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	2017-004005-40
Trial protocol	NL
Global end of trial date	20 November 2018

Results information

Result version number	v1 (current)
This version publication date	13 March 2021
First version publication date	13 March 2021
Summary attachment (see zip file)	Alkema M, Reuling IJ, de Jong GM, et al. A randomized clinical trial to compare P. falciparum gametocytaemia and infectivity following blood-stage or mosquito bite induced controlled malaria infection (jiaa157 (1).pdf)

Trial information

Trial identification

Sponsor protocol code	NL63552.000.17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03454048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	Geert Grooteplein Zuid 26-28, Nijmegen, Netherlands,
Public contact	teun.bousema@radboudumc.nl, Radboud university medical center, teun.bousema@radboudumc.nl
Scientific contact	teun.bousema@radboudumc.nl, Radboud university medical center, teun.bousema@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	20 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2018
Global end of trial reached?	Yes
Global end of trial date	20 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the safety of CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge and blood stage challenge.
2) To assess gametocyte infectiousness for Anopheles mosquitoes through mosquito feeding assay (Direct Membrane Feeding Assay, DMFA).

Protection of trial subjects:

Subjects were monitored twice daily on parasitaemia and adverse events, safety laboratory measurements were perfomed daily and a study physician is reachable 24 hours a day.
An independend safety monitoring committee reviewed all safety data throughout set timepoint during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

From a total of 41 screened volunteers, 24 healthy adults were enrolled.
Reasons for exclusion were: 4 invesigator's decision, 4 RhC and/or RhE incompatibility, 3 withdrew consent, 1 history of blood transfusion, 1 BMI>30, 1 CV risk profile (family history), 1 LFT abnormalities, 1 Recurrent UTIs.

Period 1

Period 1 title	CHMI-trans2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP

Arm description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).

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:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).

Investigational medicinal product name	malaria challenge infection by P. falciparum 3D7-infected mosquito bites
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes.

Arm title	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP

Arm description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

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:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

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

Dosage and administration details:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Investigational medicinal product name	malaria challenge infection by P. falciparum 3D7-infected mosquito bites
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes.

Arm title	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP

Arm description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 3 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg)

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:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).

Investigational medicinal product name	P. falciparum 3D7-infected human erythrocytes for the purpose controlled human malaria infection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection.

Arm title	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP

Arm description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 4 (LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

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:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

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

Dosage and administration details:

All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Investigational medicinal product name	P. falciparum 3D7-infected human erythrocytes for the purpose controlled human malaria infection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection.

Number of subjects in period 1	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP
Reporting group description:	
Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).	
Reporting group title	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP
Reporting group description:	
Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).	
Reporting group title	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP
Reporting group description:	
Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 3 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg)	
Reporting group title	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Reporting group description:	
Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 4 (LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).	

Reporting group values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP
Number of subjects	6	6	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults	0	0	0
Age continuous Units: years			
median	24.5	22.5	25.5
full range (min-max)	18 to 30	19 to 26	20 to 29

Gender categorical Units: Subjects			
Female	3	4	4
Male	3	2	2
Hemoglobin Units: mmol/L			
median	8.8	8.2	8.8
full range (min-max)	8.0 to 9.7	7.6 to 909	7.6 to 10.0
Body Mass Index Units: Kg/m2			
median	22.2	24.2	20.4
full range (min-max)	20.8 to 29.3	22.7 to 26.9	18.1 to 22.8

Reporting group values	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP	Total	
Number of subjects	6	24	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	24	
From 65-84 years	0	0	
85 years and over	0	0	
Adults	0	0	
Age continuous Units: years			
median	20		
full range (min-max)	19 to 26	-	
Gender categorical Units: Subjects			
Female	4	15	
Male	2	9	
Hemoglobin Units: mmol/L			
median	8.7		
full range (min-max)	7.5 to 9.4	-	
Body Mass Index Units: Kg/m2			
median	24.7		
full range (min-max)	20.8 to 27.7	-	

End points

End points reporting groups

Reporting group title	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP

Reporting group description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).

Reporting group title	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP

Reporting group description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Reporting group title	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP

Reporting group description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 3 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg)

Reporting group title	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP

Reporting group description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 4 (LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Primary: Frequency of adverse events

End point title	Frequency of adverse events[1]

End point description:

End point type	Primary

End point timeframe:

Up to 51 days after challenge infection

Notes:

[1] - 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: Frequency and magnitude of adverse events were primary safety endpoints to assess whether the CHMI-transmission model is in general safe and tolerable. For this purpose comparisons between study groups were not performed.

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Number of adverse events	95	95	107	52

Statistical analyses

No statistical analyses for this end point

Primary: Magnitude of adverse events

End point title	Magnitude of adverse events[2]

End point description:

symptoms will be ranked as (1) mild, (2) moderate, or (3) severe, depending on their intensity according to the following scale:

Mild (grade 1): awareness of symptoms that are easily tolerated and do not interfere with usual daily activity
Moderate (grade 2): discomfort that interferes with or limits usual daily activity
Severe (grade 3): disabling, with subsequent inability to perform usual daily activity, resulting in absence or required bed rest

End point type	Primary

End point timeframe:

Up to 51 days after challenge infection

Notes:

[2] - 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: Frequency and magnitude of adverse events were primary safety endpoints to assess whether the CHMI-transmission model is in general safe and tolerable. For this purpose comparisons between study groups were not performed.

