Day -1).
5. History or presence of diagnosed food or known drug allergies (including but not limited to allergy to any of the antimalarial rescue medications to be used in the study), or history of anaphylaxis or other severe allergic reactions.
Note: Participants with seasonal allergies/hay fever, house dust mite allergy, or allergy to animals that are untreated and asymptomatic at the time of dosing can be enrolled in the study.
6. History of a serious psychiatric condition that may affect participation in the study or preclude compliance with the protocol.
7. Any surgical or medical condition possibly affecting drug absorption (e.g. cholecystectomy, gastrectomy, bowel disease), distribution, metabolism or excretion.
8. Any history of gallbladder disease, including cholecystitis and/or cholelithiasis.
9. Any condition that in the opinion of the investigator would jeopardize the safety or rights of a person participating in the study or would render the person unable to comply with the protocol.
10. Frequent headaches of clinical relevance and/or migraine, recurrent nausea, and/or vomiting (> 2 times per month).
11. Ingestion of any poppy seeds within 24 hours prior to each Drug Abuse Screening.

12. Personal history of malaria or medical history of possible exposure to malaria.
13. Presence of acute infectious disease or fever (i.e., sublingual temperature * 38.0°C) within the 5 days prior to DVI with malaria sporozoites.

Prior/Concomitant Therapy

14. Use of medications known to interact with atovaquone-proguanil (Malarone) or artemether-lumefantrine (Riamet) such as cimetidine, metoclopramide or antacids, or an anticipated requirement for the use of these at any point during the study period (see also Section 5.1).
15. Use of systemic antibiotics with known antimalarial activity within 30 days (or 5 half-lives whichever is longer) of first study intervention administration (e.g. trimethoprim-sulfamethoxazole, doxycycline, tetracycline, clindamycin, erythromycin, fluoroquinolones or azithromycin) or an anticipated requirement for the use of these during the study period.
16. Use of any prescription drugs, herbal supplements (e.g., St John's Wort) or over-the-counter medication within 7 days or five half-lives (whichever is longer) prior to the first study intervention administration, or an anticipated requirement for the use of these during the course of the study.

Note: If necessary, the incidental use of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (2 g/day, 10 g/week), vitamins and topical treatments may be acceptable after approval by the Investigator and will be documented in the eSource system. The use of nutritional supplements during this time that are not believed to have the potential to affect participant safety or the overall results of the study, may be permitted on a case-by-case basis, following approval by the Sponsor in consultation with the Investigator.

Prior/Concurrent Clinical Study Experience

17. Participation in an investigational drug or device study within 3 months prior to first dosing or more than 4 times a year or plans to participate in other investigational drug or vaccine research during the study period.

Diagnostic Assessments

None.

Other Exclusions

18. Personnel (e.g. investigator, sub-investigator, research assistant, pharmacist, study coordinator or anyone mentioned in the delegation log) directly involved in the conduct of the study or students of the departments involved.
19. Intake of grapefruit, Seville oranges, cranberries, star fruit or juices of these fruits, as well as quinine-containing food/beverages (e.g., tonic water, bitter lemon), within 14 days prior to study intervention administration until the end of the ambulatory period.
20. Participant has travelled to or lived in a malaria-endemic area for more than 4 weeks during the 12 months prior to first study intervention administration or spent any time in an endemic area during the 4 weeks prior to first study intervention administration.
21. Plans to travel to a malaria-endemic region during the study period up to last Follow-Up (FU) visit.
22. Previous participation in any malaria vaccine or CHMI study.

23. Participant with a whole blood donation or loss of > 450 mL within 60 days before administration of study drug or unwilling to defer blood donations for 6 months.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-09-2020
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	M5717
Generic name:	1□[2-8{6-fluoro-2-[4-(morpholin-4-ylmethyl)phenyl]quinolin-4-yl}formamido) pyrrolidin-1-ium 3-carbox

Ethics review

Approved WMO

Date:	20-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	06-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-003414-14-NL
CCMO	NL71266.056.19