Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Zithromax
Azithromycin (dehydrate)

PT/W/0007/pdWS/001

Marketing Authorisation Holder:
PFIZER

Rapporteur:	Portugal
Finalisation procedure (day 120):	04/01/2019

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Zithromax
INN (or common name) of the active substance(s):	Azithromycin (dehydrate)
MAH:	Pfizer
Currently approved Indication(s)	***Current therapeutic indication(s):*** *from the Company Core Data Sheet* Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in odontostomatological infections, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.) In sexually transmitted diseases in men and women, azithromycin is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi*, and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*; concurrent infection with *Treponema pallidum* should be excluded. Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium-intracellulare complex* (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV). Azithromycin is indicated in combination with ethambutol for the treatment of disseminated MAC (DMAC) infection in patients with advanced HIV infection. Azithromycin intravenous (IV) is indicated for the treatment of community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy. Azithromycin intravenous (IV) is indicated for the treatment of pelvic inflammatory diseases (PID) caused by susceptible organisms (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis*), in patients who require initial intravenous therapy. **Azithromycin prolonged-release granules for oral suspension in adults:** Acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenzae, Haemophilus

	parainfluenzae, Moraxella catarrhalis, or Streptococcus pneumoniae. Acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae. Community acquired pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae or Streptococcus pneumoniae. Pharyngitis/tonsillitis caused by Streptococcus pyogenes in subjects intolerant to beta-lactam antimicrobials.
Pharmaco-therapeutic group (ATC Code):	J01FA10
Pharmaceutical form(s) and strength(s):	Prolonged-release granules for oral suspension, 2 g Powder For Solution, For Infusion, 100mg/ml Powder For Suspension, Oral 200mg/5ml Film Coated, Oral 500mg

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I. EXECUTIVE SUMMARY

SmPC changes are proposed in section 5.1.

II. RECOMMENDATION[1]

Based on the data submitted, the MAH should consider an update of the SmPC in section 5.1. to include the following information:
Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

A Type IB variation, usually, should be submitted within 30 days after the end of the procedure, in order to update the SmPC, with the text proposed in section 5.1.
However, the Rapporteur has agreed with the Applicant request for submission of the Type IB variation until 31st January 2019, to allow the submission as a worksharing.

III. INTRODUCTION

On 4th June 2015, the MAH submitted four completed paediatric studies for Azithromycin, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided for each one of the trials.

The MAH stated that the submitted paediatric studies did not influence the benefit risk for Azithromycin and that there was no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Azithromycin (AZ) received the first regulatory approval on 04 April 1991 in the United Kingdom and has been approved in 141 countries, and is currently marketed in 133 countries. AZ Prolonged-Release Formulation (PRF; 2 g granules, extended, prolonged, or sustained release, for suspension, oral) has approval in 94 countries and currently marketed in 59 countries.
Anaphylaxis, Severe Cutaneous Adverse Reactions (SCARs), hepatic toxicity, Clostridium difficile associated diarrhoea (CDAD), hearing impairment, QT prolongation/Torsade de pointes and drug-drug interactions with digoxin and cyclosporine are important identified risks for azithromycin; vomiting is an important identified risk specific to the prolonged release granules formulation categorized during the current reporting period.

[1] *The recommendation from section V can be copied in this section*

Superinfection and drug-drug interactions with ergot derivatives, and coumarin-type oral anticoagulants are important potential risks for azithromycin.

The following tables summarize lot and formulation identification numbers of the administered drugs for:

> **Study A0661190**

Study Drug and Potency	Dosage Form	Lot Number	Dosage Material Number
Azithromycin Extended Release for Oral Suspension 2G	Suspension	08-069635	D0804286
Azithromycin for Oral Suspension 300 mg	Suspension	08-069644	D0804287

> **Study A0661157**

Drug	Lot Number	Dosage Material Number	Potency	Formulation
300mg Azithromycin and 100mg Chloroquine Immediate Release	07-058517	D0703486	300az /100cq	TABLET
Riamet Tablets	08-063301	D0703229	20/120	TABLET
Riamet Tablets	09-074349	D0703229	20/120	TABLET
Riamet Tablets	08-067906	D0703229	20/120	TABLET
150mg Azithromycin and 50mg Chloroquine Immediate Release Tablet	07-058546	D0703598	150az / 50cq	TABLET
Riamet Tablets	09-078984	D0703229	20/120	TABLET
Riamet Tablets	07-052344	D0703229	20/120	TABLET
Riamet Tablets	07-052308	D0703229	20/120	TABLET

> **Study A0661158**

Drug	Formulation	Lot Number	Dosage Material Number
250 mg Azithromycin/ 155 mg Chloroquine Immediate-Release Tablet	Tablet	08-068753	D0804147
250 mg Azithromycin/ 155 mg Chloroquine Immediate-Release, White to Off-White Tablet	Tablet	11-009182	D1100306
Sulfadoxine-pyrimethamine (Fansidar) tablets 500/ 25 mg	Tablet	09-078464	A0901223
		09-079687	A0901223

> **Study A0661201**

Drug	Formulation	Lot Number	Dosage Material Number
250 mg Azithromycin/155 mg Chloroquine Immediate Release Tablet	Tablet	08-068753	D0804147
250 mg Azithromycin/155 mg Chloroquine Immediate Release, White to off-White Tablet	Tablet	11-009182	D1100306

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final report(s) for:

- **<u>Study A0661190</u> - a Phase 2, open-label, randomised, single-dose, parallel-arm study to determine the pharmacokinetics of azithromycin following oral administration of an immediate-release (IR) or extended-release (ER) oral suspension in paediatric subjects with Acute Otitis Media (AOM).**

- **<u>Study A0661157</u> - a Phase 3, open-label, comparative, multicentre, multicountry study in which subjects were randomised to 1 of the 2 active treatment arms of either azithromycin-chloroquine (AZ-CQ) or artemether-lumefantrine (AL) for the treatment of symptomatic, uncomplicated *Plasmodium falciparum* in children.**

- **<u>Study A0661158</u> - a Phase 3, open-label, randomised, comparative study to evaluate AZ plus chloroquine (CQ) and sulfadoxine plus pyrimethamine combinations for intermittent preventive treatment of *Falciparum* malaria infection in pregnant women in Africa.**

- **<u>Study A0661201</u> - a Phase 3, open-label, non-comparative study evaluating parasitological clearance rates and pharmacokinetics (PK) of azithromycin and chloroquine (AZCQ) following administration of a fixed-dose combination of AZCQ in asymptomatic pregnant women during their second and third trimesters of pregnancy with *Plasmodium falciparum* parasitaemia in Sub-Saharan Africa.**

2. Clinical studies

Study A0661190 - a Phase 2, open-label, randomised, single-dose, parallel-arm study to determine the pharmacokinetics of azithromycin following oral administration of an immediate-release (IR) or extended-release (ER) oral suspension in paediatric subjects with Acute Otitis Media (AOM).

➢ Description

Study A0661190 was designed to compare the pharmacokinetics of azithromycin ER with those of the azithromycin IR formulations approved for AOM, to show that azithromycin serum levels with a 60 mg/kg dose of ER formulation are closely similar to or greater than a 30 mg/kg dose of IR formulation at all time points.

➢ Methods

- Objective(s)

The primary objective of the study was to compare the pharmacokinetics of azithromycin following a single dose of either 30 mg/kg IR or 60 mg/kg ER formulation in paediatric subjects with AOM.

The secondary objectives were to evaluate the safety of azithromycin following a single dose of either 30 mg/kg IR or 60 mg/kg ER formulation in paediatric subjects with AOM, and to evaluate clinical response to azithromycin following a single dose of either 30 mg/kg IR or 60 mg/kg ER formulation in paediatric subjects with AOM.

- Study design

This was an open-label, randomised, single-dose, parallel-arm pharmacokinetic study conducted at a single site in Costa Rica in 36 paediatric subjects with AOM, aged 6 months to 6 years, inclusive.

The patients who fulfilled the below-mentioned diagnostic criteria were included in the study:

Clinical signs/symptoms of AOM in at least 1 ear, as follows:

- Purulent otorrhoea of ≤24 hours duration; or
- At least 2 otoscopic signs of middle ear effusion:
    - Decreased or absent tympanic membrane mobility by pneumatic otoscopy
    - Yellow or white discolouration of tympanic membrane
    - Opacification of tympanic membrane (other than scarring) and
- At least 1 indicator of acute inflammation to support the diagnosis of AOM:
    - Ear pain, including unaccustomed tugging or rubbing
    - Marked redness of tympanic membrane
    - Distinct fullness or bulging of tympanic membrane

A set of exclusion criteria was also established (not described here).

The subjects were screened within 48 hours prior to dosing on Day 1. The subjects who satisfied all inclusion/exclusion criteria at the end of the screening phase were randomized on Day 1 in a ratio of 1:1 to receive either a single oral dose of 30 mg/kg azithromycin IR formulation or a single oral dose of 60 mg/kg azithromycin ER formulation.

The subjects were confined to the clinical research unit (CRU) until the 8 hour post-dose pharmacokinetic sample on Day 1 and returned on Days 2 to 4 for pharmacokinetic blood sampling. Serum blood samples were collected on Days 1 to 4 for evaluation of azithromycin pharmacokinetics. In addition to the blood sample for safety laboratory tests at screening, 8 blood samples (approximately 0.75 mL per sample) were collected from each subject for evaluation of azithromycin at the following time points: 1, 2, 3, 4, 8, 24, 48 and 72 hours post-dose. Clinical response was assessed by the investigator 7 to 10 days after dosing. Exclusive of the screening period, total participation in the study for each subject was approximately 10 days.

- Study population / Sample size

Thirty-eight (38) subjects were treated in the study, 19 in each treatment group.

- Treatments

Each subject received a single oral dose of the study drug (30 mg/kg azithromycin IR formulation or 60 mg/kg azithromycin ER formulation) in the CRU on Day 1. The study drug was administered on an empty stomach, that is, at least 1 hour before or 2 hours following breakfast. Azithromycin was supplied by the Sponsor as a white to off-white powder with a cherry/banana/vanilla flavour, for administration as an oral suspension.

- Outcomes/endpoints

Pharmacokinetic (PK) Evaluations: Blood samples for pharmacokinetic analysis were collected at 1, 2, 3, 4, 8, 24, 48 and 72 hours post-dose. Samples were analysed using a validated analytical method in compliance with the Sponsor's standard operating procedures.

Clinical Response Assessments: At the final visit or at the time of subjects discontinuation from the study (if applicable), the investigator assessed the subject's response to therapy as cure or failure.

Cure: Clinical sign and symptoms related to the acute illness had resolved or clinical improvement is such that no additional therapy was necessary

Failure: 1 or more of the following:

- Sign and symptoms related to the acute illness had persisted or worsened and additional therapy was necessary
- New clinical sign and symptoms, or new sign and symptoms, were documented as AEs

This was an investigator assessment; there were no formal analyses of clinical response set out in the protocol.

Safety Evaluations: Safety evaluations included monitoring of AEs throughout the study, safety laboratory tests performed at screening (Day 2 for subjects who were discontinued from the study) and vital signs measurements taken at screening, at 0 hours post-dose on Day 1 and on Days 7 to 10.

- Statistical Methods

One-way analysis of variance was used to compare the natural log transformed AUC_{72} and C_{max}. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% ICs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the rations. The IR formulation (30mg/Kg) was the Reference treatment and the ER formulation (60mg/Kg) was the Test treatment.

The pharmacokinetic parameters AUC_{inf}, AUC_{72}, C_{max}, T_{max}, and $t_{1/2}$ were summarized by treatment. For AUC_{inf}, AUC_{72} and C_{max}, individual subject parameters were plotted by treatment.
The criterion for the summary pharmacokinetic parameter (primary endpoint AUC_{72}) as well as each time point (secondary endpoints) comparison between treatments (ER versus IR) was predetermined as maintaining at least a lower 90% CI bound of 80% and 70% respectively, to demonstrate that the ER formulation is closely similar to or greater than the IR formulation.
Similar ANOVA analyses as above were performed to compare each time point (C_{TPD}) separately between treatments (ER versus IR) using log transformed concentration data.

Concentration data were summarized by pharmacokinetic sampling time and treatment.
The response to therapy as Cure or Failure was listed.
Safety data including demographics, vital signs, safety laboratory tests and AEs were presented in tabular and/or graphical format and summarized descriptively, where appropriate.

- **Results**

- Recruitment / Number analysed and Baseline data

38 Hispanic subjects were treated in the study, 19 in each treatment group; 23 males and 15 females. Demographic data were similar between the 2 treatment groups, although mean age was slightly higher in the 30mg/kg azithromycin IR group (34.5months) compared to the 60mg/Kg azithromycin ER group (24.3 months).

One (1) subject in each treatment group discontinued from the study (10011004 [60 mg/kg azithromycin ER] discontinued due to AE vomiting; 10011002 [60 mg/kg azithromycin IR] discontinued due to protocol deviation of inappropriate dosing). All completed subjects were analyzed for pharmacokinetics and clinical response, and all treated subjects were analyzed for safety (AEs).

- Pharmacokinetic Evaluation

Seven (7) subjects had inconsistent serum concentration-time profiles, therefore, pharmacokinetic and statistical analyses were performed with (complete data set) and without (reduced data set) the data from these subjects. The following are the pharmacokinetic results:

- For area under the serum concentration-time profile from time zero to 72 hours post-dose (AUC_{72}; reduced data set): The ratio of the adjusted means (90% confidence interval [CI]) was 141.18% (80.45%, 247.78%) when comparing the 60 mg/kg ER formulation to the 30 mg/kg IR formulation. For C_{max} (reduced data set), the ratio for the adjusted means (90% CI) was 82.09% (45.59%, 147.83%). The lower boundary of the 90% CI for the ratio of AUC_{72} fell above the predetermined acceptance criterion of ≥80%. The median time for C_{max} (T_{max}) was slightly delayed and the mean terminal elimination half-life ($t_{½}$) was slightly prolonged with the ER formulation compared with the IR formulation.

- For AUC_{72} (complete data set): The ratio of the adjusted means (90% CI) was 157.98% (98.87%, 252.44%). For C_{max} (complete data set), the ratio for the adjusted means (90% CI) was 91.63% (56.21%, 149.38%).

- For the concentration data at each serial time point (reduced data set): The lower boundary of the 90% CI for the ratio of Test to Reference concentrations at the first 3 time points (reduced data set, C_1, C_2 and C_3) fell below the predetermined criterion of ≥70%. The lower boundary of the 90% CI for the ratio of Test to Reference concentrations at all remaining time points (reduced data set, C_4, C_8, C_{24}, C_{48} and C_{72}) was greater than the predetermined criterion of ≥70%. The ratios of the adjusted means were higher than 100% for ER compared with IR at C_4, C_8, C_{24}, C_{48} and C_{72}.

Parameter (units)	Adjusted Geometric Mean		Ratio[a] (Test/Reference)	90% Confidence Interval for Ratio[a]
	60 mg/kg Azithromycin ER [Test] N=15	30 mg/kg Azithromycin IR [Reference] N=13		
AUC_{72} (ng.h/mL)	9065	6421	141.18	(80.45, 247.78)
C_{max} (ng/mL)	569.3	693.4	82.09	(45.59, 147.83)

Source: Table 13.5.4.1. N = Number of subjects in the treatment group, ER = Extended release, IR = Immediate release
[a] Ratios (and 90% confidence intervals) are expressed as percentages

- For the concentration data at each serial time point (complete data set): The lower boundary of the CI for ratio of Test to Reference concentrations at the first 3 time points (complete data set, C_1, C_2 and C_3) fell below the predetermined criterion of ≥70%. The lower boundary of the CI for the ratio of Test to Reference concentrations at all remaining time points (complete data set, C_4, C_8, C_{24}, C_{48} and C_{72}) was greater than the predetermined criterion of ≥70%. The ratio of the adjusted means was higher than 100% for the ER formulation compared with IR formulation at C_3, C_4, C_8, C_{24}, C_{48} and C_{72}.

Parameter (units)	Adjusted Geometric Mean		Ratio[a] (Test/Reference)	90% Confidence Interval for Ratio[a]
	60 mg/kg Azithromycin ER [Test] N=18	30 mg/kg Azithromycin IR [Reference] N=18		
AUC_{72} (ng.h/mL)	9848	6234	157.98	(98.87, 252.44)
C_{max} (ng/mL)	611.5	667.3	91.63	(56.21, 149.38)

Source: Table 13.5.3.1. N = Number of subjects in the treatment group, ER = Extended release, IR = Immediate release
[a] Ratios (and 90% confidence intervals) are expressed as percentages

- Clinical Response Assessments Results:

Sixteen (16; 88.9%) subjects in the 30 mg/kg azithromycin IR group and 18 (100%) subjects in the 60 mg/kg azithromycin ER group had clinical response assessed as cure. Two (2; 11.1%) subjects in the 30 mg/kg azithromycin IR group had clinical response assessed as fail.

- Safety results

There were no deaths during the study.

Five (5) subjects in the 30 mg/kg azithromycin IR group reported 5 treatment-emergent AEs (TEAE) and 4 subjects in the 60 mg/kg azithromycin ER group reported 4 TEAEs. There were no serious AEs and no dose reductions or temporary discontinuations because of AEs. One (1) subject (10011004) in the 60 mg/kg azithromycin ER group was permanently discontinued because of an AE (vomiting), which was mild in severity and resolved after approximately 19 hours.

The most commonly reported AE during the study was Vomiting, which was reported by 1 subject in the 30 mg/kg azithromycin IR group and by 3 subjects in the 60 mg/kg azithromycin ER group (table below). Only 1 AE (Vomiting), in the 60 mg/kg azithromycin ER group, was considered treatment related. In the 30 mg/kg azithromycin IR group 2 subjects experienced treatment-related Treatment failure and 1 subject experienced treatment related Anorexia. All AEs were mild or moderate in severity and all resolved by the end of the study.

