Clinical trial results:
An Open Label, Non-Comparative Study To Evaluate Parasitological Clearance Rates And Pharmacokinetics Of Azithromycin And Chloroquine Following Administration Of A Fixed Dose Combination Of Azithromycin And Chloroquine (AZCQ) In Asymptomatic Pregnant Women With Plasmodium Falciparum Parasitemia In Sub-Saharan Africa.

Summary

EudraCT number	2014-004906-14
Trial protocol	Outside EU/EEA
Global end of trial date	25 October 2013

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	A0661201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01103713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	06 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the peripheral parasitological clearance rate of Azithromycin/chloroquine (AZCQ) on Day 28 (Polymerase chain-reaction [PCR] corrected) following first dose of 3-day dosing regimen of AZCQ in asymptomatic pregnant women with P. falciparum parasitemia.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Benin: 1
Country: Number of subjects enrolled	Kenya: 67
Country: Number of subjects enrolled	Malawi: 50
Country: Number of subjects enrolled	Tanzania, United Republic of: 1
Country: Number of subjects enrolled	Uganda: 49
Worldwide total number of subjects	168
EEA total number of subjects	0

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)	41
Adults (18-64 years)	127
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 5 active sites in 5 countries: Benin (site 1012), Kenya (site 1004), Malawi (site 1015), Tanzania (site 1008), and Uganda (site 1013). The enrollment of the first subject took place on 07 March 2011 and the last subject last visit was on 25 October 2013.

Pre-assignment

Screening details:

A total of 404 subjects were screened and 168 subjects were assigned to study drug, enrolled and treated. Of the 168 subjects, two subjects were excluded from the pharmacokinetic (PK) analysis, modified intent-to-treat (MITT), intent-to-treat (ITT) and per protocol (PP) populations due to informed consent protocol deviations.

Period 1

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

Arms

Arm title	Azithromycin (AZ)/Chloroquine (CQ)

Arm description:

Study drug AZCQ is a fixed dose combination tablet of AZ and CQ given orally once daily for 3 days (Days 0, 1, 2).

Arm type	Experimental
Investigational medicinal product name	AZCQ fixed dose combination tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug AZCQ is a fixed dose combination tablet of AZ and CQ containing 250 milligram (mg) AZ and 155 mg CQ base. The dosing regimen evaluated in this study consisted of four AZCQ tablets (a total of 1000 mg AZ/620 mg CQ base), given orally once daily for 3 days (Days 0, 1, 2).

Number of subjects in period 1	Azithromycin (AZ)/Chloroquine
Started	168
Completed	155
Not completed	13
Consent withdrawn by subject	8
Not specified	1
Study terminated by sponsor	2
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Azithromycin (AZ)/Chloroquine (CQ)
Reporting group description:	
Study drug AZCQ is a fixed dose combination tablet of AZ and CQ given orally once daily for 3 days (Days 0, 1, 2).	

Reporting group values	Azithromycin (AZ)/Chloroquine	Total	
Number of subjects	168	168	
Age, Customized Units: subjects			
<16 years	0	0	
16-17 years	41	41	
18-25 years	125	125	
26-30 years	1	1	
31-35 years	1	1	
>35 years	0	0	
Gender, Male/Female Units: subjects			
Female	168	168	
Male	0	0	

End points

End points reporting groups

Reporting group title	Azithromycin (AZ)/Chloroquine (CQ)

Reporting group description:

Study drug AZCQ is a fixed dose combination tablet of AZ and CQ given orally once daily for 3 days (Days 0, 1, 2).

