Clinical trial results:
Controlled Human Malaria Infection (CHMI) After Immunization With Cryopreserved Plasmodium Falciparum Sporozoites Under Chloroquine Prophylaxis

Summary

EudraCT number	2012-000322-21
Trial protocol	NL
Global end of trial date	25 February 2014

Results information

Result version number	v1 (current)
This version publication date	17 August 2016
First version publication date	16 May 2015

Trial information

Trial identification

Sponsor protocol code	TIP5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01728701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanaria Inc.
Sponsor organisation address	9800 Medical Center Drive, Suite A209, Rockville, MD, United States, 20850
Public contact	Alexander Hoffman, Sanaria Helpdesk, +1 301-339-0092, ahoffman@sanaria.com
Scientific contact	Alexander Hoffman, Sanaria Helpdesk, +1 301-339-0092, ahoffman@sanaria.com

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	02 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2013
Global end of trial reached?	Yes
Global end of trial date	25 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the safety and tolerability of ID administration of PfSPZ Challenge to volunteers taking chloroquine chemoprophylaxis (an approach called PfSPZ-CVac)

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Treatment: Malarone® 4 tablets (250 mg atovaquone / 100 mg proguanil per tablet) once daily for three days.

Background therapy:

All groups received weekly chloroquine phosphate chemoprophylaxis for a period of 14 weeks (300 mg chloroquine base per dose). Groups 3 and 4 received additional weekly chloroquine phosphate chemoprophylaxis from Day 225 to 259.

Evidence for comparator: -

Actual start date of recruitment	11 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from September 2012 to February 2014 in 1 clinic center in Netherlands.

Pre-assignment

Screening details:

From the total volunteers screened, 30 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Volunteers, investigators and laboratory personnel were blinded regarding receipt of vaccine or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: PfSPZ Challenge

Arm description:

Group 1 (n=10) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 10 volunteers enrolled, all 10 were challenged of which 2 volunteers were protected.

Arm type	Experimental
Investigational medicinal product name	Plasmodium falciparum (Pf) Sporozoite (SPZ) Challenge
Investigational medicinal product code	PfSPZ Challenge
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

PfSPZ Challenge containing a total of 75,000 PfSPZ of the Pf NF54 strain in 6 injections

Arm title	Group 2: Normal Saline (NS)

Arm description:

Group 2 (n=5) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 5 control volunteers enrolled, all 5 were challenged of which none of the volunteers were protected.

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	NS
Other name	Placebo
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Six NS injections

Arm title	Group 3: PfSPZ Challenge

Arm description:

Group 3 (n=10) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Eight of 10 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Four of these 8 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Arm type	Experimental
Investigational medicinal product name	Plasmodium falciparum (Pf) Sporozoite (SPZ) Challenge
Investigational medicinal product code	PfSPZ Challenge
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

PfSPZ Challenge containing a total of 75,000 PfSPZ of the Pf NF54 strain in 6 injections

Arm title	Group 4: Normal Saline (NS)

Arm description:

Group 4 (n=5) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. All 4 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Three of these 4 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	NS
Other name	Placebo
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Six NS injections

Number of subjects in period 1	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge
Started	10	5	10
Completed	10	5	4
Not completed	0	0	6
Logistical reasons	-	-	5
Tetanus vaccination	-	-	1

Number of subjects in period 1	Group 4: Normal Saline (NS)
Started	5
Completed	4
Not completed	1

Logistical reasons	1
Tetanus vaccination	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: PfSPZ Challenge

Reporting group description:

Group 1 (n=10) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 10 volunteers enrolled, all 10 were challenged of which 2 volunteers were protected.

Reporting group title	Group 2: Normal Saline (NS)

Reporting group description:

Group 2 (n=5) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 5 control volunteers enrolled, all 5 were challenged of which none of the volunteers were protected.

Reporting group title	Group 3: PfSPZ Challenge

Reporting group description:

Group 3 (n=10) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Eight of 10 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Four of these 8 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Reporting group title	Group 4: Normal Saline (NS)

Reporting group description:

Group 4 (n=5) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. All 4 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Three of these 4 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Reporting group values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge
Number of subjects	10	5	10
Age categorical Units: Subjects			
Adults (18-35 years)	10	5	10
Age continuous Units: years			
arithmetic mean	22	22	21.1
standard deviation	± 2.67	± 3.24	± 1.97
Gender categorical Units: Subjects			
Female	5	2	4
Male	5	3	6

