Clinical trial results:
Controlled Human Malaria Infection study to assess gametocytaemia and mosquito transmissibility in participants challenged with Plasmodium falciparum by sporozoite challenge to establish a model for the evaluation of transmission-blocking interventions

Summary

EudraCT number	2016-001379-66
Trial protocol	NL
Global end of trial date	29 June 2017

Results information

Result version number	v1 (current)
This version publication date	28 March 2018
First version publication date	28 March 2018
Summary attachment (see zip file)	2018 eLife - Reuling et al. A randomized feasibility trial comparing four antimalarial drug regimens to induce Pf gametocytemia in CHMI (2018 eLife - Reuling et al. A randomized feasibility trial comparing four antimalarial drug regimens to induce Pf gametocytemia in CHMI.pdf)

Trial information

Trial identification

Sponsor protocol code	CHMI-trans1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02836002
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	Geert-grootplein 26, Nijmegen, Netherlands, 6500HB
Public contact	Center for Clinical Malaria Studies, Radboud university medical center, isaie.reuling@radboudumc.nl
Scientific contact	Center for Clinical Malaria Studies, Radboud university medical center, isaie.reuling@radboudumc.nl

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	29 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2017
Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the safety of four different CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge.
- To determine the best CHMI-trans protocol for induction of stable gametocytaemia at densities detectable by qRT-PCR

Protection of trial subjects:

The study represents a challenge infection by bites of 5 (3D7 P. falciparum) infected mosquitoes. After the challenge there will be a period (42 days) of intense clinical monitoring with frequent site visits (up to two times a day) and blood examinations. Depending on the group, the subjects will receive a sub-curative treatment (DT1) with either sulfadoxine-pyrimethamine or piperaquine when 18S qPCR positive at 5000 par/ml (threshold of microscopic detection). Using blood samples taken twice daily, the initial clearance of parasitaemia will be carefully monitored. After DT1, volunteers will receive a curative treatment (DT2) when a recrudescence of asexual parasitaemia occurs or on day 21 post challenge infection, whichever comes first. Recrudescence of asexual parasitaemia will be carefully monitored until parasite densities reach 1,500 par/ml by 18S qPCR, at which time participants will receive a curative dose of sulfadoxine-pyrimethamine or piperaquine (DT2) depending on the study group to provide clearance of asexual parasites. All volunteers will receive a final treatment (ET) according to national guidelines with Malarone® on day 42 to assure the radical clearance of all parasite stages. In case a volunteer remains 18S qPCR and Pfs25 qRT-PCR negative for 7 days after DT1, final treatment with Malarone® will also be initiated and end of study will apply for the volunteer. The exact number of site visits and blood examinations per volunteers depends on the time to positive 18S qPCR above 5000 parasites/ml and potential recrudescence - with a maximum number of 50 study visits and a maximum of 500 mL collected blood. In addition periodical physical examinations will be performed and the subject is asked to complete a diary. The duration of subject participation will be 64 days from day of challenge, following a screening period of up to 120 days.

Background therapy:

Volunteers may be advised to take tripelennamine crème for the local treatment of mosquito bites. Volunteers are advised to take paracetamol for complaints secondary to the CHMI (fever, muscle aches, headache, etc.). Tripelennamine crème, paracetamol or any other symptomatic treatment will be supplied to the volunteers. The maximum dose of paracetamol
is 4 grams a day.

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This single centre, open-label randomised trial was conducted at the Radboud university medical center (Radboudumc), Nijmegen, the Netherlands. Healthy malaria-naive male and female participants aged 18–35 years were recruited from June until November 2016.

Pre-assignment

Screening details:

Screening included physical examination, electrocardiography (ECG), hematology and biochemistry parameters and serology for human immunodeficiency virus (HIV), hepatitis B and C, and asexual stages of P. falciparum. Informed consent was provided by all participants at screening visit.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Experimental: Group 1 - SP low/SP high

Group 1 will be treated with a course of subcurative sulfadoxine-pyrimethamine (SP) (SP low, 500mg/25mg) as treatment 1.

As treatment 2 (SP high) volunteers will receive a treatment with sulfadoxine-pyrimethamine (1000mg/50mg).

Group 1 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Arm type	Experimental
Investigational medicinal product name	sulphadoxine-pyrimethamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Sulfadoxine-pyrimethamine (low dose)
- subcurative regimen (500mg/25mg)

Other Name: Fansidar
Drug: Sulfadoxine-pyrimethamine (high dose)
- curative regimen (1000mg/50mg)

Other Name: Fansidar
Biological: malaria challenge infection, P. falciparum 3D7
malaria challenge infection by P. falciparum 3D7-infected mosquito bites

Other Name: 3D7 Plasmodium falciparum
Drug: Atovaquone-proguanil
- curative regimen: 1000/400 mg, for 3 days

Other Name: Malarone

Arm title	Group 2

Arm description:

Experimental: Group 2 - SP low/Pip high

Group 2 will be treated with a course of subcurative sulfadoxine-pyrimethamine (SP) (SP low, 500mg/25mg) as treatment 1.

As treatment 2 (Pip high) volunteers will receive a treatment with piperaquine (960mg).

Group 2 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Arm type	Experimental
Investigational medicinal product name	sulphadoxine-pyrimethamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Sulfadoxine-pyrimethamine (low dose)
- subcurative regimen (500mg/25mg)

Investigational medicinal product name	piperaquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Piperaquine (high dose)
- curative regimen (960 mg)

Arm title	Group 3

Arm description:

Experimental: Group 3 - Pip low/Pip high

Group 3 will receive piperaquine (Pip) in a low-dose (Pip low, 480 mg) as treatment 1.