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Number of adverse events				
Mild	64	56	86	41
Moderate	22	22	17	8
Severe	9	17	4	3

Statistical analyses

No statistical analyses for this end point

Primary: Infectious for Mosquitoes Through DMFA

End point title	Infectious for Mosquitoes Through DMFA

End point description:

Prevalence of gametocyte infectiousness for Anopheles mosquitoes through Direct Membrane Feeding Assays (DMFA).

End point type	Primary

End point timeframe:

up to day 51 after challenge infection

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Number of subjects	0	0	5	2

Statistical analyses

Statistical analysis title	Infectiousness to mosquitoes

Statistical analysis description:

The infectiousness to mosquitoes as determined by direct membrane feeding assay (DMFA) was compared between subjects of cohort A (groups 1 and 2) that were infected by mosquito bite and subjects of cohort B (groups 3 and 4) that were infected by induced blood stage malaria.

Comparison groups	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP v Group 2 (Cohort A) LD-PIP/LD-PIP2/SP v Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP v Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	Fisher exact

Secondary: Gametocyte prevalence

End point title	Gametocyte prevalence

End point description:

Number of individuals in each study arm that show prevalence of gametocytes as defined by quantitative reverse-transcriptase PCR (qRT-PCR) for CCp4 (female) and PfMGET (male) mRNA with a threshold of 5 gametocytes/mL for positivity.

End point type	Secondary

End point timeframe:

up to day 51 after challenge infection

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Number of subjects	5	6	6	6

Statistical analyses

No statistical analyses for this end point

Secondary: Peak density gametocytes

End point title	Peak density gametocytes

End point description:

Peak density of gametocytes by qRT-PCR.

End point type	Secondary

End point timeframe:

up to day 51 after challenge infection

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: gametocytes/mL				
median (full range (min-max))	13.9 (2.5 to 727.9)	21.4 (6.16 to 181.6)	1442.2 (246.6 to 3826.1)	813.2 (179.5 to 1617.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Infectiousness for Mosquitoes Through DFA

End point title	Infectiousness for Mosquitoes Through DFA

End point description:

Prevalence of gametocyte infectiousness for Anopheles mosquitoes through Direct Feeding Assays (Direct Skin Feeding Assay, DFA).

End point type	Secondary

End point timeframe:

Up to day 51 after challenge infection

End point values	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Number of subjects	0	0	5	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to day 51 after challenge infection

Assessment type	Systematic

Dictionary used

Dictionary name	ICD
Dictionary version	10

Reporting groups

Reporting group title	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP

Reporting group description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 1 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg).

Reporting group title	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP

Reporting group description:

Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 2(LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Reporting group title	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP

Reporting group description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 3 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg)

Reporting group title	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP

Reporting group description:

Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection. All volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia occurs before day 21 post challenge infection. Volunteers in group 4 (LD-PIP/LD-PIP2/SP) will be curatively treated with sulfadoxine-pyrimethamine (1000mg/50mg).

Serious adverse events	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Group1 (Cohort A) LD-PIP/LD-PIP2/PIP	Group 2 (Cohort A) LD-PIP/LD-PIP2/SP	Group 3 (Cohort B) LD-PIP/LD-PIP2/PIP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Fever	Additional description: Tympanic or oral temperature >38.0 degrees Celcius		
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
occurrences (all)	16	11	13
Chils			
subjects affected / exposed	6 / 6 (100.00%)	1 / 6 (16.67%)	4 / 6 (66.67%)
occurrences (all)	13	2	7
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	5 / 6 (83.33%)
occurrences (all)	0	2	6
Fatigue			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	5 / 6 (83.33%)
occurrences (all)	7	13	12
Headache			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
occurrences (all)	27	26	33
Malaise			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	1 / 6 (16.67%)
occurrences (all)	8	15	3
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	5 / 6 (83.33%)	4 / 6 (66.67%)
occurrences (all)	1	6	7
Decreased appetite			

subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	3
Nausea			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	6 / 6 (100.00%)
occurrences (all)	13	12	9
Dizziness			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	5	3	8
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Palpitations			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thoracic pain	Additional description: non specific		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2

Non-serious adverse events	Group 4 (Cohort B) LD-PIP/LD-PIP2/SP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Fever	Additional description: Tympanic or oral temperature >38.0 degrees Celcius		
subjects affected / exposed	6 / 6 (100.00%)		
occurrences (all)	5		
Chils			

subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Fatigue				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	6			
Headache				
subjects affected / exposed	6 / 6 (100.00%)			
occurrences (all)	20			
Malaise				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Myalgia				
subjects affected / exposed	4 / 6 (66.67%)			
occurrences (all)	5			
Decreased appetite				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	5			
Dizziness				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	4			
Diarrhoea				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Palpitations				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Back pain				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Arthralgia				

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Thoracic pain	Additional description: non specific		
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

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? No

Limitations and caveats

None reported