Race Units: Subjects			
Caucasian	10	5	10
BMI Units: Subject			
arithmetic mean	22.3	21.82	21.63
standard deviation	± 1.52	± 2.22	± 1.17
Height Units: meter			
arithmetic mean	1.75	1.77	1.8
standard deviation	± 0.08	± 0.11	± 0.09
Weight Units: kg			
arithmetic mean	68.5	69.2	69.8
standard deviation	± 7.74	± 15.32	± 5.79

Reporting group values	Group 4: Normal Saline (NS)	Total	
Number of subjects	5	30	
Age categorical Units: Subjects			
Adults (18-35 years)	5	30	
Age continuous Units: years			
arithmetic mean	20.6		
standard deviation	± 1.52	-	
Gender categorical Units: Subjects			
Female	3	14	
Male	2	16	
Race Units: Subjects			
Caucasian	5	30	
BMI Units: Subject			
arithmetic mean	22.2		
standard deviation	± 1.19	-	
Height Units: meter			
arithmetic mean	1.73		
standard deviation	± 0.09	-	
Weight Units: kg			
arithmetic mean	67		
standard deviation	± 9.35	-	

End points

End points reporting groups

Reporting group title	Group 1: PfSPZ Challenge

Reporting group description:

Group 1 (n=10) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 10 volunteers enrolled, all 10 were challenged of which 2 volunteers were protected.

Reporting group title	Group 2: Normal Saline (NS)

Reporting group description:

Group 2 (n=5) received weekly chloroquine (CQ) chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. Volunteers had CHMI by the bites of five mosquitoes infected with PfSPZ of the Pf NF54 strain 33 days after the last dose of chloroquine which is day 124. Of the 5 control volunteers enrolled, all 5 were challenged of which none of the volunteers were protected.

Reporting group title	Group 3: PfSPZ Challenge

Reporting group description:

Group 3 (n=10) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of PfSPZ Challenge [75,000 PfSPZ (per dose) of the Pf NF54 strain] on days 8, 36 and 64. Eight of 10 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Four of these 8 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Reporting group title	Group 4: Normal Saline (NS)

Reporting group description:

Group 4 (n=5) received weekly chloroquine chemoprophylaxis for 14 weeks (98 days), and 6 ID injections of normal saline on days 8, 36 and 64. All 4 volunteers restarted 6 weeks of CQ (days 225-259), and received 4th immunization on day 232. Three of these 4 volunteers received homologous CHMI (by bites of 5 NF54-infected mosquitoes) on day 369, and none were protected.

Per protocol, if ≥75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would have heterologous CHMI with mosquitoes infected with Pf NF135.C10 strain 75 days after the last dose of chloroquine. If <75% of volunteers in group 1 were protected against homologous CHMI, groups 3 and 4 would receive additional 6 weeks of CQ (starting day 225), a 4th immunization (75,000 PfSPZ Challenge or NS) on day 232 and homologous CHMI 110 days after last dose of CQ.

Primary: Frequency of adverse events (AEs) in study groups - Solicited

End point title	Frequency of adverse events (AEs) in study groups - Solicited[1]

End point description:

All events pertaining to immunization phase (before CHMI) were recorded.

End point type	Primary

End point timeframe:

During immunization phase (up to day 124 for groups 1 and 2 and up to day 369 for groups 3 and 4)

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: This endpoint does not require statistical analysis.

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	10	5
Units: Events				
Fever	0	0	0	0
Malaise	0	0	0	0
Fatigue	0	0	0	0
Dizziness	0	0	0	0
Myalgia	0	0	0	0
Arthralgia	0	0	0	0
Chest pain	0	0	0	0
Chills	2	0	0	0
Diarrhoea	1	0	0	0
Headache	12	2	5	6
Nausea	2	2	4	0
Vomiting	2	0	1	1
Abdominal pain	0	1	2	5
Palpitations	0	0	0	0
Shortness of breath	0	0	0	0
Erythema or induration/swelling at injection site	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Magnitude of AEs in study groups - Solicited AEs

End point title	Magnitude of AEs in study groups - Solicited AEs[2]

End point description:

All events pertaining to immunization phase (before CHMI) were recorded.

End point type	Primary

End point timeframe:

During immunization phase (up to day 124 for groups 1 and 2 and up to day 369 for groups 3 and 4)

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: This endpoint does not require statistical analysis.

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	10	5
Units: Subjects				
Grade 1	6	1	4	2
Grade 2	3	3	3	3
Grade 3	0	0	1	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of adverse events (AEs) in study groups - Unsolicited

End point title	Frequency of adverse events (AEs) in study groups - Unsolicited[3]

End point description:

All events pertaining to immunization phase (before CHMI) were recorded.