Primary: Percentage of Subjects With Parasitologic Response (Polymerase Chain Reaction (PCR) Corrected) at Day 28 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (Polymerase Chain Reaction (PCR) Corrected) at Day 28 Post First Dose of Study Medication[1]

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected). A subject will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR corrected) through the day of consideration, otherwise she is a parasitological failure. Modified Intent To Treat (MITT) population was used. MITT is a subset of the Intent To Treat (ITT) population who had Plasmodium falciparum monoinfection (confirmed by microscopy) parasite count in the range of 80-100,000/microlitre on their baseline blood smear. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Primary

End point timeframe:

Day 28

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: percentage of subjects				
number (confidence interval 95%)	99.35 (97.76 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Parasitologic Response (PCR Corrected) at Day 28 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Corrected) at Day 28 Post First Dose of Study Medication[2]

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected). A subjects will be a

parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR corrected) through the day of consideration, otherwise she is a parasitological failure. Per Protocol (PP) population was used. PP is a subset of MITT population who had received all 3 days of study medication. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Primary

End point timeframe:

Day 28

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: percentage of subjects				
number (confidence interval 95%)	99.35 (97.76 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 35, and 42 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 35, and 42 Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected). A subjects will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR corrected) through the day of consideration, otherwise she is a parasitological failure. MITT population was used. MITT is a subset of the ITT population who had Plasmodium falciparum monoinfection (confirmed by microscopy) parasite count in the range of 80-100,000/microlitre on their baseline blood smear. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: percentage of subjects				
number (confidence interval 95%)				

Day 7 (n=156)	100 (97.66 to 100)			
Day 14 (n=154)	100 (97.63 to 100)			
Day 21 (n=154)	100 (97.63 to 100)			
Day 35 (n=148)	96.65 (93.42 to 99.87)			
Day 42 (n=138)	95.19 (91.35 to 99.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 35, and 42 , Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 35, and 42 , Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected). A subjects will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR corrected) through the day of consideration, otherwise she is a parasitological failure. PP population was used. PP is a subset of MITT population who had received all 3 days of study medication. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: percentage of subjects				
number (confidence interval 95%)				
Day 7 (n=156)	100 (97.66 to 100)			
Day 14 (n=154)	100 (97.63 to 100)			
Day 21 (n=154)	100 (97.63 to 100)			
Day 35 (n=148)	96.65 (93.42 to 99.87)			
Day 42 (n=138)	95.19 (91.35 to 99.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Corrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected). A subject will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR corrected) through the day of consideration, otherwise she is a parasitological failure. ITT population was used. ITT is defined as all subjects who received at least one dose of study medication and who had a baseline blood smear positive for Plasmodium falciparum monoinfection, asexual parasitemia. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	165			
Units: percentage of subjects				
number (confidence interval 95%)				
Day 7 (n=158)	100 (97.69 to 100)			
Day 14 (n=156)	100 (97.66 to 100)			
Day 21 (n=156)	100 (97.66 to 100)			
Day 28 (n=156)	99.36 (97.79 to 100)			
Day 35 (n=150)	96.69 (93.51 to 99.88)			
Day 42 (n=140)	95.26 (91.47 to 99.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR uncorrected). A subject will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR uncorrected) through the day of consideration, otherwise she is a parasitological failure. MITT population was used. MITT is a subset of the ITT population who had Plasmodium falciparum monoinfection (confirmed by microscopy) parasite count in the range of 80-100,000/microlitre on their baseline blood smear.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: percentage of subjects				
number (confidence interval 95%)				
Day 7 (n=156)	100 (97.66 to 100)			
Day 14 (n=154)	100 (97.63 to 100)			
Day 21 (n=154)	100 (97.63 to 100)			
Day 28 (n=154)	95.45 (91.84 to 99.07)			
Day 35 (n=154)	87.66 (82.14 to 93.18)			
Day 42 (n=152)	78.43 (71.59 to 85.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR uncorrected). A subject will be a

parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR uncorrected) through the day of consideration, otherwise she is a parasitological failure. PP population was used. PP is a subset of MITT population who received all 3 days of study medication. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: percentage of subjects				
number (confidence interval 95%)				
Day 7 (n=156)	100 (97.66 to 100)			
Day 14 (n=154)	100 (97.63 to 100)			
Day 21 (n=154)	100 (97.63 to 100)			
Day 28 (n=154)	95.45 (91.84 to 99.07)			
Day 35 (n=154)	87.66 (82.14 to 93.18)			
Day 42 (n=152)	78.43 (71.59 to 85.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Percentage of Subjects With Parasitologic Response (PCR Uncorrected) at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