Incidence of Treatment Emergent Adverse Events

Number of Subjects With MedDRA (v11.1) Preferred Term	60 mg/kg Azithromycin ER N = 19		30 mg/kg Azithromycin IR N = 19	
	AC	TR	AC	TR
Diarrhoea	0	0	1	0
Treatment Failure	0	0	2	2
Vomiting	3	1	1	0
Anorexia	0	0	1	1
Nausea	1	0	0	0

AC = All-causality; ER = Extended-release; IR = Immediate-release; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects; TR = Treatment-related.
Includes data up to 35 days after last dose of the study drug.

There were no clinically significant laboratory tests or vital sign results other than the signs and symptoms attributable to AOM.

Study A0661157 - a Phase 2/3, open-label, comparative, multicentre, multicountry study in which subjects were randomised to 1 of the 2 active treatment arms of either azithromycin-chloroquine (AZ-CQ) or artemether-lumefantrine (AL) for the treatment of symptomatic, uncomplicated *Plasmodium falciparum* in children.

- **Description**

This was a Phase 2/3, open-label, comparative, multicentre, multicountry study in which subjects were randomised to 1 of the 2 active treatment arms of either azithromycin-chloroquine (AZ-CQ) or artemether-lumefantrine (AL) for the treatment of symptomatic, uncomplicated *Plasmodium falciparum* in children.

- **Methods**

- Objective(s)

The primary objective of the study was to confirm the hypothesis that AZ, when used in combination with CQ, is noninferior to AL for the treatment of symptomatic, uncomplicated malaria because of *P. falciparum* in children in Africa.

Secondary objectives included additional efficacy measurements and an assessment of the safety and tolerability of both treatment regimens.

- Study design

This was a Phase 3, open-label, comparative, multicentre, multicountry study in which subjects were randomised to 1 of the 2 active treatment arms of either AZ-CQ or AL. The duration of dosing was 3 days. Each subject was asked to participate for a total of 42 days.

The study was conducted in 7 centers in Africa; 1 each in Kenya, Ghana, Mali, Zambia (did not enroll any subjects), Ivory Coast, and 2 centers in Burkina Faso.

Subjects were recruited into 2 age-based cohorts: Cohort 1 included subjects who were ≥5 and ≤12 years of age. This cohort was assumed to have some degree of 'immunity' to *falciparum* malaria infection, and therefore, was at less risk for untoward outcome. Only after demonstration of successful treatment and adequate safety and tolerability in this cohort, subjects aged $\geq$ 6 to $\leq$ 59 months were enrolled into Cohort 2, which were the primary study population for this study.

A rapid malaria test (eg, Binax NOW ICT [immunochromatographic test]) was used to screen for the presence of *P. falciparum* parasites in children with fever or a recent history of fever. Any positive rapid blood test was confirmed by microscopy on a Giemsa-stained blood smear. Subjects were monitored closely during the acute stage of the illness. All subjects (in both cohorts) who fulfilled study criteria were admitted to a hospital for the 3 days of study drug administration and until 2 consecutive blood smears (thin and thick) were negative for asexual parasitemia and the investigator deemed that discharge from the hospital was appropriate.

Smears were also prepared on Days 3, 7, 14, 21, 28, 35, and 42. Unscheduled smears were obtained for subjects presenting with signs and/or symptoms of malaria at any time during unscheduled follow-up visits. Subjects were monitored frequently for clinical evidence of improvement or cure.

Smear results and clinical assessment at the study location guided subject management, and any subject with persistent or recurrent parasitemia during the follow-up period was treated with antimalarial drugs according to local treatment guidelines. These subjects were followed through Day 42 for clinical and parasitologic outcomes and adverse event (AE) monitoring. The malaria

parasites from subjects who developed parasitemia after treatment and initial parasitic clearance were genotyped in order to differentiate recrudescence (treatment failure) from reinfection. Genetic markers indicative of CQ resistance in *P. falciparum* were determined from blood blots obtained on Day 0 and at the time of failure.

- Study population / Sample size

A total of 361 subjects were enrolled and treated in this study (106 subjects in Cohort 1 and 255 subjects in Cohort 2).

A total of 4 subjects in Cohort 1 and 5 subjects in Cohort 2 were discontinued from the study. The reason for discontinuation from Cohort 1 was that the subjects were no longer willing to participate in the study (4 AZ-CQ subjects). Reasons for discontinuation from Cohort 2 were that the subjects were no longer willing to participate in the study (1 AZ-CQ subject and 3 AL subjects) and lost to follow-up (1 AZ-CQ subject). Four (4) subjects in the AZ-CQ group of Cohort 1 and 1 subject in the AL treatment group of Cohort 2 had no follow-up laboratory data, and therefore, were not included in the analysis of laboratory data.

Main Criteria for Inclusion: Males and females ≥5 years to ≤12 years (Cohort 1); and ≥6 months to ≤59 months of age (Cohort 2) were enrolled if they had uncomplicated, symptomatic malaria, as indicated by blood smears positive for monoinfection with *P. falciparum* and asexual parasitemia between 1000 to 100,000 parasites/uL; as well as documented fever, or history of fever within the 24 hours prior to enrollment.

Several **exclusion criteria** (not listed here) were also define to insure safety of participants and exclusion of possible confounders to evaluation of the endpoint.

- Treatments

Subjects were randomised in a 1:1 ratio to either AZ-CQ or AL treatment given open-label by the investigator. AZ-CQ was administered as a combination tablet (300 mg AZ and 100 mg CQ or 150 mg AZ and 50 mg CQ), scored to allow for dosing by weight [Azithromycin (~30 mg/kg); chloroquine (~10 mg/kg base)]. AL was supplied as Riamet tablets (20 mg artemether/120 mg lumefantrine).

Subjects were administered AZ-CQ study treatment once daily, by mouth, for 3 consecutive days. AL was administered for 3 consecutive days as per instructions in the package insert. When possible, study drugs were administered with or immediately after food consumption.

- Outcomes/endpoints

The **primary endpoint** was the proportion of subjects with adequate clinical and parasitologic response (ACPR; polymerase chain reaction corrected [PCR-corrected]) at the test of cure Day 28 evaluation. ACPR (PCR-corrected) was defined as asexual *P. falciparum* parasitologic clearance at Day 28 irrespective of axillary, oral, rectal, or tympanic temperature without previously meeting the criteria of Early Treatment Failure (ETF) or PCR-corrected Late Treatment Failure (LTF). ACPR was derived from the analysis of time to the first occurrence of treatment failure. The estimated proportion of subjects with ACPR (PCR-corrected) at Day 28 was determined from the corresponding Kaplan-Meier curve.
P. *falciparum* genotyping using the Merozoite Surface Peptide was used to distinguish recrudescence from reinfection.

Secondary efficacy evaluations included:

- Percentage of subjects with ACPR (PCR-corrected) at Days 7, 14, 21, 35, and 42;
- Percentage of subjects with ACPR (PCR-uncorrected) at Days 7, 14, 21, 28, 35, and 42;

- Asexual *P. falciparum* parasite clearance rate at Days 7, 14, 21, 28, 35, and 42;
- *P. falciparum* gametocyte clearance rate at Days 7, 14, 21, 28, 35, and 42;
- Fever clearance time;
- Asexual *P. falciparum* parasite clearance time;
- Hemoglobin level changes from the nadir defined from Day 0 through Day 3;
- Time to recurrence of *P. falciparum* parasitemia;
- CQ Resistance Transporter gene (PfCRT) status at Baseline.

Pharmacokinetic (PK) Evaluations: PK blood samples were collected only in the AZ-CQ treatment group to determine AZ, CQ and desethylchloroquine (desethyl-CQ) concentrations. PK blood samples were collected at 0 hour (window: -1 to 0 hour) on Day 0, at 0 hour (predose; window: -1 to 0 hour), 3 hours (window: 2 to 4 hours), and 8 hours (window: 6 to 10 hours) postdose on Day 2, and randomly on Day 7.

Safety Evaluations: At each study visit, vital signs (including temperature, sitting and supine blood pressure, respiration rate, and heart rate), clinical signs and symptoms, AEs, and concomitant medications were monitored and recorded. Electrocardiograms (ECGs) were obtained on Day 0 and Day 2 when feasible. On Days 0 and 3, hematology and serum chemistry tests were performed and were also performed at each subsequent study visit as clinically indicated. Hemoglobin was measured on Days 0, 14, 28, and 42.

- Statistical Methods

Cohorts 1 and 2 enrolled subjects from different age groups. Progression from Cohort 1 to Cohort 2 was contingent upon meeting pre-specified criterion. Thus, data from Cohort 1 will be analyzed separately from that of Cohort 2.

Analysis was made considering the following definitions:
a) All Treated Subjects: All subjects who are randomized and received at least one dose of study medication.
b) Modified Intent-To-Treat (MITT): MITT is a subset of the All Treated Subjects Population meeting all the disease criteria at baseline particularly as listed below:

- Blood smears positive for *Plasmodium falciparum* monoinfection; asexual parasitemia between 1000 -100,000 parasites/µL;
- Fever or history of fever ≥ 38.0°C/100.4°F (rectal), 37.2°C/99.0°F (axillary), or < 37.5°C/99.5°F (oral) within the prior 24 hours;

c) Per Protocol (PP): PP is a subset of MITT that received all 3 days of study medication to which they were assigned;

Efficacy Analyses: Cohort 2 was the group used to establish noninferiority between AZ-CQ and AL treatment. The primary efficacy endpoint was based on the proportion of subjects with ACPR (PCR-corrected) at the test of cure Day 28 evaluation.
One formal planned interim analysis was performed when approximately 50% of the subjects enrolled in Cohort 2 (approximately 52 evaluable subjects per arm) had completed the Day 28 Visit. The objective of the interim analysis was to assess safety and trial futility.
In the final analyses, a significance level of 0.05 was used when evaluating all statistical tests, and confidence intervals (CIs) were computed with a 95% level of confidence.
Cohort 1 data were analyzed, but no formal statistical inference was made.

The proportion of subjects with ACPR (PCR-corrected) at Day 28 was estimated from the Kaplan-Meier curve of the time to the first occurrence of treatment failure and its standard error estimated by the Greenwood formula. A 2-sided 95% confidence interval (CI) for the difference in ACPR (PCR-corrected) proportions (AZ-CQ minus AL) using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR (PCR-

corrected) proportions from the Kaplan-Meier curves and their standard errors estimated by the Greenwood formula.
Noninferiority was concluded if the lower boundary of this CI was greater than or equal to –10 percentage points for both the modified intent-to-treat (MITT) and per-protocol (PP) populations.

Pharmacokinetic (PK) Analysis: Azithromycin serum concentration, CQ plasma concentration, and desethyl-CQ plasma concentration data were listed by treatment group, cohort, subject, study day, nominal time postdose and actual time postdose. In addition, age, weight, and drug (AZ-CQ) dose for each subject were also included. Descriptive statistics (N, mean, standard deviation [SD], coefficient of variation [CV], median, minimum and maximum) of AZ serum concentration, CQ plasma concentration, and desethyl-CQ plasma concentration data were provided for treatment, cohort, study day, and nominal time postdose. Population PK analysis using nonlinear mixed effects modeling was performed to characterize the PK of AZ and CQ in subjects with sparse PK samples collected. The sparse PK samples collected from this study will be pooled with other studies for a meta-analysis.

Safety Analysis: Summary tabulations of AEs, deaths, discontinuations, vital signs measurements, ECG results, and laboratory data, and listings of subjects who discontinued, or had clinically significant laboratory abnormalities, are presented for all treated subjects by treatment regimen. AEs were reported using preferred terms and summarized by body system.
An independent external Data Safety Monitoring Committee (DSMC) provided oversight of the evaluation of the safety data.

- **Results**

- Recruitment / Number analysed

A total of 361 subjects were enrolled and treated in this study (106 subjects in Cohort 1 and 255 subjects in Cohort 2). A total of 4 subjects in Cohort 1 and 5 subjects in Cohort 2 discontinued from the study. Four subjects in the AZ-CQ group of Cohort 1 and 1 subject in the AL treatment group of Cohort 2 had no follow-up laboratory data and therefore were not included in the analysis of laboratory data. Subject disposition and datasets analyzed are summarized in the Table below.

	AZ-CQ N (%)	AL N (%)
	COHORT 1	
Screened	55	51
Assigned study treatment	55 (100.0)	51 (100.0)
Treated	55 (100.0)	51 (100.0)
Completed	51 (92.7)	51 (100.0)
Discontinued from study	4 (7.3)	0
No longer willing to participate in study	4 (7.3)	0
Discontinued from treatment		
Permanent discontinuation	4 (7.3)	0
Adverse event	4 (7.3)	0
Temporary discontinuation	1 (1.8)	0
Adverse event	1 (1.8)	0
Analyzed for safety		
Adverse events	55 (100.0)	51 (100.0)
Laboratory	51 (92.7)	51 (100.0)
	COHORT 2	
Screened	124	131
Assigned study treatment	124 (100.0)	131 (100.0)
Treated	124 (100.0)	131 (100.0)
Completed	122 (98.4)	128 (97.7)
Discontinued from study	2 (1.6)	3 (2.3)
Lost to follow-up	1 (0.8)	0
No longer willing to participate in study	1 (0.8)	3 (2.3)
Discontinued from treatment		
Permanent discontinuation	7 (5.6)	1 (0.8)
Adverse event	7 (5.6)	1 (0.8)
Temporary discontinuation	1 (0.8)	0
Adverse event	1 (0.8)	0
Analyzed for safety		
Adverse events	124 (100.0)	131 (100.0)
Laboratory	124 (100.0)	130 (99.2)

AZ-CQ = azithromycin + chloroquine; AL = artemether-lumefantrine; N=number of subjects

- Baseline data

All subjects in both cohorts were black. Within each cohort, demographics characteristics were similar between treatment groups, with the exception of gender ratio. Cohort 1 subjects in the AL group had a higher percentage of males (58.8%) than females (41.2%); whereas the gender distribution in the AZ-CQ group was fairly equal (49.1% males and 50.9% females). In Cohort 2, there was a higher percentage of males (59.7%) compared with females (40.3%) in the AZ-CQ group. All subjects in Cohort 1 met the age criterion. Three (3) subjects who were enrolled into Cohort 2 were slightly older than 5 years (by less than 2 months). A summary of baseline demographic characteristics is listed in the following table.

	Cohort 1		Cohort 2	
	AZ-CQ N=55	AL N=51	AZ-CQ N=124	AL N=131
Sex, n (%)				
Male	27 (49.1)	30 (58.8)	74 (59.7)	66 (50.4)
Female	28 (50.9)	21 (41.2)	50 (40.3)	65 (49.6)
Age (years); n (%)				
6 months to <5 years	0	0	123 (99.2)	129 (98.5)
5 years to 12 years	55 (100.0)	51 (100.0)	1 (0.8)	2 (1.5)
Mean (SD)	7.4 (2.0)	7.9 (2.2)	2.4 (1.3)	2.7 (1.0)
Range	5.0-12.0	5.0-12.0	0.5-5.0	0.5-5.0
Weight (kg)				
N	55	51	124	131
Mean (SD)	23.3 (5.6)	23.7 (5.7)	12.5 (3.1)	12.8 (2.5)
Range	15.0-37.0	11.5-37.0	6.1-19.0	6.9-18.0
Height (cm)				
N	55	51	124	131
Mean (SD)	124.9 (13.2)	125.4 (13.9)	90.2 (11.6)	92.7 (9.5)
Range	98.0-155.0	81.0-152.0	59.0-115.0	66.3-116.0
Body Mass Index (kg/m^2)				
N	55	51	124	131
Mean (SD)	14.9 (2.6)	15.0 (1.8)	15.2 (1.6)	14.9 (1.6)
Range	7.3-29.2	9.0-22.6	9.5-20.7	8.4-20.3

AZ-CQ = azithromycin + chloroquine; AL = artemether-lumefantrine; N (n) = number of subjects; SD = standard deviation; ITT=intent-to-treat
All subjects were black. Body mass index was calculated as weight/ (height *0.01)^2.

All subjects in Cohort 2 had fever present at Baseline or a history of fever within the 24 hours prior to study consent. The most common symptoms present at Baseline in the AZ-CQ and AL groups, respectively, were pyrexia (71.8% and 64.1%), cough (12.1% and 9.9%), decreased appetite (6.5% and 6.1%), and rhinorrhoea (4.8% and 5.3%).

The mean duration between subjects' first symptoms of malaria infection and the start of informed consent was 1.9 days for both treatment groups, ranging from 0-7 days for both treatment groups.

All subjects in Cohort 2 were diagnosed with *P. falciparum* infection following blood smear microscopy. Mean parasite counts at Baseline ranged from 1000/µL to 107160/µL (Table 13). Mean Baseline parasite counts were similar between treatment groups.

- Pharmacokinetic Evaluation

On the basis of the combined data from both cohorts, mean AZ serum concentrations were 201, 983, 510 and 32.0 ng/mL on Day 2 (predose, and 3 and 8 hours postdose) and Day 7. Mean CQ plasma concentrations were 144, 362, 318 and 41.0 ng/mL on Day 2 (predose, and 3 and 8 hours postdose) and Day 7. Mean desethyl-CQ plasma concentrations were 82.9, 148, 151 and 46.8 ng/mL on Day 2 (predose, and 3 and 8 hours postdose) and Day 7.

For the determination of serum concentrations of each compound, large ranges in the coefficient of variation (CV) were observed. This may, partially, have been caused by the PK sampling time window and approximate weight-based dose, according to design.

- Efficacy results

Cohort 2 was the primary focus of the efficacy analysis.

A total of 89% of AZ-CQ subjects (95% confidence interval [CI]: 83%, 96%) and 98% of AL subjects (95% CI: 96%, 100%) achieved ACPR in the modified intent-to-treat (MITT) population. There were 12 and 2 ACPR failures in the AZ-CQ group and the AL group, respectively. The difference between the treatment groups ([AZ-CQ] minus AL) was -9.10% (95% CI: -16.02, -2.18). As the lower bound of the CI for the difference in ACPR between the treatment groups was not ≥-10%, noninferiority of the AZ-CQ group relative to the AL group was not achieved.