End point type	Primary

End point timeframe:

During immunization phase (up to day 124 for groups 1 and 2 and up to day 369 for groups 3 and 4)

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: This endpoint does not require statistical analysis.

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	10	5
Units: Events				
Acute pharyngitis	2	0	0	0
Atypical facial pain	0	1	0	0
Common cold	4	0	2	5
Commotio cerebri	0	0	1	0
Contusion of ankle	0	0	1	0
Cough	0	0	0	1
Cystitis	0	0	2	1
Dermatitis unspecified	0	0	1	0
Follow-up care involving plastic surgery of left u	0	0	1	0
Inflammation of eyelid	0	0	1	0
Influenza with other manifestation; virus not ide	0	0	2	0
Lumbago NOS	0	0	0	1
Open wound of finger without damage to nail	0	1	0	0
Open wound of thumb without damage to nail	0	0	1	0
Pain after removal wisdom tooth	1	0	0	0
Pain in throat	0	1	0	0
Raised d-dimer	0	0	2	0
Urticaria	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Magnitude of AEs in study groups - Unsolicited AEs

End point title	Magnitude of AEs in study groups - Unsolicited AEs[4]

End point description:

All events pertaining to immunization phase (before CHMI) were recorded.

End point type	Primary

End point timeframe:

During immunization phase (up to day 124 for groups 1 and 2 and up to day 369 for groups 3 and 4)

Notes:

[4] - 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: This endpoint does not require statistical analysis.

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	10	5
Units: Subjects				
Grade 1	4	1	6	4
Grade 2	3	2	1	2
Grade 3	0	0	1	0
Grade 4	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of parasitemia after CHMI as assessed by microscopy in cohort 1 (Groups 1 and 2)

End point title	Presence of parasitemia after CHMI as assessed by microscopy in cohort 1 (Groups 1 and 2)[5]

End point description:

Number of volunteers who became thick smear positive (TS+)

End point type	Secondary

End point timeframe:

Up to Day 21 after CHMI of cohort 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, this endpoint was analysed only for Cohort 1 (Groups 1 and 2).

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	5		
Units: Subjects	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to parasitemia after CHMI as assessed by microscopy in cohort 1 (Groups 1 and 2)

End point title	Time to parasitemia after CHMI as assessed by microscopy in cohort 1 (Groups 1 and 2)[6]

End point description:

End point type	Secondary

End point timeframe:

Up to Day 21 after CHMI of cohort 1

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, this endpoint was analysed only for Cohort 1 (Groups 1 and 2).

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	5		
Units: days				
geometric mean (full range (min-max))	13.7 (10.5 to 15)	12.7 (10.5 to 16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of parasitemia after CHMI as assessed by qPCR in cohorts 1 and 2

End point title	Presence of parasitemia after CHMI as assessed by qPCR in cohorts 1 and 2

End point description:

End point type	Secondary

End point timeframe:

Up to Day 21 after CHMI of cohorts 1 and 2

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	4	4
Units: Subjects	10	5	4	4

Statistical analyses

No statistical analyses for this end point

Secondary: Time to parasitemia after CHMI as assessed by qPCR in cohorts 1 and 2

End point title	Time to parasitemia after CHMI as assessed by qPCR in cohorts 1 and 2

End point description:

End point type	Secondary

End point timeframe:

Up to Day 21 after CHMI of cohort 1 and 2

End point values	Group 1: PfSPZ Challenge	Group 2: Normal Saline (NS)	Group 3: PfSPZ Challenge	Group 4: Normal Saline (NS)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	4	4
Units: day				
geometric mean (full range (min-max))	8.1 (7 to 10.5)	7.6 (7 to 10.5)	9.5 (7 to 10.5)	7.7 (7 to 10)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded during immunization phase (up to day 124 for groups 1 and 2 and up to day 369 for groups 3 and 4)

Adverse event reporting additional description:

All adverse events/reactions (solicited and unsolicited), observed by the investigators or by the subject, is documented.