The proportion of subjects with parasitological response was estimated from the Kaplan Meier curve based on the time to the first occurrence of parasitological failure (PCR uncorrected). A subject will be a parasitological responder if she has a zero parasite count on the Day 7 visit without subsequent recurrence (PCR uncorrected) through the day of consideration, otherwise she is a parasitological failure. ITT population was used. ITT is defined as all subjects who received at least one dose of study medication and had a baseline blood smear positive for Plasmodium falciparum monoinfection, asexual parasitemia. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	165			
Units: percentage of subjects				
number (confidence interval 95%)				
Day 7 (n=158)	100 (97.69 to 100)			
Day 14 (n=156)	100 (97.66 to 100)			
Day 21 (n=156)	100 (97.66 to 100)			
Day 28 (n=156)	95.51 (91.94 to 99.08)			
Day 35 (n=156)	87.82 (82.37 to 93.27)			
Day 42 (n=154)	78.71 (71.94 to 85.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

Parasite counts (actual counts per microliter of blood) was measured at various time points. ITT population was used. ITT is defined as all subjects who received at least one dose of study medication and had a baseline blood smear positive for Plasmodium falciparum monoinfection, asexual parasitemia. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	165			
Units: parasite count per microliter				
arithmetic mean (standard error)				

Day 7 (n=155)	0 (± 0)			
Day 14 (n=154)	0 (± 0)			
Day 21 (n=156)	0 (± 0)			
Day 28 (n=156)	216.91 (± 110.04)			
Day 35 (n=156)	555.36 (± 246.77)			
Day 42 (n=155)	907.88 (± 470.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

Parasite counts (actual counts per microliter of blood) was measured at various time points. MITT population was used. MITT is a subset of the ITT population who had Plasmodium falciparum monoinfection (confirmed by microscopy) parasite count in the range of 80-100,000/microlitre on their baseline blood smear. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: parasite count per microliter				
arithmetic mean (standard error)				
Day 7 (n=153)	0 (± 0)			
Day 14 (n=152)	0 (± 0)			
Day 21 (n=154)	0 (± 0)			
Day 28 (n=154)	219.73 (± 111.46)			
Day 35 (n=154)	562.57 (± 249.94)			
Day 42 (n=153)	919.75 (± 476.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point title	Number of Asexual P. Falciparum per Microliter of Blood at Days 7, 14, 21, 28, 35, and 42 Post First Dose of Study Medication

End point description:

Parasite counts (actual counts per microliter of blood) was measured at various time points. PP population was used. PP is a subset of MITT population who received all 3 days of study medication. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: parasite count per microliter				
arithmetic mean (standard error)				
Day 7 (n=153)	0 (± 0)			
Day 14 (n=152)	0 (± 0)			
Day 21 (n=154)	0 (± 0)			
Day 28 (n=154)	219.73 (± 111.46)			
Day 35 (n=154)	562.57 (± 249.94)			
Day 42 (n=153)	919.75 (± 476.92)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Location of Delivery

End point title	Summary of Pregnancy Outcome: Location of Delivery

End point description:

All subjects were followed up for exposure-in-utero (EIU) safety assessments following delivery or termination of pregnancy. The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 160 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: subjects				
number (not applicable)				
Medical facility	130			
Home	27			
Other (Not specified)	3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Mode of Delivery

End point title	Summary of Pregnancy Outcome: Mode of Delivery

End point description:

All subjects were followed up for EIU safety assessments following delivery or termination of pregnancy. The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 160 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: subjects				
number (not applicable)				
Vaginal	145			
Cesarean section	15			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Delivery Assisted by Trained Obstetric Personnel?