In the per protocol (PP) population, a total of 93% of AZ-CQ subjects (95% CI: 87%, 99%) and 99% of AL subjects (95% CI: 97%, 100%) achieved ACPR. There were 7 and 1 ACPR failures in the AZ-CQ group and the AL group, respectively. The difference between treatment groups ([AZ-CQ] minus AL) was -6.08% (95% CI: -12.10, -0.05). Noninferiority of the AZ-CQ group relative to the AL group was not achieved based on the PP population.

In a PCR-corrected analysis, molecular testing results allowed for the differentiation of recrudescence (true treatment failures-[ie, recurrence of the same genotypic parasite identified at Baseline]) from reinfection (relapse of a different genotypic parasite not present at Baseline).
Early treatment failures (PCR-corrected) were more frequently observed among subjects in the AZ-CQ group (5.83% [MITT] and 1.75% [PP]) than among subjects in the AL treatment group (0.79% [MITT] and 0% [PP].
There were no late clinical failures (PCR-corrected) in either treatment group in either the MITT or PP population.
A higher proportion of LPFs were observed in the AZ-CQ group (4.17% [MITT] and 4.39% [PP]) than in the AL group (0.79% [MITT] and 0.81% [PP].

The median time to clearance of *P. falciparum* in Cohort 2 was 48 hours in the AZ-CQ treatment group and 24 hours in the AL treatment group (MITT; PCR-uncorrected). This difference was statistically significant (P<0.0001).

Since the failure rates observed for asexual parasitologic response in Cohort 2 were less than 50% (MITT; PCR-corrected), median time to recrudescence of asexual parasitemia could not be calculated.

Median time to recurrence (based on PCR-uncorrected parasitologic response rates) was calculated to be 34 days for the AZ-CQ subjects in Cohort 2 that was statistically significantly (P=0.0006) different from the time to recurrence observed in the AL group.

P. falciparum gametocyte clearance rates for Cohort 2 were consistently above 80% in the AZ-CQ group and 90% in the AL group.

Median time to fever clearance in Cohort 2 was 24 hours in both the treatment groups.

A total of 68 (54.8%) AZ-CQ subjects and 49 (37.4%) AL subjects received rescue medication in Cohort 2.

In the AZ-CQ group, approximately 56% of subjects expressed either mutant or mixed genotype whereas in the AL group, this proportion was approximately 69%

ACPR (PCR-Corrected) at Day 28 (MITT and PP, Cohort 2)

	AZ-CQ	AL
MITT Day 28		
N	120	126
Number (%) of Treatment Failures	12 (10.00)	2 (1.59)
ETF	7 (5.83)	1 (0.79)
LCF	0	0
LPF	5 (4.17)	1 (0.79)
Number (%) of Censored	108 (90.00)	124 (98.41)
Completed Day 28 Visita	60 (50.00)	90 (71.43)
Premature discontinuation	2 (1.67)	2 (1.59)
Received antimalarial drugs for treating reinfection	46 (38.33)	32 (25.40)
Breastfeeding mother received antimalarial drugs	0	0
ACPR (%)b [95% CI]c	89.27 [82.77, 95.77]	98.37 [95.59, 100]
ACPR Differenced: AZCQ-AL [95% CI]c	-9.10 [-16.02, -2.18]	
PP Day 28		
N	114	124
Number (%) of Treatment Failures	7 (6.14)	1 (0.81)
ETF	2 (1.75)	0
LCF	0	0
LPF	5 (4.39)	1 (0.81)
Number (%) of Censored	107 (93.86)	123 (99.19)
Completed Day 28 Visita	60 (52.63)	90 (72.58)
Premature discontinuation	2 (1.75)	1 (0.81)
Received antimalarial drugs for treating reinfection	45 (39.47)	32 (25.81)
Breastfeeding mother received antimalarial drugs	0	0
ACPR (%)b [95% CI]c	93.08 [87.32, 98.84]	99.16 [96.97, 100]
ACPR Differenced: AZCQ-AL [95% CI]c	-6.08 [-12.10, -0.05]	

ACPR = adequate clinical and parasitologic response; AL = artemether-lumefantrine; AZ-CQ = azithromycin + chloroquine; CI = confidence interval; ETF = early treatment failure; N = number of subjects; LCF = late clinical failure; LPF = late parasitologic failure; MITT = modified intent-to- treat; PP = per-protocol; PCR = polymerase chain reaction.

Cohort 2 = subjects aged ≥6 months to ≤59.

a. Subject completed Day 28 visit without a failure event and without other censoring.

b. Estimated from the Kaplan-Meier curve.

c. CI by large sample approximation to the binomial with continuity correction using the standard error estimated by the Greenwood formula.

d. The difference calculated from rates estimated from the Kaplan-Meier curves.

- Safety results

There were no deaths during the study in either cohort.

A total of 200 AEs were reported by 78 subjects in Cohort 1 and 473 AEs were reported by 202 subjects in Cohort 2. In both the cohorts, the percentage of subjects with AEs in each treatment group was similar (74.5% and 72.5% for the AZ-CQ and AL groups, respectively, in Cohort 1; 83.1% and 75.6% for the AZ-CQ and AL groups, respectively, in Cohort 2).

The incidence of treatment-related AEs was higher among AZ-CQ subjects than in AL subjects (36.4% and 19.6% for the AZ-CQ and AL groups, respectively in Cohort 1; 50.8% and 35.9% for the AZ-CQ and AL groups, respectively in Cohort 2).

The most frequently reported AEs in both cohorts and both treatment groups were asymptomatic parasitaemia (coded as infection parasitic), vomiting and abdominal pain, as well as pyrexia in Cohort 2. Vomiting and pruritus were more frequently reported in the AZ-CQ group than in the AL dosing group for both cohorts (for vomiting: 20.0% and 9.8% in the Cohort 1 AZ-CQ and AL groups, respectively, and 30.6% and 9.9%, respectively, in Cohort 2; for pruritus: 16.4% and 2.0% in the Cohort 1 AZ-CQ and AL groups, respectively, and 6.5% and 1.5%, respectively, in Cohort 2). Among all subjects with vomiting, most had vomiting within 5 minutes or less that usually resolved within the same day of onset. Most AEs were mild or moderate in severity.

A total of 6 AEs were considered to be severe and were reported for 5 subjects (2 subjects in Cohort 1 [malaria, n = 1 and asymptomatic parasitaemia, coded as infection parasitic, n = 1] and 3 subjects in Cohort 2 [colitis, n = 1; pyrexia, n = 2; malaria, n = 1; pyrexia and colitis occurred in a single subject]). The AE of severe malaria (AZ-CQ; Cohort 1) was considered a serious adverse event (SAE).

Overall, there were 4 SAEs reported during the study (3 SAEs in Cohort 1: malaria [AZ-CQ group] and sepsis and hepatitis B [both in AL group] and 1 SAE in Cohort 2: convulsion [AL group]). None of the SAEs were considered by the investigator to be related to the study drug.

50.8% of AZ-CQ and 35.9% of AL subjects in Cohort 2 experienced treatment-related AEs. The most frequently occurring AEs considered to be related to study drug included vomiting, abdominal pain, infection parasitic, malaria, pyrexia, and pruritus.

Two (2) subjects had temporary discontinuations from dosing because of vomiting after dosing on Day 0 (1 subject in Cohort 1 and 1 subject in Cohort 2). Both subjects were in the AZ-CQ group. The subject in Cohort 1 had a repeat dose on Day 0, following the first instance of vomiting and vomited again. This subject was then permanently discontinued from further dosing. Permanent discontinuations from study drug dosing were noted for 4 subjects in Cohort 1 (all in the AZ-CQ group) and 8 subjects in Cohort 2 (7 subjects in the AZ-CQ group and 1 subject in the AL group).

Two (2) subjects in the AL group (1 in each cohort) had increases in transaminases that were related to viral hepatitis. No other clinically significant changes in laboratory values were noted during the study.

Vital signs values were similar between dosing groups for both cohorts. In Cohort 1, there were no subjects in the AZ-CQ dosing group who had corrected postbaseline QT values above 500 milliseconds (msec). Four subjects in the AZ-CQ group had QTc changes from Baseline of greater than or equal to 60 msec. One subject in the AL group had corrected QT (QTcB and QTcF) values above 500 msec and had changes in QTc from Baseline of greater than or equal to 60 msec.

An AE of mild QT interval prolongation in Cohort 1 was reported for a single subject in the AL dosing group that began approximately 3 hours postdose on study Day 2. The Day 2 QTc interval was 546 msec compared to 423 msec at Baseline. QTcB and QTcF values were consistent with QTc for this timepoint. This subject had a medical history of fever within 24 hours of Baseline and was also reported as having a fever from Day 0 to Day 1, a day prior to the diagnosis of the QT prolongation. The subject received paracetamol 600mg on Day 0 and Day 1. The AE of QT prolongation was assessed as resolved on Day 13 and was considered by the investigator to be related to study drug.

An additional subject in the AL dosing group had an AE of tachycardia which began immediately following dosing on study Day 1. This AE was mild and considered to be related to study drug. This subject also had a concurrent AE of mild anemia which had an onset of Day 1 and a resolution on Day 7.

No subjects in Cohort 2 had ECG values of clinical concern.

Study A0661158, a Phase 3, open-label, randomised, comparative study to evaluate AZ plus chloroquine (CQ) and sulfadoxine plus pyrimethamine combinations for intermittent preventive treatment of *Falciparum* malaria infection in pregnant women in Africa.

➢ Description

A Phase 3, open-label, randomised, comparative study to evaluate AZ plus chloroquine (CQ) and sulfadoxine plus pyrimethamine (SP) combinations for intermittent preventive treatment (IPTp) of *Falciparum* malaria infection in pregnant women in Africa.

➢ Methods

- Objective(s)

Primary Objective

The primary objective was to establish superiority of AZCQ over SP in protective efficacy for IPTp as measured by the proportion of subjects with sub-optimal pregnancy outcome.

Secondary Objectives

The key secondary objectives were to include comparison of IPTp regimens of AZCQ and SP in:

1. Proportion of subjects with LBW (<2500 g) live neonates
2. Proportion of subjects with severe anaemia (haemoglobin <8 g/dL)
3. Proportion of subjects with anaemia (haemoglobin <11 g/dL)
4. Proportion of subjects with placental parasitaemia
5. Occurrence of STIs
6. Safety and tolerability of the 2 treatment regimens
7. Presence of subjects with a sub-optimal pregnancy outcome including neonatal deaths and congenital malformations, defined as any of the following:
   - Live-borne neonate (singleton) with LBW (<2500 g)
   - Premature birth (<37 weeks)
   - Abortion (≤28 weeks)
   - Still birth (>28 weeks)
   - Neonatal death
   - Congenital malformation
   - Lost to follow-up before termination of pregnancy or delivery
   - Missing birth weight of the neonates

- Study design

This was a Phase 3, open-label, randomised, parallel-group study that compared the efficacy of IPTp regimens of AZCQ and SP in asymptomatic pregnant subjects enrolled during the second trimester of pregnancy.

The study was designed to demonstrate superiority of AZCQ over SP, the current standard of care for IPTp indication. The study was conducted in sub-Saharan Africa where SP resistance is evident.

The study was conducted in asymptomatic pregnant subjects enrolled during second trimester of pregnancy, and about half of the subjects were primigravidae or secundigravidae and the other half could be any other gravidae. An outpatient design was implemented in order to closely resemble the scenario where IPTp is implemented in healthy pregnant women attending antenatal care (ANC) clinics/hospitals.

Subjects were to be followed up at delivery or within 2 days of subject reporting home delivery (report within 24 hours of delivery), and on Day 28 (window Day 28 to Day 42) post delivery.
Long lasting insecticide treated bednets (LLINs) were to be given to all subjects on Day 0 of the study with the instructions to use them; the installation of LLINs was to be verified during the first home visits of Treatment Course 1 by field worker(s).

- Study population / Sample size

In total, 2602 to 5044 subjects (16 to 35 years of age) were planned to participate in this study. A total of 3259 subjects were screened for the study and 2891 subjects were enrolled, randomised and treated. A total of 1993 (68.9%) subjects completed the study and 898 (31.1%) subjects discontinued from the study.

Subjects were randomised at 6 active sites in 5 countries: Benin, Kenya, Malawi, Tanzania and Uganda. An additional site in Kenya did not enrol any subjects.

Diagnosis and Main Criteria for Inclusion:
1. Pregnant women (all gravidae) with ≥14 and ≤26 weeks of gestational age (defined by ultrasound).
2. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative if a subject was <18 years of age) had been informed of all pertinent aspects of the study and that all questions by the subject had been sufficiently answered. Assent was to be obtained from subjects <18 years of age.
3. Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
4. Subjects who agreed to be supervised for treatment administration, and were to be available for all follow-up visits.

Several **exclusion criteria** (not listed here) were also define to insure safety of participants and exclusion of possible confounders to evaluation of the endpoint.

- Treatments

The study drug was a fixed-dose tablet formulation of AZCQ containing 250 mg AZ and 155 mg CQ base. The comparator drug was SP and was supplied as Fansidar (Roche) tablet (500 mg sulfadoxine/25 mg pyrimethamine).

Subjects were randomised in a 1:1 ratio to receive either AZCQ or SP IPTp regimens. Both the regimens consisted of 3 treatment courses:

- AZCQ treatment course: 1000 mg AZ and 620 mg of CQ base (4 combination tablets of AZCQ with individual strength of 250 mg/155 mg), by mouth (PO) once daily for 3 days (Day 0, 1, and 2)

- SP treatment course: 1500 mg sulfadoxine and 75 mg pyrimethamine (3 fixed tablets of SP strength at 500 mg/25 mg), PO single dose once daily on Day 0

Each subject received 3 IPTp treatment courses of AZCQ or SP during ANC visits at 4- to 8-week intervals (maximum treatment duration of treatment 13 to 25 weeks, including screening). The first treatment course was administered during the second trimester (14-26 weeks of gestation as confirmed by ultrasound). The last treatment course was administered to subjects before or during 36 weeks of gestation. Subjects were evaluated at delivery or within 2 days of subject reporting home delivery (report within 24 hours of delivery), and on Day 28 (window Days 28-42) post delivery.

The first dose of each AZCQ treatment course was administered under supervision during the ANC visits. The subsequent 2 doses of AZCQ were administered at home under supervision of the field worker(s).

Each dose of SP was administered under supervision during the ANC visits.

AZCQ and SP were not administered on an empty stomach. Each dose was administered with a glass of water.

Doses of medication regurgitated within 30 minutes of administration were repeated. If vomiting re-occurred after the re-dose, the subject did not receive further study drug but was referred to the investigator and was given standard ANC care. If subjects in the AZCQ treatment group vomited after re-dose during the first or second treatment course, they were given additional course(s) of standard IPTp courses with SP. If vomiting on re-dosing of AZCQ occurred during the home visits, the subject was advised to return to the study site within 7 days for appropriate treatment by the study physician.

- Outcomes/endpoints

The primary efficacy endpoint was sub-optimal pregnancy outcome, defined as any of the following:

- Live-borne neonate (singleton) with LBW (<2500 g)
- Premature birth (<37 weeks)
- Abortion (≤28 weeks)
- Still birth (>28 weeks)
- Lost to follow-up before termination of pregnancy or delivery
- Missing birth weight of the neonates

The key secondary efficacy endpoints included:

1. Occurrence at birth of a LBW live neonate
2. Occurrence of severe maternal anaemia (haemoglobin <8 g/dL) at 36-38 weeks of gestation
3. Occurrence of anaemia (haemoglobin <11 g/dL) at 36-38 weeks of gestation
4. Occurrence of placental parasitaemia at delivery
5. Occurrence of placental malaria as determined by histology
6. Number of episodes of STIs per subject, including *T. pallidum*, *N. gonorrhoeae* and *C. trachomatis*, during the study period following first dose (diagnosis based on clinical presentation any time from first IPTp dose to delivery and/or on laboratory test results between Weeks 36 and 38)
7. Presence of subjects with a sub-optimal pregnancy outcome including neonatal deaths and congenital malformations, defined as any of the following:
    - Live-borne neonate (singleton) with LBW (<2500 g)
    - Premature birth (<37 weeks)
    - Abortion (≤28 weeks)
    - Stillbirth (>28 weeks)
    - Neonatal death
    - Congenital malformation
    - Lost to follow-up before termination of pregnancy or delivery
    - Missing birth weight of the neonates

Other Secondary Efficacy Endpoints

1. Hemoglobin concentration at 36-38 weeks of gestation;
2. Occurrence at birth of a neonates with congenital abnormalities;
3. Occurrence of a perinatal or neonatal death;
4. Birth weight of the live-borne neonate (singleton);
5. Number of episodes of symptomatic malaria per subject anytime from first IPTp dose administration to delivery;
6. Occurrence of a subject requiring additional treatment for symptomatic malaria during the study period following the first dose (diagnosed based on clinical presentation and/or lab test results);
7. Occurrence of peripheral parasitemia at 36-38 weeks of gestation;
8. Occurrence of peripheral parasitemia at delivery;
9. Occurrence of cord blood parasitemia at delivery;
10. Occurrence of STIs including *T. pallidum, N. gonorrhoeae, C. trachomatis* during the study period following first dose (diagnosed based on clinical presentation prior to Week 36-38 and/or lab test results between Week 36-38 of gestation);
11. Occurrence of a positive result for *C. trachomatis* infection at 36-38 weeks of gestation (diagnosed based on lab result);
12. Occurrence of a positive result for *N. gonorrhoeae* infection at 36-38 weeks of gestation (diagnosed based on lab result);
13. Occurrence of a positive result for *T. pallidum* test at 36-38 weeks of gestation (diagnosed based on lab result);
14. Occurrence of a *T. vaginalis* infection at 36-38 weeks of gestation (diagnosed based on lab result);
15. Occurrence of bacterial vaginosis at 36-38 weeks of gestation (diagnosed based on lab result);
16. Occurrence of ophthalmia neonatorum (diagnosed based on lab test results) in the neonate;
17. Occurrence of bacterial infections including pneumonia and other lower respiratory tract infections anytime from first IPTp dose administration to delivery;
18. Occurrence of pre-eclampsia from Week 20 to delivery;
19. Occurrence of nasopharyngeal swabs positive for macrolide resistant and penicillin resistant *Streptococcus pneumoniae* at baseline, at Day 28 (window Day 28 - Day 42) post delivery, and at about 6 months following last IPTp course. This test will be done in about 600 subjects each from the AZCQ and SP arms from two or more sites.

