Summary of Clinical Study Report

Safety and protective efficacy of a simplified Plasmodium falciparum sporozoite Chemoprophylaxis Vaccine (PfSPZ-CVac) regimen in healthy malaria-naïve adults in Germany

"CVaC-Tü3"

Name of test drug/investigational product:	PfSPZ Challenge (Strain NF54) PfSPZ Challenge (Strain 7G8) Chloroquine
Indication studied:	Malaria vaccine
Development phase of study:	Phase 1
EudraCT Number:	2018-004523-36
Protocol identification code:	CVac-Tü3
Date of the report:	01 Nov 2021
Version:	1.0

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Author(s) Study Report Zita Sulyok Universitätsklinikum Tübingen Institut für Tropenmedizin Wilhelmstraße 27 D-72074 Tübingen, Germany	

Study initiation date (first patient enrolled, or any other verifiable definition): 30APR2019 (first ICF signed)
Date of last patient last visit: 30APR2020

Signatures

The Authors confirm the reported content by signature. The study (including the archiving of essential documents) was performed in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable laws.
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor's delegated person	Peter G. Kremsner, Prof. Dr. Name, Titel	05 Nov 2021 Date
Principle Investigator	Zita Sulyok, Dr. Name, Titel	04 Nov 2021 Date
Biometrician	Benjamin Mordmüller, Prof. Dr. Name, Titel	04 Nov 2021 Date

Content

1 Name of Sponsor/Company

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2 Name of Finished Product and Active Substance

Investigational Medicinal Product	**Active Substance**
PfSPZ-Challenge	Aseptic, purified, vialed, cryopreserved, infectious *P. falciparum* sporozoites, strain NF54, produced by Sanaria Inc. – Sanaria® PfSPZ Challenge (NF54). Aseptic, purified, vialed, cryopreserved, infectious *P. falciparum* sporozoites, clone 7G8, produced by Sanaria Inc. – Sanaria® PfSPZ Challenge (7G8)
Chloroquine	Chloroquine

3 Individual Study Table

Not applicable

4 Title of Study

Safety and protective efficacy of a simplified Plasmodium falciparum sporozoite Chemoprophylaxis Vaccine (PfSPZ-CVac) regimen in healthy malaria-naïve adults in Germany.

Version 6.0 from the 22 March 2018

5 Investigator(s) and Study centre(s)

Investigator	**Study centre**
Zita Sulyok	Universitätsklinikum Tübingen, Institut für Tropenmedizin, Wilhelmstraße 27, D-72074 Tübingen, Germany

6 Publication

One publication was prepared with the results of the first CHMI and published in the journal "Nature Communications":

Sulyok Z, Fendel R, Eder B, Lorenz FR, Kc N, Karnahl M, Lalremruata A, Nguyen TT, Held J, Adjadi FAC, Klockenbring T, Flügge J, Woldearegai TG, Lamsfus Calle C, Ibáñez J, Rodi M, Egger-Adam D, Kreidenweiss A, Köhler C, Esen M, Sulyok M, Manoj A, Richie TL, Sim BKL, Hoffman SL, Mordmüller B, Kremsner PG. Heterologous protection against malaria by a simple chemoattenuated PfSPZ vaccine regimen in a randomized trial. Nat Commun. 2021 May 4;12(1):2518. doi: 10.1038/s41467-021-22740-w. PMID: 33947856; PMCID: PMC8097064.

7 Studied period (years)

- First ICF signed: 30APR2019
- End of study: 30 APR 2020 (early terminated)
- Last visit: 30 APR 2020
- Reason for early termination: The clinical trial was stopped because of safety concerns in combination with the upcoming COVID-19 pandemic and due to a lack of immunity after the second controlled human malaria infection.

8 Phase of Development

Phase 1

9 Objectives

The objective of the clinical trial was to establish that an immunization regimen of three injections of PfSPZ Challenge by direct venous injection (DVI) and oral chloroquine chemoprophylaxis administered on Days 0, 5 and 28, is safe and well tolerated.

10 Methodology

- Prospective, single center, randomized, placebo-controlled, double-blind, PfSPZ Challenge with chloroquine (PfSPZ-CVac) trial with repeat controlled human malaria infection (CHMI).

- 2 arms, one with IMP and one with placebo (normal saline):
  - **Group A**: Verum (n = 14)
  - **Group B**: Placebo (n = 7)

- Participants were randomized on the day of first vaccine administration by a computer algorithm. An external party generated the allocation table and transmitted randomization cards to the formulation team. Following preparation of the investigational product, the formulator signed the randomization card and filed them in a secure place. One copy, marked with the participant identifier was sealed in an envelope and handed to the local safety monitor. Members of the formulation team had no role in clinical or

further endpoint-relevant laboratory activities. A detailed description of the randomization process and code is given in the Statistical Analysis Plan.

- An independent Safety Monitoring Committee (SMC) was appointed before the start of the study by the sponsor to review safety data at specified intervals. The membership of the SMB included expertise in clinical vaccine trials in malaria endemic settings. The role of the SMB was to provide safety oversight over the conduct of the study. It reviewed safety continuously during the study and advised on progression of the study. The SMB hold conference calls to review the safety data provided by the PI. The purpose of these conference calls was to review the accumulated safety data in order to advise whether or not dose escalation could proceed, whether or not the study could be transitioned to Benin, whether or not the study integrity remained intact and whether or not there were any safety concerns worth early notice. The SMB's procedures, communications and roles were defined in a SMB charter.