As treatment 2 (Pip high) volunteers will receive a treatment with piperaquine (960mg).

Group 3 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

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

Dosage and administration details:

Drug: Piperaquine (high dose)
- curative regimen (960 mg)

Investigational medicinal product name	piperaquine
Investigational medicinal product code	
Other name	piperaquine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Piperaquine (low dose)
- subcurative regimen (480 mg)

Other Name: piperaquine phosphate

Arm title	Group 4

Arm description:

Experimental: Group 4 - Pip low/SP high

Group 4 will receive piperaquine (Pip) in a low-dose (Pip low, 480 mg) as treatment 1.

As treatment 2 (SP high) volunteers will receive a treatment with sulfadoxine-pyrimethamine (1000mg/50mg).

Group 4 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Arm type	Experimental
Investigational medicinal product name	piperaquine
Investigational medicinal product code	
Other name	piperaquine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Piperaquine (low dose)
- subcurative regimen (480 mg)

Other Name: piperaquine phosphate

Investigational medicinal product name	sulphadoxine-pyrimethamine
Investigational medicinal product code	
Other name	Fansidar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Sulfadoxine-pyrimethamine (high dose)
- curative regimen (1000mg/50mg)

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	8	8	8
Completed	4	4	4
Not completed	4	4	4
safety assessment	4	4	4

Number of subjects in period 1	Group 4
Started	8
Completed	4
Not completed	4
safety assessment	4

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	32	32	
Age categorical			
Healthy malaria-naive male and female participants aged 18–35 years			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	23		
standard deviation	± 2	-	
Gender categorical			
Healthy malaria-naive male and female participants aged 18–35 years			
Units: Subjects			
Female	24	24	
Male	8	8	

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Experimental: Group 1 - SP low/SP high

Group 1 will be treated with a course of subcurative sulfadoxine-pyrimethamine (SP) (SP low, 500mg/25mg) as treatment 1.

As treatment 2 (SP high) volunteers will receive a treatment with sulfadoxine-pyrimethamine (1000mg/50mg).

Group 1 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Reporting group title	Group 2

Reporting group description:

Experimental: Group 2 - SP low/Pip high

Group 2 will be treated with a course of subcurative sulfadoxine-pyrimethamine (SP) (SP low, 500mg/25mg) as treatment 1.

As treatment 2 (Pip high) volunteers will receive a treatment with piperaquine (960mg).

Group 2 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Reporting group title	Group 3

Reporting group description:

Experimental: Group 3 - Pip low/Pip high

Group 3 will receive piperaquine (Pip) in a low-dose (Pip low, 480 mg) as treatment 1.

As treatment 2 (Pip high) volunteers will receive a treatment with piperaquine (960mg).

Group 3 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Reporting group title	Group 4

Reporting group description:

Experimental: Group 4 - Pip low/SP high

Group 4 will receive piperaquine (Pip) in a low-dose (Pip low, 480 mg) as treatment 1.

As treatment 2 (SP high) volunteers will receive a treatment with sulfadoxine-pyrimethamine (1000mg/50mg).

Group 4 will receive a malaria challenge infection, P. falciparum 3D7 -infected mosquito bites Final treatment with a curative regimen of atovaquone/proguanil (malarone).

Primary: Frequency and magnitude of adverse events

End point title	Frequency and magnitude of adverse events

End point description:

End point type	Primary

End point timeframe:

up to day 42 after challenge infection

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: numbers	4	4	4	4

Attachments (see zip file)	manuscript/2018 eLife - Reuling et al. A randomized feasibility

Statistical analyses

Statistical analysis title	anova between groups adverse events

Statistical analysis description:

There were no serious adverse events or significant differences in the occurrence and severity of adverse events between study arms (p=0.49 and p=0.28).

Comparison groups	Group 1 v Group 2 v Group 3 v Group 4
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05 [2]
Method	ANOVA

Notes:

[1] - There were no serious adverse events or significant differences in the occurrence and severity of adverse events between study arms (p=0.49 and p=0.28).

[2] - There were no serious adverse events or significant differences in the occurrence and severity of adverse events between study arms (p=0.49 and p=0.28).

Primary: gametocyte prevalence

End point title	gametocyte prevalence[3]

End point description:

End point type	Primary

End point timeframe:

up to day 42 after challenge infection

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: all subjects had gametocytes as measured by RT-qPCR. Therefore no differences were found in prevalence between groups.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: numbers	4	4	4	4

Attachments (see zip file)	manuscript/2018 eLife - Reuling et al. A randomized feasibility

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: up to day 42 after challenge infection	
Adverse event reporting additional description: daily questionnaire	
Assessment type	Systematic

Dictionary used	
Dictionary name	none
Dictionary version	0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events are shown in table 3 and 4 of the manuscript attached. these results are not differentiated if drug- or malaria infection related. therefore it is not specified in the adverse events section as such.

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? Yes

Date	Interruption	Restart date
11 November 2016	After observed transient liver enzyme elevations in the first cohort, the study was temporarily put on hold and the already initiated infections in the second cohort of 13 participants were abrogated by curative treatment on day 3 post challenge. The hold was lifted after reviewing safety data. Participants from the first cohort completed all study visits, and form the basis of the study results	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29482720