Safety Endpoints

Safety and tolerability were to be assessed by spontaneously reported adverse event (AE) reports, by vital signs, physical examination, laboratory tests including hemoglobin and urine test for glucose and protein, and adverse pregnancy outcomes for mothers and by the general physical examination for the neonates through Day 28 (window Day 28 to Day 42) post delivery. Adverse event reports were to be collected both for the mother and corresponding neonate, with a link between the two.

Outcome Research Endpoints

The purpose of these outcome research endpoints was to assess the health economic impact from the health system and provider perspective, as measured by in-hospital and out-of-hospital healthcare utilization for the newborn/infant. The endpoints were to include:

1. Incidence and number of times a newborn/infant was taken to a local health clinic/physician's office/outpatient hospital clinic including Emergency Room (without having to be admitted) during the first 28 days (window Day 28 to Day 42) of life to attend to a health complication.
2. Incidence and number of times a newborn/infant was admitted to a hospital during the first 28 days (window Day 28 to Day 42) of life.

3. Number of times a mother was taken to a local health clinic/physician's office/outpatient hospital clinic including Emergency Room (without having to be admitted) from the time of the administration of the first dose of IPTp through Visit 6 on Day 28 (window Day 28 to Day 42) post delivery for treatment (or follow up) of anemia, malaria, sexually transmitted disease or other complications and primary reason for the visit.
4. Number of times a mother was admitted to a hospital from the time of the administration of the first dose of IPTp through Visit 6 on Day 28 (window Day 28 to Day 42) post delivery, including length of stay in hospital.

- Statistical Methods

Analysis Populations:
• The primary analysis set for all endpoints was the intent-to-treat (ITT) population, which consisted of all subjects who were randomized, received at least 1 dose of study drug, and had a single fetus.
• Efficacy analyzable (EA) was defined as a subject whose pregnancy outcome occurred on or before 27 August 2013 (the date of written notification of study termination to the investigators) or who withdrew from the study prior to that point.
• The per protocol (PP) EA analysis set included all ITT subjects who were EA, compliant with study drug (ie, took at least 6 of the 9 AZCQ doses or at least 2 of the 3 SP doses), and did not switch to standard of care IPTp treatment or have a neonate birth weight measured more than 7 days after birth.
• The safety analysis set for mothers was to consist of subjects who received at least 1 dose of study drug. The safety analysis set for neonates was to include all live-borne babies. In addition to the Safety Analysis Set for neonates, there could be other data summarized separately for other birth outcomes (eg, stillborns).

The primary efficacy endpoint of the trial was the presence of subjects with a sub-optimal pregnancy outcome defined as any of the following: live newborn (singleton) with low birth-weight (or LBW, defined as live birth weight <2,500 g), premature birth (<37 weeks), abortion (<28 weeks), still birth (>28 weeks), lost to follow-up prior to termination of pregnancy or delivery, or missing birth weight of the neonate. The primary analysis set was the intent-to-treat (ITT), and excluded multiple gestations. Secondary analyses were also repeated using the per protocol analysis set, also excluding multiple gestations.
The Mantel-Haenszel estimate of the common risk ratio was computed using SAS Proc Freq, adjusted for the randomization strata. The risk ratio was the proportion of AZCQ subjects with suboptimal pregnancy outcome over the proportion of SP subjects with sub-optimal pregnancy outcome. The p-value was calculated using the Wald test statistic on the natural log risk ratio scale.

All secondary efficacy endpoints that were dichotomous, expressed as a proportion, were summarized and analyzed using the same methods as for the primary endpoint. Secondary efficacy endpoints that were not dichotomous were analyzed using analysis of covariance or analysis of variance.

Interim Analysis
Unblinded sequential analyses were performed following completion of the primary endpoint (pregnancy outcome) assessment at 50%, 70%, and 100% (final analysis) of the accrued number of subjects.

Since the study was negative for the primary endpoint (sub-optimal pregnancy outcome and LBW), all inferences for the other secondary endpoints were to be considered exploratory.

- **Results**

The AZCQ IPTp malaria clinical development program was terminated by Pfizer based on the results of the pre-planned interim analysis for this pivotal study A0661158.

- Recruitment/ Number analysed

The safety analysis population included 1446 (100%) subjects in the AZCQ treatment group and 1445 (100%) subjects in the SP treatment group. The intent-to-treat (ITT) population included 1445 (99.9%) subjects in the AZCQ treatment group and 1445 (100%) subjects in the SP treatment group. The ITT efficacy analysable (EA) population included 1237 (85.5%) subjects in the AZCQ treatment group and 1231 (85.2%) subjects in the SP treatment group. The per protocol (PP) EA population included 1089 (75.3%) subjects in the AZCQ treatment group and 1176 (81.4%) subjects in the SP treatment group. A total of 1149 live-borne neonates were born to mothers in the AZCQ treatment group and 1196 live-borne neonates were born to mothers in the SP treatment group; all live-borne neonates were included in the safety population.

A total of 898 (31.1%) subjects discontinued from the study (477 [33.0%] subjects in the AZCQ treatment group and 421 [29.1%] subjects in the SP treatment group). The most common reasons for discontinuation were study termination by the sponsor (326 [22.5%] subjects in the AZCQ treatment group and 342 [23.7%] subjects in the SP treatment group), lost to follow up (68 [4.7%] subjects in the AZCQ treatment group and 51 [3.5%] subjects in the SP treatment group), and subjects who were no longer willing to participate in the study (60 [4.1%] subjects in the AZCQ treatment group and 15 [1.0%] subjects in the SP treatment group).

- Baseline data

All subjects were female and 99.9% were black. The majority of subjects were 21 to 29 years of age. The treatment groups were comparable with respect to weight, height, and body mass index.

- Efficacy results

Regarding Primary Efficacy Endpoints

In the ITT population, 378 (26.2%) subjects in the AZCQ treatment group and 342 (23.7%) subjects in the SP treatment group had sub-optimal pregnancy outcomes. The treatment group difference (AZCQ – SP) was 2.49%, and the relative risk (RR) was 1.11. The Mantel-Haenszel estimate of the common relative risk (RRMH) was 1.11 (95% confidence interval, CI [0.97, 1.25]; p = 0.12237). In the ITT EA population, 200 (16.2%) subjects in the AZCQ treatment group and 154 (12.5%) subjects in the SP treatment group had sub-optimal pregnancy outcomes. The treatment group difference (AZCQ – SP) was 3.66%, and the RR was 1.29. The RRMH was 1.29 (95% CI [1.06, 1.57]; p = 0.01017).

In the PP EA population, 113 (10.4%) subjects in the AZCQ treatment group and 119 (10.1%) subjects in the SP treatment group had sub-optimal pregnancy outcomes. The treatment group difference (AZCQ – SP) was 0.26%, and the RR was 1.03. The RRMH was 1.03 (95% CI [0.80, 1.31]; p = 0.84117).

In the ITT EA population, 94 (8.3%) subjects in the AZCQ treatment group and 102 (8.7%) subjects in the SP treatment group had sub-optimal pregnancy outcomes, excluding unknown and missing pregnancy outcomes. The treatment group difference (AZCQ – SP) was –0.34%, and the RR was 0.96. The RRMH was 0.96 (95% CI [0.73, 1.25]; p = 0.76512).

The primary endpoints were not achieved.

Regarding Secondary Efficacy Endpoints

Occurrence at birth of a LBW live neonate: In the ITT population, 57 (5.0%) subjects in the AZCQ treatment group and 68 (5.7%) subjects in the SP treatment group had LBW neonates (defined as <2500 g). The treatment group difference (AZCQ – SP) was −0.72%, and the RR was 0.88. The RRMH was 0.87 (95% CI [0.62, 1.23]; p = 0.4428). In the ITT EA population, 56 (5.1%) subjects in the AZCQ treatment group and 64 (5.5%) subjects in the SP treatment group had LBW neonates (defined as <2500 g). The treatment group difference (AZCQ – SP) was −0.47%, and the RR was 0.92. The RRMH was 0.92 (95% CI [0.65, 1.30]; p = 0.6200). In the PP EA population, 49 (4.7%) subjects in the AZCQ treatment group and 59 (5.2%) subjects in the SP treatment group had LBW neonates (defined as <2500 g). The treatment group difference (AZCQ – SP) was −0.49%, and the RR was 0.91. The RRMH was 0.91 (95% CI [0.63, 1.31]; p = 0.6086).

Occurrence of severe maternal anaemia (<8 g/dL) at 36-38 weeks of gestation: In the ITT population, 1222 and 1299 subjects had available haemoglobin measurements in the AZCQ and SP treatment groups, respectively. A total of 22 (1.8%) subjects in the AZCQ treatment group and 26 (2.0%) subjects in the SP treatment group had severe maternal anaemia (defined as haemoglobin <8 g/dL) at 36-38 weeks of gestation. The treatment group difference (AZCQ – SP) was −0.20%, and the RR was 0.90. The RRMH was 0.90 (95% CI [0.51, 1.57]; p = 0.7035). In the ITT EA population, 1118 and 1176 subjects had available haemoglobin measurements in the AZCQ and SP treatment groups, respectively. A total of 20 (1.8%) subjects in the AZCQ treatment group and 24 (2.0%) subjects in the SP treatment group had severe maternal anaemia (defined as haemoglobin <8 g/dL) at 36-38 weeks of gestation. The treatment group difference (AZCQ – SP) was −0.25%, and the RR was 0.88. The RRMH was 0.88 (95% CI [0.49, 1.58]; p = 0.6571).

Occurrence of maternal anaemia (haemoglobin <11 g/dL) at 36-38 weeks of gestation: In the ITT population, 1222 and 1299 subjects had available haemoglobin measurements in the AZCQ and SP treatment groups, respectively. A total of 618 (50.6%) subjects in the AZCQ treatment group and 638 (49.1%) subjects in the SP treatment group had maternal anaemia (defined as haemoglobin <11 g/dL) at 36-38 weeks of gestation. The treatment group difference (AZCQ – SP) was 1.46%, and the RR was 1.03. The RRMH was 1.03 (95% CI [0.95, 1.11]; p = 0.4605). In the ITT EA population, 1118 and 1176 subjects had available haemoglobin measurements in the AZCQ and SP treatment groups, respectively. A total of 564 (50.5%) subjects in the AZCQ treatment group and 578 (49.2%) subjects in the SP treatment group had maternal anaemia (defined as haemoglobin <11 g/dL) at 36-38 weeks of gestation. The treatment group difference (AZCQ – SP) was 1.30%, and the RR was 1.03. The RRMH was 1.03 (95% CI [0.95, 1.11]; p = 0.5330).

Occurrence of the placental parasitaemia at delivery: In the ITT and ITT EA populations, 1019 and 1076 subjects had available placental parasitaemia measurements in the AZCQ and SP treatment groups, respectively. A total of 54 (5.3%) subjects in the AZCQ treatment group and 61 (5.7%) subjects in the SP treatment group tested positive for placental parasitaemia at delivery. The treatment group difference (AZCQ – SP) was −0.37%, and the RR was 0.93. The RRMH was 0.93 (95% CI [0.65, 1.33]; p = 0.7105).

Occurrence of placental malaria as determined by histology: In the ITT and ITT EA populations, 1040 and 1100 subjects had available placental histology measurements in the AZCQ and SP treatment groups, respectively. A total of 50 (4.8%) subjects in the AZCQ treatment group and 63 (5.7%) subjects in the SP treatment group had placental malaria at delivery based on histology. The treatment group difference (AZCQ – SP) was –0.92%, and the RR was 0.84. The RRMH was 0.84 (95% CI [0.59, 1.21]; p = 0.3468). Of the subjects in the AZCQ treatment group with placental malaria, 3 (6.0%) subjects had mild parasitaemia, 25 (50.0%) subjects had moderate parasitaemia, and 22 (44.0%) subjects had severe parasitaemia; 38 (3.7%) subjects had a chronic infection, 12 (1.2%) subjects had an acute infection, and 184 (17.7%) subjects had a past infection. Of the subjects in the SP treatment group with placental malaria, 7 (11.1%) subjects had mild parasitaemia, 22 (34.9%) subjects had moderate parasitaemia, and 34 (54.0%) subjects had severe parasitaemia; 51 (4.6%) subjects had a chronic infection, 12 (1.1%) subjects had an acute infection, and 237 (21.5%) subjects had a past infection.

Number of episodes of STIs per subject from first dose to delivery: In the ITT population, there were 202 STI episodes from first dose to delivery (mean [standard deviation; SD] = 0.14 [0.40]) in the AZCQ treatment group and 278 STI episodes (mean [SD] = 0.19 [0.47]) in the SP treatment group. The treatment group difference (AZCQ – SP; least squares [LS] mean estimate) was –0.05 (95% CI [–0.08, –0.02]; p = 0.0011). In the AZCQ treatment group, 156 (10.8%) subjects had 1 STI episode, 20 (1.4%) subjects had 2 STI episodes, and 2 (0.1%) subjects had 3 or more STI episodes. In the SP treatment group, 202 (14.0%) subjects had 1 STI episode, 33 (2.3%) subjects had 2 STI episodes, and 3 (0.2%) subjects had 3 or more STI episodes. In the ITT EA population, there were 200 STI episodes from first dose to delivery (mean [SD] = 0.16 [0.42]) in the AZCQ treatment group and 277 STI episodes (mean [SD] = 0.23 [0.50]) in the SP treatment group. The treatment group difference (AZCQ – SP; LS mean estimate) was –0.06 (95% CI [–0.10, –0.03]; *p* = 0.0006). In the AZCQ treatment group, 156 (12.6%) subjects had 1 STI episode, 19 (1.5%) subjects had 2 STI episodes, and 2 (0.2%) subjects had 3 or more STI episodes. In the SP treatment group, 201 (16.3%) subjects had 1 STI episode, 33 (2.7%) subjects had 2 STI episodes and 3 (0.2%) subjects had 3 or more STI episodes.

Presence of subjects with a sub-optimal pregnancy outcome, including neonatal deaths and congenital malformations: In the ITT population, 412 (28.5%) subjects in the AZCQ treatment group and 383 (26.5%) subjects in the SP treatment group had sub-optimal pregnancy outcomes, including neonatal deaths and congenital malformations. The treatment group difference (AZCQ – SP) was 2.01%, and the RR was 1.08. The RRMH was 1.08 (95% CI [0.96, 1.21]; p = 0.2265). In the ITT EA population, 234 (18.9%) subjects in the AZCQ treatment group and 195 (15.8%) subjects in the SP treatment group had sub-optimal pregnancy outcomes, including neonatal deaths and congenital malformations. The treatment group difference (AZCQ – SP) was 3.08%, and the RR was 1.19. The RRMH was 1.19 (95% CI [1.00, 1.42]; p = 0.0443).

The secondary endpoints were not achieved.

Other secondary endpoints

Hemoglobin concentrations at 36 to 38 weeks of gestation

In the ITT population, 1221 and 1298 subjects had available hemoglobin measurements in the AZCQ and SP treatment groups, respectively. The mean change in hemoglobin from baseline to 36 to 38 weeks of gestation was 0.2 g/dL in the AZCQ treatment group and 0.3 g/dL in the SP treatment group. The treatment group difference (AZCQ – SP; LS mean estimate) was -0.14 (95% CI [-0.24, -0.03]; *p*=0.0131).

In the ITT EA population, 1118 and 1175 subjects had available hemoglobin measurements in the AZCQ and SP treatment groups, respectively. The mean change in hemoglobin from baseline to 36 to 38 weeks of gestation was 0.2 g/dL in the AZCQ treatment group and 0.3 g/dL in the SP treatment group. The treatment group difference (AZCQ – SP; LS mean estimate) was -0.12 (95% CI [-0.24, -0.01]; *p*=0.0313).

Occurrence at birth of a neonate with congenital abnormalities

In the ITT population, there were 25 (2.2%) neonates with congenital abnormalities born to mothers in the AZCQ treatment group and 29 (2.4%) neonates with congenital abnormalities born to mothers in the SP treatment group. The treatment group difference (AZCQ – SP) was -0.24%, and the RR was 0.90. The RRMH was 0.90 (95% CI [0.53, 1.53];*p*=0.6978).

In the ITT EA population, there were 25 (2.3%) neonates with congenital abnormalities born to mothers in the AZCQ treatment group and 29 (2.5%) neonates with congenital abnormalities born to mothers in the SP treatment group. The treatment group difference (AZCQ – SP) was -0.25%, and the RR was 0.90. The RRMH was 0.90 (95% CI [0.53, 1.53]; *p*=0.6978).

Occurrence of perinatal or neonatal deaths

In the ITT population, there were 25 (2.2%) perinatal or neonatal deaths in the AZCQ treatment group and 22 (1.9%) perinatal or neonatal deaths in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.34%, and the RR was 1.18. The RRMH was 1.14 (95% CI [0.64, 2.01]; *p*=0.6542).

In the ITT EA population, there were 24 (2.2%) perinatal or neonatal deaths in the AZCQ treatment group and 21 (1.8%) perinatal or neonatal deaths in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.35%, and the RR was 1.19. The RRMH was 1.15 (95% CI [0.64, 2.05]; *p*=0.6463).

