



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 $\geq 75\%$ 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 $\geq 75\%$ 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 $\geq 75\%$ 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 $\geq 75\%$ 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 $\geq 75\%$ 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 $\geq 75\%$ 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 |
| Comotio 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 occurred during immunization phase and SAE occurred 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 occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 4 / 10 (40.00%) 12 | 2 / 5 (40.00%) 2 | 2 / 10 (20.00%) 5 |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Atypical facial pain subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 | 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 |
| Eye disorders Inflammation of eyelid subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| 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) | 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 2 2 / 10 (20.00%) 2 | 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 1 / 5 (20.00%) 2 0 / 5 (0.00%) 0 | 2 / 10 (20.00%) 2 0 / 10 (0.00%) 0 3 / 10 (30.00%) 4 1 / 10 (10.00%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |

| | | | |
|--|----------------------|---------------------|----------------------|
| Pain in throat subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 10 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Dermatitis unspecified subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Musculoskeletal and connective tissue disorders Lumbago NOS subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Infections and infestations Acute pharyngitis subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Common cold subjects affected / exposed occurrences (all) | 4 / 10 (40.00%) 4 | 0 / 5 (0.00%) 0 | 2 / 10 (20.00%) 2 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 2 |
| Influenza with other manifestations; virus not identified subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 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 occurrences (all) | 0 / 5 (0.00%) 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) | 3 / 5 (60.00%) 5 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Pain in throat subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Dermatitis unspecified subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Urticaria subjects affected / exposed occurrences (all) | 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) | 0 / 5 (0.00%) 0 | | |
| Common cold | | | |

| | | | |
|--|----------------|--|--|
| 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- Deleted statement from adverse event data collection section regarding not grading intensity of fever |
| 28 September 2012 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- Changes specific to the "Odor profile" sub-study only, were made to the study schedule |
| 16 May 2013 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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>