11 Number of Patients

- Planned sample size: 21 (14 Verum, 7 Placebo)
- 35 screened
- 21 enrolled
- 20 randomized
- 5 drop out
- 20 analyzed for safety (ITT), 18 analyzed for efficacy (ATP);

12 Diagnosis and Main Criteria for Inclusion

The study population was composed of healthy malaria-naïve adults aged between 18- and 45-years adults.
The other inclusion criteria were as follows:

- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow the investigators to discuss the volunteer's medical history with their general practitioner if required.
- Residence in Tübingen or surroundings for the period of the trial.
- Women only: Must agree to practice continuous effective contraception for the duration of the study (a method which results in a low failure rate; i.e. less than 1% per year).
- Agreement to refrain from blood donation during the course of the study and after the end of their involvement in the study according to the local and national blood banking eligibility criteria.
- Provision of written informed consent to receive PfSPZ Challenge products for immunization and subsequently for CHMI.
- Reachable (24/7) by mobile phone during the immunization and CHMI period.
- Willingness to take CQ during immunization and a curative antimalarial regimen following CHMI.

- Agreement to stay overnight for observation during the period of intensive follow-up post-challenge if required.
- Answer all questions on the informed consent quiz correctly.
- A body mass index <35.

13 Test product

Dose of IMP
PfSPZ Challenge (NF54): 110.000 PfSPZ
PfSPZ Challenge (7G8):3.200 PfSPZ
Chloroquine base 10 mg/kg to maximum of 620 mg

Route of administration:
PfSPZ Challenge (NF54, 7G8): Injection into a superficial vein of the arm
Chloroquine: oral

Batch numbers:

Item	Batch no.
Albumin 25% Solution	092018
PBS	060617
PfSPZ NF54 Challenge	032416-02
PfSPZ 7G8 Challenge	052319-02A 100114-02

Reference product:
Physiological saline solution (NaCl 0.9%), produced by B. Braun Melsungen AG, provided by Fortuna Herstellung GmbH, Mannheim.

Dose:
500 µl per injection

Route of administration:
Intramuscular injection

Batch number:
T201905

14 Duration of treatment

Three injections of either placebo or PfSPZ under chemoprophylaxis with chloroquine (10mg/kg) on Days 0, 5 and 28.

15 Reference therapy

A vaccine against malaria is not available.

16 Criteria for evaluation

16.1 Efficacy

Proportion of protected volunteers. Protection is defined as the absence of parasites in the peripheral blood for +28 days following CHMI with PfSPZ Challenge (7G8) in volunteers receiving PfSPZ-CVac. Parasitemia is defined as at least one qPCR result above 100 parasites per mL among three positives results at least 12 hours apart or as a positive thick blood smear after CHMI with PfSPZ Challenge. Statistical testing is done hierarchically: 1) protection against first CHMI, 2) protection against second CHMI, 3) protection against third CHMI.

16.2 Safety

Number or occurrence of at least possibly related Grade 3-4 AEs and serious adverse events SAEs from time of first administration of CQ until the end of the study.

17 Statistical methods

Demographics

Baseline characteristics (age, gender, height, weight, laboratory variables) were tabulated.

Categorical variables were presented as count and percentage. Numerical variables were summarized as mean and standard deviation or median and interquartile range, as well as minimum and maximum.

Safety

Adverse events (AE) were recorded from the screening visit until the last visit of the trial. Safety data of ITT population were analysed. Adverse events were tabulated and presented as a heat map of at least possibly related adverse events over time and color to code for the maximal AE grade present at the time. Verbatim-recorded AEs were coded using the MedDRA terminology and the proportion of subjects with grade 3 or 4 AE and SAE classified by MedDRA preferred term level, were tabulated.

18 Summary/Conclusions

18.1 Demographic Data

From the 20 participants, 11 were male and 9 females, all young adults between 19 and 42 years. The distribution between the two groups (verum and placebo) was similar for all collected demographic data, see table below.

Number of participants (n = 20)	Verum	Placebo	P value
Sex Male (n, percentage) Female (n, percentage)	 6 (46%) 7 (54%)	 5 (71%) 2 (29%)	 p = 0.37*
Age in years (median, range)	25 (19–42)	26 (21–36)	p = 0.79**
Height in cm (median, range)	171 (159–184)	178 (165–188)	p = 0.14**
Weight in kg (median, range)	69 (50–100)	73 (51–86)	p = 0.92**
BMI in kg/m2 (median, range)	23.8 (16.9–33.8)	23.2 (18.7–25.6)	p = 0.50**

*Two-sided Fisher's exact test.
**Two-sided Student's t-test.

18.2 Efficacy Results

After the first CHMI, 10/13 verum and 0/5 placebo volunteers were protected. Vaccine efficacy compared to placebo was 77% (95% CI: 13%-95%). After the second CHMI 5/13 verum and 0/3 placebo were protected, that means a 39 % (95% CI: 5%-60%) efficacy of the vaccine compared to placebo.

18.3 Safety Results

A total 438 AE was observed in the study period, and 305 was deemed at least possibly related to IMP. 222 grade 1 or 2 AEs occurred during the immunization period and 216 after CHMI. There were no related grade 3 AEs or SAEs during the immunization phase, but there was one unrelated grade 3 AE, a case of diastolic hypertension.
The most frequent AE overall was headache, followed by fatigue and dizziness.

In both the verum and placebo group, all participants developing parasitemia, experienced at least one adverse event (AE) related to malaria, including 4 grade 3 AE (neutropenia, hypotension and two cases of fever). Volunteers were treated with atovaquone/proguanil according to the German national guidelines and recovered uneventfully.

One unrelated serious adverse event (SAE) occurred in the late follow-up
period. On day 63 after the first CHMI, one vaccinee underwent an elective surgery because of a condition in medical history.

18.4 Conclusion

The tested PfSPZ-CVac regimen was simple, safe, well tolerated and highly immunogenic, but vaccine efficacy decreased within 4 months in a controlled human challenge model.

19 Appendices

Not applicable.