Birth weight of the live-borne neonate (singleton)
In the ITT population, the mean (SD) birth weight was 3134.4 (489.53) g in the AZCQ treatment group and 3132.4 (468.76) g in the SP treatment group. The treatment group difference (AZCQ – SP; LS mean estimate) was 2.1 (95% CI [-36.5, 40.8]; *p*=0.9145).
In the ITT EA population, the mean (SD) birth weight was 3134.1 (490.05) g in the AZCQ treatment group and 3137.7 (466.1) g in the SP treatment group. The treatment group difference (AZCQ – SP; LS mean estimate) was -3.7 (95% CI [-42.8, 35.3]; *p*=0.8518).

Number of episodes of symptomatic malaria per subject
In the ITT population, there were 91 episodes of symptomatic malaria (mean [SD] = 0.06 [0.27]) in the AZCQ treatment group and 190 episodes of symptomatic malaria (mean [SD] = 0.13 [0.42]) in the SP treatment group from first IPTp dose administration to delivery. The treatment group difference (AZCQ – SP; LS mean estimate) was -0.07 (95% CI [-0.09, -0.04]; *p*<0.0001). In the AZCQ treatment group, 76 (5.3%) subjects had 1 episode of symptomatic malaria, 6 (0.4%) subjects had 2 episodes of symptomatic malaria, and 1 (0.1%) subject had 3 or more episodes of symptomatic malaria. In the SP treatment group, 119 (8.2%) subjects had 1 episode

of symptomatic malaria, 28 (1.9%) subjects had 2 episodes of symptomatic malaria, and 5 (0.4%) subjects had 3 or more episodes of symptomatic malaria.
In the ITT EA population, there were 89 episodes of symptomatic malaria (mean [SD] = 0.07 [0.29]) in the AZCQ treatment group and 181 episodes of symptomatic malaria (mean [SD] = 0.15 [0.44]) in the SP treatment group from first IPTp dose administration to delivery.
The treatment group difference (AZCQ – SP; LS mean estimate) was -0.08 (95% CI [-0.10, -0.05]; *p*<0.0001). In the AZCQ treatment group, 74 (6.0%) subjects had 1 episode of symptomatic malaria, 6 (0.5%) subjects had 2 episodes of symptomatic malaria, and 1 (0.1%) subject had 3 or more episodes of symptomatic malaria. In the SP treatment group, 110 (8.9%) subjects had 1 episode of symptomatic malaria, 28 (2.3%) subjects had 2 episodes of symptomatic malaria, and 5 (0.4%) subjects had 3 or more episodes of symptomatic malaria.

Occurrence of a subject requiring additional treatment for malaria
In the ITT population, 83 (5.7%) subjects in the AZCQ treatment group and 152 (10.5%) subjects in the SP treatment group required additional treatment for symptomatic malaria between first dose and delivery. The treatment group difference (AZCQ – SP) was -4.78%, and the RR was 0.55. The RRMH was 0.49 (95% CI [0.38, 0.62]; p<0.0001).
In the ITT EA population, 81 (6.6%) subjects in the AZCQ treatment group and 143 (11.6%) subjects in the SP treatment group required additional treatment for symptomatic malaria between first dose and delivery. The treatment group difference (AZCQ – SP) was -5.07%, and the RR was 0.56. The RRMH was 0.50 (95% CI [0.39, 0.64]; p<0.0001).

Occurrence of peripheral parasitemia at 36 to 38 weeks of gestation
In the ITT population, 1069 and 1142 subjects had available peripheral parasitemia measurements at 36 to 38 weeks of gestation in the AZCQ and SP treatment groups, respectively. A total of 29 (2.7%) subjects in the AZCQ treatment group and 50 (4.4%) subjects in the SP treatment group had peripheral parasitemia at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -1.67%, and the RR was 0.62.
The RRMH was 0.62 (95% CI [0.39, 0.97]; *p*=0.0360) (Section 14.2, Table 14.2.5.7.1). In the ITT EA population, 1040 and 1110 subjects had available peripheral parasitemia measurements at 36 to 38 weeks of gestation in the AZCQ and SP treatment groups, respectively. A total of 28 (2.7%) subjects in the AZCQ treatment group and 48 (4.3%) subjects in the SP treatment group had peripheral parasitemia at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -1.63%, and the RR was 0.62.
The RRMH was 0.62 (95% CI [0.39, 0.98]; *p*=0.0419).

Occurrence of peripheral parasitemia at delivery
In the ITT and ITT EA populations, 1025 and 1086 subjects had available peripheral parasitemia measurements at delivery in the AZCQ and SP treatment groups, respectively. A total of 62 (6.1%) subjects in the AZCQ treatment group and 81 (7.5%) subjects in the SP treatment group had peripheral parasitemia at delivery. The treatment group difference (AZCQ – SP) was -1.41%, and the RR was 0.81. The RRMH was 0.81 (95% CI [0.59, 1.12]; *p*=0.1975).

Occurrence of cord blood parasitemia at delivery
In the ITT and ITT EA populations, 1015 and 1072 subjects had available cord blood parasitemia measurements at delivery in the AZCQ and SP treatment groups, respectively. A total of 5 (0.5%) subjects in the AZCQ treatment group and 8 (0.8%) subjects in the SP treatment group had cord blood parasitemia at delivery. The treatment group difference (AZCQ – SP) was -0.25%, and the RR was 0.66. The RRMH was 0.66 (95% CI [0.22, 2.01]; *p*=0.4655).

Occurrence of STIs including T. pallidum, N. gonorrhoeae, and C. trachomatis

In the ITT population, 178 (12.3%) subjects in the AZCQ treatment group and 238 (16.5%) subjects in the SP treatment group tested positive for *T. pallidum*, *N. gonorrhoeae*, and/or *C. trachomatis* between first dose and 36 to 38 weeks of gestation.
The treatment group difference (AZCQ – SP) was -4.15%, and the RR was 0.75. The RRMH was 0.75 (95% CI [0.62, 0.90]; p=0.0016).
In the ITT EA population, 177 (14.3%) subjects in the AZCQ treatment group and 237 (19.3%) subjects in the SP treatment group tested positive for *T. pallidum*, *N. gonorrhoeae*, and/or *C. trachomatis* between first dose and 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -4.94%, and the RR was 0.74. The RRMH was 0.74 (95% CI [0.62, 0.89]; p=0.0011).

Occurrence of a positive result for C. trachomatis infection at 36 to 38 weeks of gestation
In the ITT population, 746 and 794 subjects had available laboratory results in the AZCQ and SP treatment groups, respectively. A total of 11 (1.5%) subjects in the AZCQ treatment group and 5 (0.6%) subjects in the SP treatment group tested positive for *C. trachomatis* at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was 0.84%, and the RR was 2.34. The RRMH was 2.34 (95% CI [0.82, 6.66]; p=0.1113).

Occurrence of a positive result for N. gonorrhoeae infection at 36 to 38 weeks of gestation
In the ITT population, 746 and 794 subjects had available laboratory results in the AZCQ and SP treatment groups, respectively. A total of 3 (0.4%) subjects in the AZCQ treatment group and 13 (1.6%) subjects in the SP treatment group tested positive for *N. gonorrhoeae* at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -1.24%, and the RR was 0.25. The RRMH was 0.25 (95% CI [0.07, 0.86]; p=0.0284).

Occurrence of a positive result for T. pallidum test at 36 to 38 weeks of gestation
In the ITT population, 751 and 797 subjects had available laboratory results in the AZCQ and SP treatment groups, respectively. A total of 7 (0.9%) subjects in the AZCQ treatment group and 16 (2.0%) subjects in the SP treatment group tested positive for *T. pallidum* at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -1.07%, and the RR was 0.46. The RRMH was 0.46 (95% CI [0.24, 0.88]; p=0.0188).

Occurrence of a Trichomonas vaginalis infection at 36 to 38 weeks of gestation
In the ITT population, 1068 and 1143 subjects had available laboratory results in the AZCQ and SP treatment groups, respectively. A total of 88 (8.2%) subjects in the AZCQ treatment group and 122 (10.7%) subjects in the SP treatment group tested positive for *Trichomonas vaginalis* at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -2.43%, and the RR was 0.77. The RRMH was 0.77 (95% CI [0.59, 1.00]; p=0.0527).

Occurrence of bacterial vaginosis at 36 to 38 weeks of gestation
In the ITT population, 746 and 794 subjects had available laboratory results in the AZCQ and SP treatment groups, respectively. A total of 64 (8.6%) subjects in the AZCQ treatment group and 94 (11.8%) subjects in the SP treatment group tested positive for bacterial vaginosis at 36 to 38 weeks of gestation. The treatment group difference (AZCQ – SP) was -3.26%, and the RR was 0.72. The RRMH was 0.73 (95% CI [0.54, 0.98]; p=0.0384).

Occurrence of ophthalmia neonatorum in the neonate
In the ITT population, 4 (0.4%) neonates born to mothers in the AZCQ treatment group and 2 (0.2%) neonates born to mothers in the SP treatment group had ophthalmia neonatorum at birth. The treatment group difference (AZCQ – SP) was 0.18%, and the RR was 2.06. The RRMH was 2.09 (95% CI [0.38, 11.38]; p=0.3942) (Section 14.2, Table 14.2.5.16.1).
In the ITT EA population, 4 (0.4%) neonates born to mothers in the AZCQ treatment group and 2 (0.2%) neonates born to mothers in the SP treatment group had ophthalmia neonatorum at birth.

The treatment group difference (AZCQ – SP) was 0.19%, and the RR was 2.12. The RRMH was 2.10 (95% CI [0.38, 11.42]; p=0.3924).

Occurrence of bacterial infections including pneumonia and other lower respiratory tract infections

In the ITT population, 7 (0.5%) subjects in the AZCQ treatment group and 18 (1.3%) subjects in the SP treatment group had bacterial infections, including pneumonia and other lower respiratory tract infections, at any time from first IPTp dose administration to delivery. The treatment group difference (AZCQ – SP) was -0.76%, and the RR was 0.39. The RRMH was 0.39 (95% CI [0.16, 0.93]; p=0.0332).

In the ITT EA population, 6 (0.5%) subjects in the AZCQ treatment group and 17 (1.4%) subjects in the SP treatment group had bacterial infections, including pneumonia and other lower respiratory tract infections, at any time from first IPTp dose administration to delivery. The treatment group difference (AZCQ – SP) was -0.90%, and the RR was 0.35. The RRMH was 0.35 (95% CI [0.14, 0.89]; p=0.0270).

Occurrence of pre-eclampsia from Week 20 to delivery

In the ITT population, 9 (0.6%) subjects in the AZCQ treatment group and 15 (1.0%) subjects in the SP treatment group had pre-eclampsia at any time from Week 20 to delivery. The treatment group difference (AZCQ – SP) was -0.41%, and the RR was 0.60. The RRMH was 0.61 (95% CI [0.27, 1.38]; p=0.2321).

In the ITT EA population, 9 (0.7%) subjects in the AZCQ treatment group and 14 (1.1%) subjects in the SP treatment group had pre-eclampsia at any time from Week 20 to delivery. The treatment group difference (AZCQ – SP) was -0.40%, and the RR was 0.64. The RRMH was 0.64 (95% CI [0.28, 1.48]; p=0.3013).

Occurrence of nasopharyngeal swabs positive for macrolide-resistant and penicillin-resistant S. pneumoniae

Day 28 Post Delivery (Window: Day 28 to Day 42)

In the ITT population, 551 and 569 subjects in the AZCQ and SP treatment groups, respectively, had nasopharyngeal swabs tested at Day 28 post delivery (window: Day 28 to Day 42). Eight subjects in the AZCQ treatment group and 17 subjects in the SP treatment group had nasopharyngeal swabs isolating *S. pneumoniae.* No subjects in the AZCQ treatment group and 2 (11.8%) subjects in the SP treatment group had nasopharyngeal swabs positive for macrolide-resistant *S. pneumoniae.* No subjects in the AZCQ treatment group or SP treatment group had nasopharyngeal swabs positive for penicillin-resistant *S. pneumoniae*.

Visit 7 (About 6 Months Post Last IPTp Course)

In the ITT population, 478 and 489 subjects in the AZCQ and SP treatment groups, respectively, had nasopharyngeal swabs tested at Visit 7 (about 6 months post last IPTp course). Sixteen subjects in the AZCQ treatment group and 11 subjects in the SP treatment group had nasopharyngeal swabs isolating *S. pneumoniae.* No subjects in the AZCQ treatment group or SP treatment group had nasopharyngeal swabs positive for macrolide-resistant or penicillin-resistant *S. pneumoniae.*

Occurrence of stillbirth pregnancy outcome

In the ITT population, there were 17 (1.5%) stillbirths in the AZCQ treatment group and 17 (1.4%) stillbirths in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.06%, and the RR was 1.04. The RRMH was 1.04 (95% CI [0.53, 2.03]; p=0.9021).

In the ITT EA population, there were 17 (1.5%) stillbirths in the AZCQ treatment group and 17 (1.4%) stillbirths in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.06%, and the RR was 1.04. The RRMH was 1.05 (95% CI [0.54, 2.04]; p=0.8953).

Occurrence of premature birth pregnancy outcome
In the ITT population, there were 47 (4.0%) premature births in the AZCQ treatment group and 45 (3.7%) premature births in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.32%, and the RR was 1.09. The RRMH was 1.09 (95% CI [0.73, 1.62]; p=0.6833).
In the ITT EA population, there were 46 (4.1%) premature births in the AZCQ treatment group and 43 (3.6%) premature births in the SP treatment group. The treatment group difference (AZCQ – SP) was 0.42%, and the RR was 1.12. The RRMH was 1.12 (95% CI [0.74, 1.68]; p=0.5980).

There were no significant differences regarding Newborn/Infant Outpatient Healthcare Utilization, Newborn/Infant Hospital Admissions.

Outcome Research Endpoints: Assessment of the health economic impact from the health system and provider perspective was not performed once a decision was made to terminate the study.

- Safety results

Safety and tolerability were assessed by spontaneously reported adverse events (AE), by vital signs, physical examination, laboratory tests including haemoglobin and urine tests for glucose and protein, and adverse pregnancy outcomes for mothers, and by the general physical examination for the neonates through Day 28 (window Days 28-42) post delivery. AE reports were collected for both the mother and corresponding neonate, with a link between the two.

In the AZCQ treatment group, 1104 (76.3%) subjects completed all 9 treatment days. In the SP treatment group, 1245 (86.2%) subjects completed all 3 treatment days.

Three (0.2%) mothers in the AZCQ treatment group and 1 (0.1%) mother in the SP treatment group died. In the neonate group, 25 (2.2%) neonates born to mothers in the AZCQ treatment group and 22 (1.8%) neonates born to mothers in the SP treatment group died. No deaths were considered related to the study drug.

Sixty-five (4.5%) mothers in the AZCQ treatment group and 42 (2.9%) mothers in the SP treatment group had serious adverse events (SAEs) occurring on or after the first therapy date and before the last active therapy date + 35 days (the period which defined treatment emergence). Five (0.3%) subjects in the AZCQ treatment group and no subjects in the SP treatment group had SAEs that were considered treatment related. The 5 subjects in the AZCQ treatment group experienced the following treatment-related SAEs: vomiting (3), dizziness (2), diarrhoea (1), and asthenia (1). In the neonate group, 101 (8.8%) neonates born to mothers in the AZCQ treatment group and 104 (8.7%) neonates born to mothers in the SP treatment group had SAEs. No neonates born to mothers in either treatment group had SAEs that were considered treatment related.

Forty-one (2.8%) mothers in the AZCQ treatment group and 5 (0.3%) mothers in the SP treatment group permanently discontinued treatment due to treatment-emergent adverse events (TEAEs). The most common TEAEs leading to permanent discontinuation from treatment were vomiting (25 [1.7%] mothers in the AZCQ treatment group and 1 [0.1%] mother in the SP treatment group) and dizziness (9 [0.6%] mothers in the AZCQ treatment group and 0 [0.0%] mothers in the SP treatment group).

Treatment-emergent AEs were reported in 1185 (82.0%) mothers in the AZCQ treatment. The most common treatment-related AEs by preferred term were vomiting (653 [45.2%] subjects in the AZCQ treatment group and 96 [6.6%] subjects in the SP treatment group), dizziness (463 [32.0%] subjects in the AZCQ treatment group and 84 [5.8%] subjects in the SP treatment

group), and headache (300 [20.7%] subjects in the AZCQ treatment group and 219 [15.2%] subjects in the SP treatment group).

Adverse events were reported for 364 (31.7%) neonates born to mothers in the AZCQ treatment group and 389 (32.5%) neonates born to mothers in the SP treatment group. The most common all-causality AEs gastroenteritis (48 [4.2%] neonates born to mothers in the AZCQ treatment group and 39 [3.3%] neonates born to mothers in the SP treatment group), LBW baby (38 [3.3%] neonates born to mothers in the AZCQ treatment group and 49 [4.1%] neonates born to mothers in the SP treatment group), and premature baby (45 [3.9%] neonates born to mothers in the AZCQ treatment group and 40 [3.3%] neonates born to mothers in the SP treatment group).

Treatment-related AEs were reported in 996 (68.9%) mothers in the AZCQ treatment group and 286 (19.8%) mothers in the SP treatment group. The most common treatment-related AEs by preferred term in the mother group were vomiting (645 [44.6%] subjects in the AZCQ treatment group and 73 [5.1%] subjects in the SP treatment group), dizziness (454 [31.4%] subjects in the AZCQ treatment group and 62 [4.3%] subjects in the SP treatment group), headache (221 [15.3%] subjects in the AZCQ treatment group and 131 [9.1%] subjects in the SP treatment group), and asthenia (220 [15.2%] subjects in the AZCQ treatment group and 21 [1.5%] subjects in the SP treatment group).