End point title	Summary of Pregnancy Outcome: Delivery Assisted by Trained Obstetric Personnel?

End point description:

All subjects were followed up for EIU safety assessments following delivery or termination of pregnancy.

The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 159 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: subjects				
number (not applicable)				
Yes	132			
No	27			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Labor Induced?

End point title	Summary of Pregnancy Outcome: Labor Induced?

End point description:

All subjects were followed up for EIU safety assessments following delivery or termination of pregnancy. The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 158 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: subjects				
number (not applicable)				
Yes	3			
No	155			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Complications During Delivery?

End point title	Summary of Pregnancy Outcome: Complications During Delivery?

End point description:

All subjects were followed up for EIU safety assessments following delivery or termination of pregnancy. The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 159 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: subjects				
number (not applicable)				
Yes	42			
No	117			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Pregnancy Outcome: Outcome of Birth

End point title	Summary of Pregnancy Outcome: Outcome of Birth

End point description:

All subjects were followed up for EIU safety assessments following delivery or termination of pregnancy. The safety analysis set consists of subjects who received at least one dose of study medication. Data was available for 160 subjects only.

End point type	Other pre-specified

End point timeframe:

Following delivery or pregnancy termination

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: subjects				

number (not applicable)				
Full term live birth	151			
Premature birth	6			
Stillbirth	3			
Spontaneous abortion	0			
Induced/elective abortion	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of Fever Based on Oral Temperature

End point title	Incidence of Fever Based on Oral Temperature

End point description:

Oral temp was taken by the fieldworker through Day 42. ITT is defined as all subjects who received at least one dose of study medication and who had a baseline blood smear positive for Plasmodium falciparum monoinfection, asexual parasitemia. Two subjects were excluded because they had protocol deviations regarding the informed consent process.

End point type	Other pre-specified

End point timeframe:

Baseline, Days 1, 2, 7, 14, 21, 28, 35, and 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: subjects				
number (not applicable)				
Baseline (n=165)	0			
Day 1 (n=161)	0			
Day 2 (n=160)	0			
Day 7 (n=156)	0			
Day 14 (n=155)	0			
Day 21 (n=155)	0			
Day 28 (n=156)	0			
Day 35 (n=156)	0			
Day 42 (n=155)	4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Hemoglobin Concentration: Abnormal Hemoglobin Level

End point title	Summary of Hemoglobin Concentration: Abnormal Hemoglobin Level

End point description:

Abnormal hemoglobin level on Day 42 was measured. The hemoglobin levels were measured with HemoCueTM, via finger stick or peripheral blood collection. The reference range was 10-16g/dL. Any value <0.8 times lower limit of normal was considered clinically significant. The safety analysis set consists of subjects who received at least one dose of study medication.

End point type	Other pre-specified

End point timeframe:

Day 42

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: subjects				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Serum Azithromycin Concentration Versus Time

End point title	Summary of Serum Azithromycin Concentration Versus Time

End point description:

AZ concentrations in the serum was determined at specified time points as PK endpoints. Analyses population included all subjects who received at least one dose of study medication and had at least one blood sample collected for PK analysis. Here, "99999" in the arithmetic mean and standard deviation signifies data is not estimable (NA) as the summary statistics has been calculated by setting concentration values below the lower limit of quantification to zero.

End point type	Other pre-specified

End point timeframe:

Planned time: 0 (Day 0), 48 (Day 2), 50 (Day 2), 56 (Day 2), 168 (Day 7), and 336 (Day 14) hours post the first dose. Note: Assuming "hour not specified" as 0 hours on Day 7 and Day 14 for planned time post first dose calculation.