All non-serious AEs occured during immunization phase and SAE occured after CHMI.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD
Dictionary version	10

Reporting groups

Reporting group title	Group 1: PfSPZ Challenge

Reporting group description:

Ten volunteers in Group 1 received intradermal injection of PfSPZ Challenge

Reporting group title	Group 2: Normal Saline

Reporting group description:

Five volunteers in group 2 received NS

Reporting group title	Group 3: PfSPZ Challenge

Reporting group description:

Ten volunteers in Group 3 received intradermal injection of PfSPZ Challenge

Reporting group title	Group 4: Normal Saline

Reporting group description:

Five volunteers in group 4 received NS

Serious adverse events	Group 1: PfSPZ Challenge	Group 2: Normal Saline	Group 3: PfSPZ Challenge
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute Myocarditis	Additional description: Acute Myocarditis diagnosed for male (age 23), with rising troponin levels on day 2 of Malarone treatment following thick smear positivity for malaria. It is considered possibly related to CHMI Outcome was 'Recovered with Sequelae.'		
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4: Normal Saline		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute Myocarditis	Additional description: Acute Myocarditis diagnosed for male (age 23), with rising troponin levels on day 2 of Malarone treatment following thick smear positivity for malaria. It is considered possibly related to CHMI Outcome was 'Recovered with Sequelae.'		
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1: PfSPZ Challenge	Group 2: Normal Saline	Group 3: PfSPZ Challenge
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	5 / 5 (100.00%)	10 / 10 (100.00%)
Investigations			
Raised d-dimer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Commotio cerebri			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Contusion of ankle			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Open wound of finger without damage to nail			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Open wound of thumb without damage to nail			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pain after removal wisdom tooth			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Surgical and medical procedures			
Follow-up care involving plastic surgery of left upper extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 10 (40.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	12	2	5
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Atypical facial pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Inflammation of eyelid			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	2	2	4
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Pain in throat			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis unspecified			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Lumbago NOS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute pharyngitis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Common cold			
subjects affected / exposed	4 / 10 (40.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	4	0	2
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Influenza with other manifestations; virus not identified			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2

Non-serious adverse events	Group 4: Normal Saline		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Investigations			
Raised d-dimer			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Commotio cerebri subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Contusion of ankle subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Open wound of finger without damage to nail subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Open wound of thumb without damage to nail subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Pain after removal wisdom tooth subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Surgical and medical procedures Follow-up care involving plastic surgery of left upper extremity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 6		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Atypical facial pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Eye disorders Inflammation of eyelid subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 5 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Pain in throat subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis unspecified subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Musculoskeletal and connective tissue disorders Lumbago NOS subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Infections and infestations Acute pharyngitis subjects affected / exposed occurrences (all) Common cold	 0 / 5 (0.00%) 0		

subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	5		
Cystitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Influenza with other manifestations; virus not identified			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2012	- Additional labs added - Updated inclusion and exclusion criteria - Added lists of concomitant medications and conditions for both chloroquine and Malarone use - Secondary and exploratory study parameters were updated - Dose preparation and administration sections were updated - Number of injections for each immunization was updated from 2 to 6 - Added statement for performing complete physical exam at baseline visit and list of focused physical exams to be performed at follow-up visits - Updated flow chart for trial procedures - Included grading scales for adverse events and lab abnormalities - Added section on safety stopping rules
03 September 2012	- Deleted statement from adverse event data collection section regarding not grading intensity of fever
28 September 2012	- Included urinalysis for presence of hemoglobinuria and proteinuria on day before CHMI and on day of treatment - Updated flow chart for trial procedures - Updated tables for grading local and systemic adverse events, and grading lab abnormalities - Included one additional category for assessment of causality and its definition - Updated safety stopping rules based on the additional category for assessment of causality
05 November 2012	- Inclusion of four extra visits (on days 8 and 9 following the 2nd and 3rd injections) during which a small blood sample will be taken on a voluntary basis. - Updated flow chart for trial procedures
04 December 2012	- Added a sub-study called "Odor profile" study - Changes related to the addition of the sub-study were made to study population, exploratory objectives, study procedures, etc. sections
15 January 2013	- Changes specific to the "Odor profile" sub-study only, were made to the study schedule
16 May 2013	- Study schedule and timelines were updated due to trial delay after SAE occurrence - qPCR was added as method for detection of parasitemia for cohort 2 - Safety section of the protocol was updated - Protocol was updated to include the occurrence of the SAE in the study - Additional safety recommendations were added based on the SAE – updates to exclusion criteria, increased monitoring of certain lab parameters, use of qPCR post-CHMI for diagnosis of malaria - Secondary study parameters were updated - Section on treatment with Malarone was updated - Sub-study "Odor profile" modifications were made - Updated flow chart for trial procedures
04 November 2013	- Unblinding schedule for groups 3 and 4 was updated to allow unblinding to occur one week earlier than originally stated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2013	Due to cardiac SAE, trial was put on hold for 64 days (13-Mar-2013 – 16-May-2013) by the Safety Monitoring Committee, the Central Committee for Research Involving Human Subjects of the Netherlands, and the US FDA. New safety measures were adopted for follow-up after mosquito CHMI of Groups 3 and 4.	16 May 2013

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24479524