Treatment-related AEs were reported for 4 (0.3%) neonates born to mothers in the AZCQ treatment group and 2 (0.2%) neonates born to mothers in the SP treatment group. The treatment-related AEs by preferred term were LBW baby (2 [0.2%] neonates born to mothers in the AZCQ treatment group and 2 [0.2%] neonates born to mothers in the SP treatment group), Anaemia (1 [0.1%] neonate born to a mother in the AZCQ treatment group and 0 [0.0%] neonates born to mothers in the SP treatment group), Jaundice neonatal (1 [0.1%] neonate born to a mother in the AZCQ treatment group and 0 [0.0%] neonates born to mothers in the SP treatment group) and Premature baby (0 [0.0%] neonates born to mothers in the AZCQ treatment group and 1 [0.1%] neonate born to a mother in the SP treatment group).

Most of the all-causality TEAEs were mild or moderate in severity.

Severe TEAEs were reported in 54 (3.7%) mothers in the AZCQ treatment group and 23 (1.6%) mothers in the SP treatment group. Severe AEs were reported for 54 (4.7%) neonates born to mothers in the AZCP treatment group and 64 (5.4%) neonates born to mothers in the SP treatment group.

In the mother group, 65/4068 (1.6%) TEAEs in the AZCQ treatment group and 27/2117 (1.3%) TEAEs in the SP treatment group were considered severe by the investigator. In the neonate group, 67/677 (9.9%) AEs in neonates born to mothers in the AZCQ treatment group and 75/645 (11.6%) AEs in neonates born to mothers in the SP treatment group were considered severe by the investigator.

In the mother group, 24/2593 (0.9%) treatment-related AEs in the AZCQ treatment group and 0/449 treatment-related AEs in the SP treatment group were considered severe by the investigator. In the neonate group, 1/4 (25.0%) treatment-related AEs in neonates born to mothers in the AZCQ treatment group and 0/3 treatment-related AEs in neonates born to mothers in the SP treatment group were considered severe by the investigator.

The most common SAEs overall by preferred term in the neonate group were polydactyly (16 [1.4%] neonates born to mothers in the AZCQ treatment group and 21 [1.8%] neonates born to mothers in the SP treatment group), premature baby (17 [1.5%] neonates born to mothers in the AZCQ treatment group and 12 [1.0%] neonates born to mothers in the SP treatment group), and sepsis neonatal (11 [1.0%] neonates born to mothers in the AZCQ treatment group and 13

[1.1%] neonates born to mothers in the SP treatment group). None were considered related to treatment.

Regarding AEs of special interest, in the mother group, there were 12 subjects with severe dizziness in the AZCQ treatment group compared with none in the SP treatment group, 6 subjects with severe vomiting in the AZCQ treatment group compared with none in the SP treatment group, 2 subjects with severe nausea in the AZCQ treatment group compared with none in the SP treatment group, 145 subjects with blurred vision in the AZCQ treatment group compared with 1 in the SP treatment group, no subjects with severe headache in either treatment group, 5 stillbirths in the AZCQ treatment group compared with 7 in the SP treatment group, 2 subjects with severe malaria in the AZCQ treatment group compared with 6 in the SP treatment group, and no subjects with severe palpitations in either treatment group. In the neonate group, there were 9 severely premature babies in the AZCQ treatment group compared with 6 in the SP treatment group and 7 severely LBW babies in the AZCQ treatment group compared with 6 in the SP treatment group.

Three (0.2%) subjects in the AZCQ treatment group and 5 (0.3%) subjects in the SP treatment group experienced a TEAE of pre-eclampsia. One (0.1%) subject in the AZCQ treatment group experienced a non-fatal treatment-emergent SAE of eclampsia and 1 (0.1%) subject in the AZCQ treatment group experienced a fatal non-TEAE of eclampsia; no subjects in the SP treatment group experienced eclampsia. There were no other clinically relevant observations regarding vital signs or physical examinations in either treatment group.

There were 1067 (93.4%) normal new-borns born to mothers in the AZCQ treatment group and 1102 (92.6%) normal new-borns born to mothers in the SP treatment group. Congenital malformations/anomalies were reported for 25 (2.2%) neonates born to mothers in the AZCQ treatment group and 29 (2.4%) neonates born to mothers in the SP treatment group, and other neonatal problems/abnormalities were reported for 49 (4.3%) neonates born to mothers in the AZCQ treatment group and 60 (5.0%) neonates born to mothers in the SP treatment group.

Eleven (0.8%) mothers in the AZCQ treatment group and 1 (0.1%) mother in the SP treatment group temporarily discontinued treatment due to TEAEs.

Forty-one (2.8%) mothers in the AZCQ treatment group and 5 (0.3%) mothers in the SP treatment group permanently discontinued treatment due to TEAEs. The most common TEAEs leading to permanent discontinuation from treatment were vomiting (25 [1.7%] mothers in the AZCQ treatment group and 1 ([0.1%] mother in the SP treatment group) and dizziness (9 [0.6%] mothers in the AZCQ treatment group and 0 [0.0%] mothers in the SP treatment group).

Three (0.2%) mothers in the AZCQ treatment group and 1 (0.1%) mother in the SP treatment group discontinued from the study due to AEs.

Study A0661201 - a Phase 3, open-label, non-comparative study evaluating parasitological clearance rates and pharmacokinetics (PK) of azithromycin and chloroquine (AZCQ) following administration of a fixed-dose combination of AZCQ in asymptomatic pregnant women during their second and third trimesters of pregnancy with *Plasmodium falciparum* parasitaemia in Sub-Saharan Africa.

- **Description**

Phase 3, open-label, non-comparative study evaluating parasitological clearance rates and pharmacokinetics (PK) of azithromycin and chloroquine (AZCQ) following administration of a fixed-dose combination of AZCQ in asymptomatic pregnant women during their second and third trimesters of pregnancy with *Plasmodium falciparum* parasitaemia in Sub-Saharan Africa.

Study A0661201 was designed to help characterise the magnitude of expected parasitological clearance that would be observed over a 6-week period, associated with the intermittent preventive treatment of malaria in pregnancy (IPTp) effect after 1 regimen in the A0661158 study.
The study was also designed to evaluate the PK exposures of both AZ and CQ in pregnant women following administration of a single 3-day treatment course of AZCQ. Subjects were to be followed until Day 42 after the first dose, and were to be followed through delivery or to pregnancy termination in order to determine safety assessments of Exposure in Utero (EIU).

- **Methods**

- Objective(s)

The primary objective of the study was to evaluate the peripheral parasitological clearance rate of AZCQ on Day 28 (polymerase chain reaction [PCR] corrected) following a 3-day dosing regimen of AZCQ in asymptomatic pregnant women with *P. falciparum* parasitaemia.
Secondary objectives included evaluation of the following:

- Parasitological clearance rate (PCR corrected) on Days 7, 14, 21, 35 and 42 post first dose of study drug
- Parasitological clearance rate (PCR uncorrected) on Days 7, 14, 21, 28, 35 and 42 post first dose of study drug
- PK exposure of AZCQ
- Safety and tolerability of AZCQ

- Study design

This was an open label, single arm non-comparative out-patient study in pregnant women during their second and third trimesters of pregnancy.
The study did not incorporate a comparator group (ie, SP) because it was designed to provide supportive data to the pivotal study and was not intended to be a pivotal efficacy and safety study.

Subjects with asymptomatic parasitaemia (counts of 80 to 100,000/µL) were to receive a single 3-day course of AZCQ IPTp regimen. The parasitological response was to be evaluated on Days 7, 14, 21, 28, 35 and 42. Subjects were to be followed up on a weekly basis up to Day 42 after the first dose and following delivery or at termination of pregnancy for EIU safety assessments. After completing Day 42 evaluation, all subjects were to continue to receive standard antenatal care (ANC) including IPTp with sulfadoxine-pyrimethamine (SP) if the gestational age allowed additional IPTp course(s).

The PK evaluation was to be conducted on blood samples collected from the subjects who consented for such test.

Systemic concentrations of AZ, CQ and DECQ were to be evaluated on Day 0 predose, Day 2 predose, 2 hours (as close to 2 hours as possible) and 8 hours (time window: 4 to 12 hours) postdose, and at a random time point on Days 7 and 14. In addition, due to the long half-life of CQ, systemic concentrations of CQ and DECQ were also to be measured at a random time point on Days 21 and 28. All subjects were also to be followed up for EIU safety assessments following delivery or termination of pregnancy. Insecticide treated bed nets were to be provided to all subjects on Day 0 of the study, with installation verified during Day 1 home visit by field worker(s).

- Study population / Sample size

The planned enrolment was 166 subjects.
Subjects were enrolled at 6 active sites in 5 countries: Benin, Kenya, Malawi, Tanzania (2 sites) and Uganda.

The following Inclusion criteria were set:

1. Primigravidae and secundigravidae pregnant women at ≥14 and ≤30 weeks of gestational age (confirmed by ultrasound examination).
2. Evidence of asymptomatic parasitemia with *P. falciparum* monoinfection (confirmed by microscopy) with parasite counts in the range of 80 to 100,000/µL on thick blood smears.
3. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject (or a legally acceptable representative if a subject was <18 years of age) had been informed of all pertinent aspects of the study and that all questions by the subject had been sufficiently answered. Assent was to be obtained from subjects <18 years of age.
4. Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
5. Subjects who agreed to be supervised for treatment administration, and were available for all follow-up visits as per protocol.
6. Subjects residing within an area of 20 km from the study site (Site 1010 only).

The following Exclusion criteria were considered:

1. Age <16 years old or >35 years old.
2. Multiple gestations (more than 1 fetus) as per the ultrasound results at screening.
3. Clinical signs and symptoms of malaria3.
4. Hemoglobin <8 g/dL (measured at baseline).
5. Any condition requiring hospitalization or evidence of severe concomitant infection at time of presentation.
6. Use of antimalarial drugs in previous 4 weeks.
7. History of convulsions, hypertension, diabetes or any other chronic illness that might have adversely affected fetal growth and viability.
8. Inability to tolerate oral treatment in tablet form.
9. Known allergy to the study drugs (AZ, CQ, and SP) or to any macrolides or sulfonamides.
10. Present history of smoking or alcohol or drug abuse since first becoming aware of current pregnancy.
11. Participation in other studies within 30 days before the current study began and/or during study participation.
12. Inability to comprehend and/or unwillingness to follow the study protocol.
13. Concurrent participation in another investigational study.

14. Previously enrolled in this study.
15. Requirement to use medication during the study that might have interfered with the evaluation of the study drug (eg, trimethoprim-sulfamethoxazole use in subjects positive for human immunodeficiency virus [HIV] infection) or was contra-indicated during pregnancy per package inserts.
16. Severe acute or chronic medical or psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study. Examples to be included but not limited to:

- Symptomatic HIV infection, including physical findings that suggested immunocompromized status (eg, oral candidiasis).
- Neurological conditions which may predispose to complications during pregnancy, including seizure disorders.
- Severe psychosis or major disorder that could interfere with the conduct f the study or adherence to study drug.
- Known, clinically significant pre-existing renal or hepatic disease.

17. Evidence of current obstetric complications that could adversely impact the pregnancy and/or fetal outcomes, including presence of congenital anomalies, placenta previa or abruption.
18. Known severe sickle cell disease or sickle-hemoglobin C anemia.
19. Known family history of prolonged QT syndrome, serious ventricular arrhythmia, or sudden cardiac death.

- Treatments

A 3-day dosing regimen of a fixed dose combination of AZ and CQ (4 AZCQ tablets per day, each tablet with 250 mg AZ/155 mg CQ base) was used, to be given on Days 0, 1 and 2.
The first dose on Day 0 and the third dose on Day 2 were to be administered under supervision at the ANC, and the second dose on Day 1 was to be administered at home under supervision of a field worker. AZCQ was not to be administered on an empty stomach. Each dose was to be administered with a glass of water.

If a subject presented with symptoms of malaria (fever >37.5 °C, oral) on Day 1 or 2, no further AZCQ dose was to be given. The subject was to be immediately referred to the investigator for parasite counts and appropriate treatment was to be given for malaria in pregnancy as per national/local guidelines.
Any dose that was vomited within 30 minutes after administration was to be repeated. If vomiting re-occurred after re-dosing on Day 0, Day 1 and Day 2, the subject was not to receive further study drugs and was to be provided standard SP ITPp treatment for malaria in pregnancy per local ANC guideline. If this happened during the home visit on Day 1, the subject was to be asked to return to the study physician within next 24 hours and was to receive standard treatment for malaria in pregnancy. The subject was to be followed up through Day 42 and assessed for pregnancy outcomes after delivery or termination of pregnancy for EIU safety assessments.

- Outcomes/endpoints

<u>Primary Efficacy Endpoint</u>
<u>> Parasitological response rate (PCR corrected) on Day 28 post first dose of study drug.</u>
The proportion of subjects with parasitological response (PCR corrected) at Day 28 post first dose of study drug was estimated for the primary endpoint using the modified intent-to-treat (MITT) and per protocol (PP) analysis sets. The proportion was estimated from the Kaplan-Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected).

A subject was to be a parasitological responder, if she had a zero parasite count on the Day 7 visit without subsequent recrudescence (PCR corrected) through the day of consideration; otherwise, she was to be a parasitological failure.
Additional sensitivity analyses were also performed using the MITT and PP subject populations. Based on the sensitivity analyses premature discontinuation for any reason was considered as parasitological failure, if not already reported as parasitological failure because of a defined event. The same statistical methods were to be used again to estimate the proportion of subjects with parasitological response (PCR corrected) at Day 28.

Secondary Efficacy Endpoints
> Parasitological response rate (PCR corrected) on Days 7, 14, 21, 35 and 42 post first dose of study drug
> Parasitological response rate (PCR uncorrected) on Days 7, 14, 21, 28, 35 and 42 post first dose of study drug
> Parasite counts at each visit - number of asexual *P. falciparum* parasites per µL of blood

The secondary parasitological response endpoints were to be analysed in the same manner as the primary endpoint, and used the intent-to-treat (ITT), MITT and PP subject populations. These analyses were to be done using both PCR corrected and uncorrected results, and also were to include the sensitivity analyses.

Pharmacokinetic Evaluation
> PK exposure of AZCQ, ie, AZ concentrations in the serum, and CQ concentrations and desethylchloroquine (DECQ) concentrations in the plasma.

Safety Endpoints
> Safety and tolerability endpoints including spontaneously reported adverse events (AEs), temperature, physical examinations, hemoglobin concentrations, and the EIU assessment.

- Statistical Methods

This study was designed to estimate the incidence for the primary endpoint. No statistical hypothesis was tested.

Intent-to-treat (ITT) population is defined as all subjects who receive at least one dose of study medication and who have a baseline blood smear positive for *Plasmodium falciparum* monoinfection, asexual parasitemia.
Modified ITT (MITT) is a subset of the ITT population who have a *Plasmodium falciparum* monoinfection (confirmed by microscopy) parasite count in the range of 80-100,000/µL on their baseline blood smear.
Per protocol (PP) is a subset of MITT subjects who receive all 3 days of study medication.

For both primary and secondary endpoints evaluation will be based on the proportion of subjects achieving the endpoint and will use the ITT, MITT, and PP subject populations.
For the primary endpoint parasitological response (PCR corrected) at Day 28 post first dose of study medication will be estimated for the primary endpoint using the ITT, MITT, and PP subject populations. The proportion will be estimated from the Kaplan-Meier curve based on the time to the first occurrence of parasitological failure (PCR corrected).

The Safety Analysis Set for mothers consisted of subjects who received at least 1 dose of study drug. The Safety Analysis Set for neonates consisted of all liveborn babies.
For PK analysis all subjects who received at least 1 dose and had at least 1 blood sample collected for PK analysis were included in analyses and listings of the PK endpoints.

- **Results**

- Recruitment / Number analysed

A total of 404 subjects were screened and 168 subjects were assigned to study drug, enrolled and treated. The study was completed by 155 (92.3%) subjects, and 13 (7.7%) subjects discontinued from the study, none due to AEs, death, protocol violation or failing inclusion/exclusion criteria.
In total, 166 subjects were analysed for PK; 2 subjects were excluded from PK analysis because of informed consent protocol deviations.
The Safety population consisted of all 168 subjects and 157 neonates (all live born).

The ITT population, the MITT population, and the PP population consisted of 165 subjects, 163 subjects and 158 subjects, respectively.

- Baseline data

The mean (range) age of all subjects was 18.8 (16-34) years. All subjects were black females.
The median baseline asexual parasite count for all subjects in the ITT population was 1240/µL. Results for the median baseline asexual parasite count were similar for the MITT and the PP population.
For 124 (73.8%) subjects this pregnancy was the first one. One prior pregnancy was reported for 43 (25.6%) subjects (with prior live births for 42 [25.0%] subjects) and 2 prior pregnancies were reported for 1 (0.6%) subject (both resulting in a live birth.
Study bed nets were installed for 164 subjects of the ITT population.

- Pharmacokinetic Evaluation

Concentration data for serum AZ, plasma CQ and plasma desethylchloroquine (DECQ) were listed by subject, study day, nominal time postdose and actual time postdose. Descriptive statistics (N, mean, standard deviation [SD], coefficient of variation [CV], median, minimum and maximum) of concentration data for serum AZ, plasma CQ and plasma DECQ were provided with study day and nominal time postdose. The PK concentration-time data were simply presented as descriptive summary statistics and further analyses were not performed.

Summary profiles (mean and median) of the concentration-time data were plotted on linear-linear scales for serum AZ, plasma CQ and plasma DECQ using the nominal PK sampling time.

In all PK data presentations except listings, AZ, CQ and DECQ concentrations below the lower limit of quantification (BLQ) were set to zero. In listings, BLQ values were reported as "< lower limit of quantification (LLOQ)," where the LLOQ was replaced with the value for the LLOQ.