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	166			
Units: ng/mL (nanogram/milliliter)				
arithmetic mean (standard deviation)				
Hour 0 (Day 0) (n=161)	99999 (± 99999)			

Hour 48 (Day 2) (n=158)	194.145 (± 63.76829)			
Hour 50 (Day 2) (n=147)	994.463 (± 552.2373)			
Hour 56 (Day 2) (n=159)	707.682 (± 326.7237)			
Hour 168 (Day 7) (n=155)	54.444 (± 24.34615)			
Hour 336 (Day 14) (n=153)	20.307 (± 31.57879)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Plasma Chloroquine Concentration Versus Time

End point title	Summary of Plasma Chloroquine Concentration Versus Time

End point description:

CQ concentrations in the plasma were determined at specified time points as PK endpoints. Analyses population included all subjects who received at least one dose of study medication and had at least one blood sample collected for PK analysis. Here, "99999" in the arithmetic mean and standard deviation signifies data is not estimable (NA) as the summary statistics has been calculated by setting concentration values below the lower limit of quantification to zero.

End point type	Other pre-specified

End point timeframe:

Planned time: 0 (Day 0), 48 (Day 2), 50 (Day 2), 56 (Day 2), 168 (Day 7), 336 (Day 14), 504 (Day 21) and 672 (Day 28) post first dose. Note: Assuming "hour not specified" as 0 hours on Days 7, 14, 21 and 28 for planned time post first dose calculation.

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	166			
Units: ng/mL				
arithmetic mean (standard deviation)				
Hour 0 (Day 0) (n=160)	99999 (± 99999)			
Hour 48 (Day 2) (n=158)	305.827 (± 129.0277)			
Hour 50 (Day 2) (n=147)	621.134 (± 329.9273)			
Hour 56 (Day 2) (n=159)	640.679 (± 297.9762)			
Hour 168 (Day 7) (n=155)	129.835 (± 92.19161)			
Hour 336 (Day 14) (n=154)	43.119 (± 44.97312)			
Hour 504 (Day 21) (n=156)	22.382 (± 46.83029)			
Hour 672 (Day 28) (n=156)	12.721 (± 29.0538)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Plasma Desethylchloroquine Concentration Versus Time

End point title	Summary of Plasma Desethylchloroquine Concentration Versus Time

End point description:

CQ concentrations in the plasma were determined at specified time points as PK endpoints. Analyses population included all subjects who received at least one dose of study medication and had at least one blood sample collected for PK analysis. Here, "99999" in the arithmetic mean and standard deviation signifies data is not estimable (NA) as the summary statistics has been calculated by setting concentration values below the lower limit of quantification to zero.

End point type	Other pre-specified

End point timeframe:

Planned time: 0 (Day 0), 48 (Day 2), 50 (Day 2), 56 (Day 2), 168 (Day 7), 336 (Day 14), 504 (Day 21) and 672 (Day 28) post first dose. Note: Assuming "hour not specified" as 0 hours on Days 7, 14, 21 and 28 for planned time post first dose calculation.

End point values	Azithromycin (AZ)/Chloroquine (CQ)			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: ng/mL				
arithmetic mean (standard deviation)				
Hour 0 (Day 0) (n=158)	99999 (± 99999)			
Hour 48 (Day 2) (n=158)	183.622 (± 118.8648)			
Hour 50 (Day 2) (n=147)	220.424 (± 130.4834)			
Hour 56 (Day 2) (n=159)	241.831 (± 137.8858)			
Hour 168 (Day 7) (n=155)	144.088 (± 123.663)			
Hour 336 (Day 14) (n=154)	55.513 (± 54.78967)			
Hour 504 (Day 21) (n=156)	29.825 (± 32.418)			
Hour 672 (Day 28) (n=156)	19.439 (± 19.52079)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 42 follow-up visit for treatment emergent AEs for mothers and 14 days post delivery for neonates

Adverse event reporting additional description:

No treatment emergent serious adverse events (SAEs) were observed in mothers. Events related to neonatal malformation/anomalies, premature delivery, low birth weight neonates, developmental assessment, kernicterus, or any other neonatal illness, hospitalization, drug therapy etc, were recorded and presented under the "familial status = neonates"

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Azithromycin/Chloroquine (Familial Status = Neonate)

Reporting group description:

AZCQ (Familial Status = Neonate). Number of deaths due to adverse events = 4. Number of deaths related to treatment = 0.