<u>Pharmacokinetic Results</u>

Mean serum AZ concentrations were 194, 994 and 708 ng/mL at 0, 2 and 8 hours on Day 2, respectively, and 54.4 and 20.3 ng/mL on Days 7 and 14, respectively. Mean plasma CQ concentrations were 306, 621 and 641 ng/mL at 0, 2 and 8 hours on Day 2, respectively, and 130, 43.1, 22.4 and 12.7 ng/mL on Days 7, 14, 21 and 28, respectively. Mean plasma DECQ concentrations were 184, 220 and 242 ng/mL at 0, 2 and 8 hours on Day 2, respectively, and 144, 55.5, 29.8 and 19.4 ng/mL on Days 7, 14, 21 and 28, respectively.

In general, the mean concentration data of serum AZ, plasma CQ and plasma DECQ following the AZCQ dosing regimen had large CV% values (ranges of 33% to 156%, 42% to 228% and 57% to 109%, respectively). Pharmacokinetic sampling time windows and the random sampling times on Days 7, 14, 21 and 28 according to the study design may partially have contributed to

the observed large CV% values. Therefore, the serum AZ, plasma CQ and plasma DECQ concentration-time data reported in this study should be interpreted with caution because of large CV% values.

- Efficacy results

Parasitological clearance was checked by 2 blinded microscopists (3 in case of non agreement, and the parasite density being calculated by averaging the 2 most concordant counts) in peripheral blood smear (thick and thin), which was to be prepared at the study sites with the standard Giemsa staining for parasite identification and count using white blood cell counting method on thick smears. If and when the blood smears became positive after initial parasite clearance, the blood blot collected at that visit was to be tested for molecular genotyping assays to differentiate the recrudescence (reappearance of asexual *P. falciparum*) from reinfection (different genotypic parasite).

Primary Efficacy Endpoint

On Day 28, 153 of 154 subjects of the MITT population were parasitological responders (PCR corrected) (99.35% [confidence interval, CI: 97.76 to 100.00]). Results for the PP population were the same. Sensitivity analyses for parasitological response (PCR corrected) conducted regarding study dropouts considered failures supported these results.

Secondary Efficacy Endpoints

For PCR corrected, estimates of parasitological response exceeded 95% at all time points until Day 42, with lower bounds of the 95% CIs exceeding 95% out to Day 28. Results of PCR uncorrected were identical to PCR corrected out to Day 21, and only slightly lower at Day 28, but remained above 95% on Day 28. These were markedly lower at Days 35 and 42, reduced to approximately 78% at the end of the follow-up period.

For PCR corrected:

Overall, for the MITT population (163 subjects), the proportion of parasitological responders (PCR corrected) was the same on Days 7, 14 and 21 (100% for all [CI: 97.66 to 100.00, CI: 97.63 to 100.00 and CI: 97.63 to 100.00, respectively]). At Days 35 and 42, the proportion decreased slightly to 96.65% (CI: 93.42, 99.87) and 95.19% (CI: 91.35, 99.03), respectively. Results for the PP population were similar, and were also similar to the ITT population. Sensitivity analyses for parasitological response (PCR corrected) were conducted for study dropouts considered failures, and supported results by showing high parasitological responder rates. Responder rates were similar on Days 7, 14 and 21 (96.32% for all [CI: 93.12, 99.52]) and decreased slightly on Days 35 and 42 (93.09% [CI: 88.82, 97.36] and 91.69% [CI: 87.01, 96.37], respectively). The percentage of parasitological responders in the PP population was slightly higher: responder rates were similar on Days 7, 14 and 21 (99.37% [CI: 97.81, 100.00] for all) and decreased on Days 28, 35 and 42 (98.72% [CI: 96.64, 100.00], 96.04% [CI: 92.59, 99.48] and 94.59% [CI: 90.58, 98.60], respectively).

For PCR uncorrected:

Overall, for the MITT population (163 subjects), the proportion of parasitological responders (PCR uncorrected) was the same at Days 7, 14 and 21 (100% for all [CI: 97.66 to 100.00, CI: 97.63 to 100.00, and CI: 97.63 to 100.00, respectively]). At Days 28, the proportion decreased slightly to 95.45% (CI: 91.84 to 99.07), and notably so at Days 35 and 42 (87.66% [CI: 82.14 to 93.18] and 78.43% [CI: 71.59 to 85.28], respectively). Results for the PP population were similar, and were also similar to the ITT population.

Sensitivity analyses for parasitological response (PCR uncorrected) were also conducted regarding study dropouts considered failures. Responder rates were similar on Days 7, 14 and 21 (96.32% [CI: 93.12, 99.52]) and further decreased on Days 28, 35 and 42 (91.94% [CI: 87.43, 96.46], 84.44% [CI: 78.51, 90.36] and 75.55% [CI: 68.55, 82.54], respectively). The percentage of parasitological responders in the PP population was slightly higher.

For the ITT population, the mean asexual parasite count (+SD) was 0.00 (0.00) on Days 7, 14 and 21; it was 216.91 (1374.46), 555.36 (3082.21) and 907.88 (5861.63) on Days 28, 35 and 42, respectively. Parasite counts on these days represent results from 7 (4.49%), 19 (12.18%) and 33 (21.43%) parasitaemic subjects at each visit, respectively. Results for the PP and the MITT population were similar.

- Safety results

Adverse events (AEs), history of concomitant treatments, haemoglobin, temperature and the EIU safety assessment were to be recorded for each subject during the study according to the schedule of assessments. Each AE was to be counted once according to the date of onset. If the AE onset was before the first dose of study drug and the event did not increase in severity after initiation of study drug, the AE was then to be considered to be a pre-treatment AE and was not to be counted in the treatment-emergent adverse event (TEAE) incidence tables. If the onset was before the first dose of study drug and the severity increased thereafter, the event was to be counted as a TEAE. An AE with onset after the first dose of study drug was to be counted as a TEAE if it occurred on or before 35 days post last dose.

Maternal information regarding pregnancy and delivery and neonatal information were also evaluated.

<u>Safety Results</u>

All safety analyses were based upon the Safety Population which consisted of 168 treated subjects and 157 live born neonates. Three stillbirths were reported; for 8 subjects no pregnancy outcome forms were completed (7 subjects withdrew consent and 1 subject was lost to follow-up).

A total of 163 (97.0%) subjects took study drug for 3 consecutive days.

No deaths occurred in the mother group; 4 neonates died because of AEs (2 cases of neonatal asphyxia, 1 case each of premature baby and sudden infant death syndrome). None of these deaths were considered related to study drug.

In this study, 35 serious adverse events (SAEs) occurred in 22 subjects (mothers [13] and neonates [9]). No serious TEAEs occurring on or after first therapy date and before the last active therapy date + 35 (the period which defined treatment emergence) days were reported in the mother group. After this time window of 35 days, in the mother group, 17 SAEs occurred in 13 subjects. Three (3) cases of stillbirth occurred, all of which were reported as severe. There were also 3 cases of premature labour/premature delivery (1 of moderate severity and 2 of mild severity), 2 cases of severe eclampsia, 2 cases of pre-eclampsia (1 of moderate severity and 1 of mild severity) and 2 cases of malaria of mild severity. All other events (obstructed labour, haemorrhage in pregnancy, precipitate labour, uterine rupture and shoulder dystocia) occurred only once.

In neonates, 18 SAEs occurred in 9 subjects. Four SAEs of severe neonatal asphyxia occurred in the neonates group, and 2 neonates died because of neonatal asphyxia. All other events occurred in only 1 neonate each.

None of the SAEs were related to study drug.

All-causality TEAEs were reported for 92 (54.8%) mothers and 27 (17.2%) neonates. The most common all-causality TEAEs by Preferred Term (PT) in ≥5 subjects in the mother group were Vomiting (35 [20.8%]), Dizziness (33 [19.6%]), Pruritus (13 [7.7%]), Parasitic infection (12 [7.1%]), Headache (10 [6.0%]), Generalised pruritus (9 [5.4%]), Malaria (8 [4.8%]), Fatigue and Upper respiratory tract infection (7 [4.2%] subjects each) and Nausea (6 [3.6%]). The most common all-causality TEAEs by PT in ≥5 subjects in neonates group were low-birth-weight (LBW) baby (8 [5.1%]), premature baby (7 [4.5%]) and neonatal asphyxia (7 [4.5%]).

Treatment-related TEAEs were reported in 71 (42.3%) mothers (none of these was reported as severe), and no treatment-related AEs were reported in the neonate group. The most common treatment-related TEAEs by PT in ≥5 subjects in the mothers group were Vomiting (34 [20.2%]), Dizziness (33 [19.6%]), Pruritus (12 [7.1%]), Headache and Generalised pruritus (9 [5.4%] subjects each), Fatigue (7 [4.2%] subjects) and Nausea (6 [3.6%] subjects).

Most of the all-causality TEAEs were of mild or moderate severity. No TEAE in the mother group and only 7 AEs in the neonate group (sudden infant death syndrome [1 case], premature baby [1 case], and neonatal asphyxia [5 cases]) were reported as severe; all these events were considered to be unrelated to the study drug by the investigator. These AEs were also assessed as SAEs.

No discontinuations from study or treatment because of AEs were reported during the study.

Regarding pre-defined adverse events of special interests (AESIs), in the mothers group, there were no events of palpitations. Three (3) cases of severe stillbirths (all of which were considered as SAEs), and several cases of vision blurred (1 event), nausea (6 events), vomiting (35 events), malaria (8 events), dizziness (33 events) and headache (10 events) were reported (none of them were considered severe). All AEs of blurred vision, nausea and dizziness and all events but 1 of vomiting and headache, respectively, were considered to be related to study drug. The majority of the AESIs events were of mild severity. In the neonate group, there were 8 events of LBW babies (all of mild severity) and 7 events of premature baby (6 events of mild severity and 1 event of severe severity). None of the events were considered related to study drug.

For only 1 subject, a clinically significant haemoglobin value of 7.6 g/dL on Day 42 was reported which was <0.8× lower limit of normal. No other laboratory test abnormalities were reported for any other subject.

No clinically relevant observations regarding vital signs and physical examinations were reported.

For 130 (81.3%) subjects, delivery in a medical facility was reported. Vaginal delivery was reported by 145 (90.6%) subjects and caesarean section by 15 (9.4%) subjects. Induction of labour was reported by 3 (1.9%) subjects; 42 (26.3%) subjects had complications during delivery. Full-term live birth occurred in 151 (94.4%) subjects; premature birth was reported by 6 (3.8%) subjects and stillbirth by 3 (1.9%) subjects.

Of the 157 neonates, there were 144 (91.7%) normal newborns. Congenital malformations/anomalies were reported for 2 (1.3%) newborns, and other neonatal problems/abnormalities were reported for 9 (5.7%) newborns. Low birth weight (<2500 g) was reported in 9 (6.6%) of 137 neonates. Hospitalisation since birth was reported for 4 (2.70%) neonates (reason for hospitalisation included neonatal asphyxia, neonatal sepsis, asphyxia and premature birth). Unplanned visits post delivery not leading to hospitalisation were reported for 4

neonates (reasons for visits included pneumonia, upper respiratory tract infection, LBW and neonatal infection). The outcome for 2 (1.3%) newborns was unknown.

3. Discussion on clinical aspects

Study A0661190 - a Phase 2, open-label, randomised, single-dose, parallel-arm study to determine the pharmacokinetics of azithromycin following oral administration of an immediate-release (IR) or extended-release (ER) oral suspension in paediatric subjects with Acute Otitis Media (AOM).

This was a Phase 2, open-label, randomised, single-dose, parallel-arm study, to determine the pharmacokinetics of azithromycin following oral administration of an IR or ER formulation in paediatric subjects with AOM. Azithromycin has been shown to have a favourable safety profile when administered as a 60 mg/kg ER and 30 mg/kg IR formulation. The pharmacokinetic results showed that the serum concentrations following a dose of 60 mg/kg ER formulation are closely similar to or greater than the 30 mg/kg IR formulation.

The lower boundary of the 90% CI of the AUC_{72} ratio (reduced analysis set) was found to be greater than the predetermined criterion of ≥80%. It is, therefore, concluded that the ER formulation provides similar or greater systemic exposure of azithromycin compared with the IR formulation.

The observed clinical cure rates for the 2 treatments appeared to be similar, as all 18 completed paediatric subjects with AOM receiving a single dose of 60 mg/kg azithromycin ER formulation had clinical response assessed as cure compared with 16 out of 18 completed paediatric subjects receiving a single dose of 30 mg/kg azithromycin IR formulation.

Although the rather small sample size, overall, safety data support that azithromycin is safe and well tolerated following single-dose administration of either formulation (30 mg/kg IR or 60 mg/kg ER) in paediatric subjects with AOM. Azithromycin serum concentrations were lower for the first 3 hours and higher over the remaining 72 hours after dosing of the 60 mg/kg ER formulation compared with 30 mg/kg IR formulation.

No new relevant or outstanding PK, efficacy nor safety data has been generated from this study concerning EU authorized IR formulation.

According to the results of this study noninferiority of AZ-CQ treatment to AL treatment cannot be claimed.

The proportion of subjects (95% CI) in Cohort 2 achieving ACPR at Day 28 was 89% (83%, 96%) and 98% (96%, 100%) in the AZ-CQ and AL groups (MITT), respectively, and 93% (87%, 99%) and 99% (97%, 100%) in the AZ-CQ and AL groups (PP), respectively.

Median time to parasite clearance in Cohort 2 was 24 hours in the AL group and 48 hours in the AZ-CQ group.

Median time to fever clearance in Cohort 2 was 24 hours in both the treatment groups.

On the basis of the combined data from both cohorts, in subjects aged ≥6 months to ≤12 years, AZ serum concentrations were 201, 983, 510 and 32.0 ng/mL on Day 2 (0, 3 and 8 hours) and Day 7, respectively. CQ plasma concentrations were 144, 362, 318 and 41.0 ng/mL on Day 2 (0, 3 and 8 hours) and Day 7, respectively. The desethyl-CQ plasma concentrations were 82.9, 148, 151 and 46.8 ng/mL on Day 2 (0, 3 and 8 hours) and Day 7, respectively. The Large CV of the concentration data may partially be caused by the PK sampling time window and approximate weight-based dose according to design.

Although the proportion of overall AEs was similar among both treatment groups, the incidence of treatment-related AEs was higher among AZ-CQ subjects. Most AEs were mild and were primarily associated with the body systems of gastrointestinal disorders and infections and infestations.

Vomiting and pruritus were more frequently reported AEs in subjects treated with AZ-CQ than among those treated with AL. Vomiting was observed in 20.0% and 9.8% of AZ-CQ and AL subjects, respectively, in Cohort 1 and in 30.6% and 9.9% of AZ-CQ and AL subjects, respectively, in Cohort 2. Pruritus was observed in 16.4% and 2.0% of AZ-CQ and AL subjects, respectively, in Cohort 1 and in 6.5% and 1.5% of AZ-CQ and AL subjects, respectively, in Cohort 2. Most cases of vomiting and pruritus were mild.

No meaningful differences in laboratory parameters were observed between subjects dosed with AZ-CQ and AL treatment.

Benefits and Risks Conclusions

This Phase 3 study failed to demonstrate noninferiority of AZ plus CQ compared to AL for the treatment of symptomatic, uncomplicated malaria because of *P. falciparum* in children in Africa.

No new safety issues were identified during the course of the study. Being given concomitantly to cloroquine, it is not possible to insure that all the AEs reported for patients having taken AZ+CQ could be attributed to Azithromycin.

Superiority of AZCQ over SP in protective efficacy for IPTp, as measured by the proportion of subjects with sub-optimal pregnancy outcome (primary endpoint), was not demonstrated. The planned interim analysis results showed that the futility boundary for the primary endpoint was crossed, and the sponsor made the decision to terminate the study. Sub-optimal pregnancy outcome showed an increase in estimated risk in the AZCQ treatment group compared with the SP treatment group (RR of 1.11 in the ITT population), although this result was not statistically significant and showed near equality when excluding missing or unknown values (RR of 0.96 in the ITT EA population) and when including neonatal deaths and congenital malformations (RR of 1.08 in the ITT population).

The AZCQ treatment group was observed to have an estimated reduction in risk of LBW compared with SP (RR of 0.87 in the ITT population), but only marginally so and also not statistically significant.

Conclusions for the other secondary endpoints are considered exploratory and listed below:

Maternal anaemia showed an estimated RR near equality for AZCQ compared with SP (RR of 1.03 in the ITT population), and AZCQ was observed to have a marginal estimated reduction in risk of severe maternal anaemia and placental parasitaemia compared with SP (RR of 0.90 and 0.93 in the ITT population, respectively).

AZCQ was observed to have a reduction in risk of the occurrence of STIs, including *T. pallidum, N. gonorrhoeae* and *C. trachomatis*, compared with SP (RR of 0.75 in the ITT population).

AZCQ was also observed to have a reduction in risk for the following additional secondary endpoints: symptomatic malaria from first dose to delivery, peripheral parasitaemia at 36-38 weeks of gestation, and bacterial infections, including pneumonia and other lower respiratory tract infections, from first dose to delivery.

Subjects in the AZCQ treatment group were less likely to complete all treatment days than those in the SP treatment group.

In the mother group, more deaths were observed in the AZCQ treatment group (n = 3) than in the SP treatment group (n = 1), but the difference was not significant. No deaths were considered related to the study drug. The SAEs, discontinuations because of TEAEs, severe TEAEs, and AEs of special interest were more frequent in the AZCQ treatment group than in the SP treatment group. Most TEAEs were mild or moderate in severity. The incidence of vomiting (45.2% subjects in the AZCQ treatment group versus 6.6% subjects in the SP treatment group) was higher than expected.