Reporting group title	Azithromycin/Chloroquine (Familial Status = Mother)

Reporting group description:

ACZQ (Familial Status = Mother)

Serious adverse events	Azithromycin/Chloroquine (Familial Status = Neonate)	Azithromycin/Chloroquine (Familial Status = Mother)	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 157 (5.73%)	0 / 168 (0.00%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Hypospadias			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydactyly			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Premature baby			

subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Sudden infant death syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Neonatal asphyxia			
subjects affected / exposed	4 / 157 (2.55%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			
Sepsis neonatal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Azithromycin/Chloroquine (Familial Status = Neonate)	Azithromycin/Chloroquine (Familial Status = Mother)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 157 (12.74%)	92 / 168 (54.76%)	
Investigations			
White blood cells urine positive			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Dizziness			

subjects affected / exposed	0 / 157 (0.00%)	33 / 168 (19.64%)	
occurrences (all)	0	33	
Headache			
subjects affected / exposed	0 / 157 (0.00%)	10 / 168 (5.95%)	
occurrences (all)	0	10	
Pregnancy, puerperium and perinatal conditions			
False labour			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Low birth weight baby			
subjects affected / exposed	8 / 157 (5.10%)	0 / 168 (0.00%)	
occurrences (all)	8	0	
Premature baby			
subjects affected / exposed	6 / 157 (3.82%)	0 / 168 (0.00%)	
occurrences (all)	6	0	
Umbilical cord around neck			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 157 (0.00%)	3 / 168 (1.79%)	
occurrences (all)	0	3	
Chills			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 157 (0.00%)	7 / 168 (4.17%)	
occurrences (all)	0	7	
Pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Macrosomia			

subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 157 (0.00%)	2 / 168 (1.19%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Abdominal pain lower			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 157 (0.00%)	2 / 168 (1.19%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 157 (0.00%)	3 / 168 (1.79%)	
occurrences (all)	0	3	
Food poisoning			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 157 (0.00%)	6 / 168 (3.57%)	
occurrences (all)	0	6	
Vomiting			
subjects affected / exposed	0 / 157 (0.00%)	35 / 168 (20.83%)	
occurrences (all)	0	35	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Nasal congestion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Neonatal asphyxia			
subjects affected / exposed	3 / 157 (1.91%)	0 / 168 (0.00%)	
occurrences (all)	3	0	
Pneumonia aspiration			
subjects affected / exposed	1 / 157 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 157 (0.00%)	13 / 168 (7.74%)	
occurrences (all)	0	13	
Pruritus generalised			
subjects affected / exposed	0 / 157 (0.00%)	9 / 168 (5.36%)	
occurrences (all)	0	9	
Infections and infestations			
Infection parasitic			
subjects affected / exposed	0 / 157 (0.00%)	12 / 168 (7.14%)	
occurrences (all)	0	12	
Malaria			
subjects affected / exposed	0 / 157 (0.00%)	8 / 168 (4.76%)	
occurrences (all)	0	8	
Trichomoniasis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 157 (1.91%)	7 / 168 (4.17%)	
occurrences (all)	3	7	
Urinary tract infection			
subjects affected / exposed	0 / 157 (0.00%)	4 / 168 (2.38%)	
occurrences (all)	0	4	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 157 (0.00%)	4 / 168 (2.38%)	
occurrences (all)	0	4	
Neonatal infection			

subjects affected / exposed occurrences (all)	1 / 157 (0.64%) 1	0 / 168 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 0 / 157 (0.00%) 0	 1 / 168 (0.60%) 1	

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