Regarding AESIs, in the mother group, there were 12 subjects with severe dizziness in the AZCQ treatment group compared to none in the SP treatment group, 6 subjects with severe vomiting in the AZCQ treatment group compared to none in the SP treatment group, 2 subjects with severe nausea in the AZCQ treatment group compared to none in the SP treatment group, 145 subjects with blurred vision in the AZCQ treatment group compared to 1 in the SP treatment group, no subjects with severe headache in either treatment group, 5 stillbirths in the AZCQ treatment group compared to 7 in the SP treatment group, 2 subjects with severe malaria in the AZCQ treatment group compared to 6 in the SP treatment group, and no subjects with severe palpitations in either treatment group. In the neonate group, there were 9 severely premature

babies in the AZCQ treatment group compared to 6 in the SP treatment group and 7 severely LBW babies in the AZCQ treatment group compared to 6 in the SP treatment group.

Occurrences of congenital malformations/anomalies, neonatal deaths and SAEs were comparable for neonates born to mothers in the AZCQ and SP treatment groups. None of the deaths were considered related to the study drugs.

Benefits and Risks Conclusions

Superiority of AZCQ over SP in protective efficacy for IPTp, as measured by the proportion of subjects with sub-optimal pregnancy outcome (primary endpoint) was not confirmed.

No new safety issues were identified during the course of the study, but information regarding exposure of pregnant women (adolescents and adult) and impact on newborn became available.

Study A0661201 - a Phase 3, open-label, non-comparative study evaluating parasitological clearance rates and pharmacokinetics (PK) of azithromycin and chloroquine (AZCQ) following administration of a fixed-dose combination of AZCQ in asymptomatic pregnant women during their second and third trimesters of pregnancy with *Plasmodium falciparum* parasitaemia in Sub-Saharan Africa.

The parasitological responder rate (PCR corrected) on Day 28 was 99.35% (MITT population). AZCQ was highly effective in clearing peripheral *P. falciparum* parasitaemia in this population.

The parasitological responder rates (PCR corrected) on Days 7, 14, 21, 35 and 42 were also high (exceeding 95% at all time points) and maintained up to Day 42 confirming the effectiveness of AZCQ in clearing peripheral *P. falciparum* parasitaemia (MITT population, PP population and ITT population).

No deaths occurred in the mother group; 4 neonates died due to AEs, none related to the study drug.

No serious TEAEs occurring on or after first therapy date and before the last active therapy date + 35 days (the period which defined treatment emergence) were reported in the mother group. SAEs were reported for 9 neonates.

TEAEs were reported for 92 (54.8%) mothers and AEs for 27 (17.2%) neonates. For no subject of the mother group and for 7 (4.5%) subjects of the neonate group severe AEs were reported. Treatment-related TEAEs were reported in 71 (42.3%) mothers, and none were reported in the neonate group. For no subjects in either the mother group or the neonate group, severe treatment-related AEs were reported.

No discontinuations from study or treatment due to AEs were reported.

Regarding AESIs, in the mothers group, there were no events of palpitations, 3 cases of severe stillbirths (all of which considered SAEs), and several cases of vision blurred (1 event), nausea (6 events), vomiting (35 events), malaria (8 events), dizziness (33 events), and headache (10 events) were reported (none of them considered severe).

In the neonate group, there were 8 events of low birth weight babies (all of mild severity) and 7 events of premature baby (6 events of mild severity and 1 event of severe severity). None of the events were considered related to study drug.

Benefits and Risks Conclusions

AZCQ was highly effective in clearing peripheral *P. falciparum* parasitaemia with parasitological responder rate (PCR corrected) on Day 28 of 99.35% in the MITT population.

No new safety issues were identified during the course of the study, but information regarding exposure of pregnant women (adolescents and adult) and impact on new-born became available.

Overall Conclusion

Due to the differences between the four studies submitted a separate evaluation/conclusion will be provided per study.

Study A0661190

No formal efficacy evaluation was performed in this study but clinical response with ER formulation appeared to be similar to IR formulation.
A similar PK profile (considering the predefined criteria) was demonstrated for the IR and ER formulations. The sample size can also be questionable for the purposes of the study.
Despite the rather small sample size, no safety concerns were identified nether for the IR nor for the new ER formulation.

Study A0661157; Study A0661158; Study A0661201

Regarding efficacy, the submitted clinical trials confirmed that:
a) AZ-CQ treatment could not be claimed to be noninferior to AL for the treatment of symptomatic, uncomplicated *Plasmodium falciparum* in children.
b) AZ plus CQ (AZCQ) was not superior to sulfadoxine plus pyrimethamine (SP) combinations for intermittent preventive treatment of *Falciparum* malaria infection in pregnant women in Africa, as measured by the proportion of subjects with sub-optimal pregnancy outcome (primary endpoint). Nevertheless the AZCQ treatment group was observed to have an estimated (and not statistically significant) reduction in risk of LBW compared with SP for intermittent preventive treatment of *Falciparum* malaria infection in pregnant women in Africa.
d) AZCQ was highly effective in clearing peripheral *P. falciparum* parasitaemia in asymptomatic pregnant women with *P. falciparum* parasitaemia in sub-Saharan Africa up to Day 42 post-treatment.

Regarding safety:
a) The AE profile was not different from what is already known for Azithromycin. The trial/studied condition specific AEs were pyrexia and asymptomatic parasitaemia,
b) Frequencies of the different reported AEs changed between studies but the most frequent AEs were vomiting, pruritus, dizziness, abdominal pain, headache, fatigue and nausea in frequencies not substantially different from the already reported for Azithromycin. The only exception may be vomiting with some series of 40% prevalence. Nevertheless this AE cannot be clearly link to AZ and may also be attributable to Chloroquine. Most of the AEs were mild to moderate severity.
c) No reported deaths were associated with Azithromycin.
d) Some information following pregnant women exposure (both adolescents and adult ones) has been generated.
e) Also safety information regarding new-borns of mothers previously treated with AZCQ has been generated.

Regarding PK data:
Some PK information has been generated both in the pregnant and paediatric population. Caution evaluation of these results has been advised considering technical aspects (sample time windows and random samples).

V. REQUEST FOR SUPPLEMENTARY INFORMATION

Following the revision of the procedure:

a) The MAH should consider to amend the SmPC to include safety information for pregnancy use and new-born outcome, by using data retrieved from the presented trials. The MAH should made a proposal for the text to be included in the appropriate section of the SmPC.

b) In light of the conflicting results of the presented studies on the efficacy of Azithromycin in the studied indication, the MAH is requested to better review all available efficacy results of azithromycin monotherapy or azithromycin-chloroquine combination for the treatment of P. falciparum infection in the paediatric population to conclude whether clinically relevant results should be included in Section 5.1 of the SmPC for this indication.
If finally the information collected supports its inclusion in the SmPC than a proposal of the text to be added should be submitted by the MAH.

Assessment of responses to questions

The MAH submitted the following answers to the request sent on D90.

a) The MAH should consider to amend the SmPC to include safety information for pregnancy use and new-born outcome, by using data retrieved from the presented trials. The MAH should made a proposal for the text to be included in the appropriate section of the SmPC.

MAH's Response

Inclusion of safety information on pregnancy use and new-born outcomes based on the data from the presented trials in the azithromycin SmPC is not considered appropriate for the following reasons:

Only 2 of the 4 clinical trials which were presented are relevant to pregnant women:

- Study A0661158 - a Phase 3, open-label, randomised, comparative study to evaluate azithromycin (AZ) plus chloroquine (CQ) and sulfadoxine plus pyrimethamine combinations for intermittent preventive treatment of Falciparum malaria infection in pregnant women in Africa.

- Study A0661201 - a Phase 3, open-label, non-comparative study evaluating parasitological clearance rates and pharmacokinetics (PK) of azithromycin and chloroquine (AZCQ) following administration of a fixed-dose combination of AZCQ in asymptomatic pregnant women during their second and third trimesters of pregnancy with Plasmodium falciparum parasitaemia in Sub-Saharan Africa.

The, investigational fixed-dose combination product AZCQ used in these studies is neither commercially available nor is proposed as a standard therapy for HCPs to prescribe. The outcomes described for the patients enrolled in these studies are specific to this combination therapy and are relevant neither to the monotherapy product nor to its approved indications of use. Moreover, neither efficacy nor safety endpoints could be attributed to the individual components of the combination product.
Additionally, neither of the completed studies enrolled the targeted number of patients due to premature study termination. Study A0661201 was a single arm, non-comparative estimation

study (target sample size 166) and was not powered for formal hypothesis testing. In Study A0661158, which had a target sample size of 5,044 subjects, a pre-specified interim analysis was conducted in this study following completion of pregnancy outcome in the first 35% of subjects; results of this analysis demonstrated that achieving a statistically significant reduction in risk in the AZCQ treatment group compared to SP, for the primary endpoint, would be unlikely if the study were to continue to full enrolment of subjects. Based on the results of this analysis, both of these studies (A0661201 and A0661158) were terminated prematurely. Furthermore it was noted from the conclusion in the assessment report that the PK data obtained from Study A0661201 (concentration data of serum azithromycin, plasma CQ, and plasma desethylchloroquine) exhibited large coefficient of variation values and as a result was to be interpreted with caution. Therefore, the conclusions that can be drawn from these data are not sufficient to support an update to the label.

It should also be noted that the fixed dose combination of AZCQ was developed specifically to support the malaria clinical trial program, and it was available for the Pfizer program only when it was ongoing. It is therefore not intended for general use by practitioners or patients. All of the pharmacokinetics (PK) results reported in the MAH study 066 1201 conducted in pregnant women with asymptomatic P. falciparum malaria is based upon the fixed dose combination product.

Moreover, no pharmacokinetic studies to confirm and define the bio-equivalence of the fixed dose combination have been conducted, this precluding final assessment on the bioavailability achieved when azithromycin and chloroquine standard formulations are administered to patients separately.
The MAH is therefore concerned that since the bioequivalence has not been confirmed, it is unreasonable to extrapolate the PK results of the 1201 study. Accordingly, Pharmacokinetic data derived from the 1201 study are not clinically relevant and not appropriate for inclusion in *the* SmPC.

Current EU SmPCs contain the same contextual message on pregnancy and lactation as the Company's Core Data Sheet (CDS) which is reproduced below.

> **"4.6. Fertility, pregnancy and lactation Pregnancy**
> Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed."

The MAH considers that these studies do not provide relevant information to the prescriber and therefore proposes not to update this section.
Current UK malaria treatment guidelines[11] for infection prevention in travelers recommend that pregnant women be treated with chloroquine and proguanil (in any trimester) or mefloquine (in the second and third trimesters), and do not include azithromycin in combination with other antimalarials. Finally, UK as well as WHO guidelines[12] recommend to treat uncomplicated P. falciparum infection with an artesimin-based combination, this reinforcing that AZCQ is not an alternative option, especially in pregnant women, in line with the ineffectiveness data that led to the program discontinuation.
In light of the above considerations, the MAH does not consider that an update to the SmPC is warranted.

Rapporteur's comments

The reasoning of the MAH is acknowledged:
a) data that can be retrieved from the mentioned studies (*Study A0661158* and *Study A0661201*) concerns the use of a fixed-dose combination product AZCQ and the outcomes/results (either efficacy or safety) cannot be extrapolated for the individual components of the combination product. Also it is noted that neither the studies were finalized (proposed patient enrolment numbers were not reached). PK data retrieved from this study also exhibited large coefficient of variation values.

b) the studied combination was specifically developed for this program, will not be commercially available/no longer is produced;

c) there is a very low probability for the off-label use of azithromycin-chloroquine in this indication, considering all available guidelines and standard of care. This is even less probable for pregnant women for whom specific recommendations on the most adequate regimen (not including azithromycin) exist and a caution sign for use of azithromycin in pregnancy is already reflected in the SmPC.

So, although the inclusion of information regarding study results on non-authorised indications in the SmPC may be warranted, in fact the available results will probably not be the most adequate to address azithromycin use in pregnant women, as the impact of this drug use in this specific population will not be possible to isolate, considering the use of the combination.

Finally, the MAH claim that an update to the SmPC is not warranted is endorsed.

b) In light of the conflicting results of the presented studies on the efficacy of Azithromycin in the studied indication, the MAH is requested to better review all available efficacy results of azithromycin monotherapy or azithromycin-chloroquine combination for the treatment of P.falciparum infection in the paediatric population to conclude whether clinically relevant results should be included in Section 5.1 of the SmPC for this indication.
If finally the information collected supports its inclusion in the SmPC than a proposal of the text to be added should be submitted by the MAH.

MAH's Response

With regard to the above, the MAH has performed a comprehensive literature search of publications reporting on the use of azithromycin monotherapy and azithromycin combination therapy for treatment of P. falciparum malaria in children and pregnant women, including one meta-analysis and a review of current treatment guidelines. It has no further internal data to those supplied in the original Article 46 submission of June 2015.

Literature Review

In Sub-Saharan Africa most severe cases of malaria and deaths from malaria occur in children younger than five years and in pregnant women.

> Reference: Fairhurst RM, Wellems TE Malaria (*Plasmodium* species) Chapter 276– Principles and Practice of Infectious diseases, Mandell, Douglas & Bennett , 8th edition – Elsevier Saunders Publishers-2014

The following is a summary of results from clinical trials involving azithromycin monotherapy or combination therapy for uncomplicated *P. falciparum* malaria in pediatric and adolescent patients. Each of the citations will be provided separately.

Na-Bangchang et al[i] reported that cure rates in pediatric and adult patients (15-49 yrs) in Mae Sot, Tak Province (Thai-Myanmar border) with uncomplicated P. falciparum malaria treated with an artemether-azithromycin regimen compared with an artemether-doxycycline regimen were statistically significantly lower (14.8% vs 53.3%). The authors also reported higher rates of the reappearance of parasitemia in the artemether + azithromycin treatment group (60% vs 45%) between days 10 and 22.

Krudwood et al[i] studied Thai patients 15 yrs and older with uncomplicated *P. falciparum* malaria. The authors compared a regimen of dihydroartemisinin + azithromycin vs dihydroartemisin + mefloquine. The 28 day cure rate was 69.7% for the dihydroartemisinin + azithromycin regimen vs 100% for the dihydroartemisinin + mefloquine regimen.

In an earlier study conducted in Bangkok, Krudswood et al[ii] compared three regimens: artesunate vs artesunate + mefloquine vs artesunate + azithromycin in patients 14 yrs and older. In patients with high level parasitemia (>15,000), who received the (artesunate + azithromycin regimen, there was a 2-fold increased risk for the development of Level 1 drug resistance (95% CI, 1.06-3.58; p = 0.03). (Level 1 drug resistance was defined as the absence of parasitemia at day 7 and the reappearance of parasites in the peripheral blood within 28 days).

Thriemer et al[iii] conducted a Phase II/III trial which enrolled 228 Bangladeshi patients between the ages of 8 and 65 years. The authors compared a regimen of azithromycin + artesunate vs artemether + lumefantrine. The cure rates at day 42 were (94.6% vs 97%), respectively. The differences were not statistically significant. There were however 8/107 cases of late treatment failure in the azithromycin + artesunate group compared to 2/55 cases of late treatment failure in the artemether + lumefantrine group.

Thanh et al[iv] studied 74 patients which included 24 children (ages 6-14 yrs) in Vietnam with uncomplicated *P falciparum* malaria. They compared a regimen of artesunate monotherapy with a regimen of artesunate + azithromycin. The 42 day cure rates were 91% in both groups.
Marko et al[v] compared chloroquine monotherapy with azithromycin monotherapy in 33 patients aged 15-75 years in Jabalpur, India with uncomplicated *P falciparum* malaria and noted equivalent cure rates.

In a second study Marko et al[vi] compared three regimens in a total of 50 patients aged 15-65 years in Jabalpur, India with uncomplicated *P falciparum* malaria. They compared chloroquine monotherapy vs azithromycin monotherapy vs chloroquine + azithromycin. The efficacy results in all three arms of the study were equivalent.

Chandra et al[vii] conducted a phase II/III randomized multicentre open label study comparing a fixed dose combination of azithromycin + chloroquine with artemether + lumefantrine in 255 hospitalized children aged 6 months-12 years. Patients were enrolled from Burkina Faso, Kenya, Ghana, Mali, and Ivory Coast. Day 28 cure rates in the Modified Intent to Treat (MITT) population were 89% vs 98% respectively. Parasitemia clearance rates were 80% vs 90%. The pre-defined non-inferiority end point was not achieved.

Zhao et al[viii] pooled pharmacokinetics of azithromycin + chloroquine vs artemether + lumefantrine data from a study treating children (6 mos -12 yrs) with uncomplicated *P. falciparum* malaria in sub-Saharan Africa and a bioavailability study in healthy U.S. adult volunteers. They concluded that drug clearance in children exceeded that in adults on a weight normalized basis.

Kalilani et al (2007)[ix] conducted a randomised, open-label, pilot study in Blantyre, Malawi to compare the safety and efficacy of SP + azithromycin or SP + artesunate with SP monotherapy in 141 pregnant women with uncomplicated *P. falciparum* malaria, aged 15 to 49 years. The SP + azithromycin or SP + artesunate was well tolerated and more efficacious than SP monotherapy in treating and preventing symptomatic malaria in pregnant women.

Salman et al (2010)[x] investigated the pharmacokinetic properties of AZCQ or SP + azithromycin in pregnant and non-pregnant women from an area of Papua New Guinea with intense transmission of both *P. falciparum* and *P. vivax* malaria. A total of 31 pregnant and 29 non-pregnant women were recruited and received 2 doses of azithromycin (2 g; both at enrolment and after 24 hours). Subjects were also randomised at enrolment to receive either single-dose sulphadoxine-pyrimethamine (1500 mg or 75 mg) or chloroquine (450 mg base daily for 3 days). The most common side effects of azithromycin, especially with higher doses, were nausea and vomiting. Plasma azithromycin concentrations appeared to differ between pregnant and non-pregnant women only in the first 48 hours after the first dose, which suggested that the drug elimination and overall exposures were similar in the 2 groups. Although there was a significant increase in azithromycin volumes of distribution of the central (V_C/F) in pregnant women, there was no significant change in the $AUC_{0-\infty}$, and it is, therefore, likely that no dose adjustments will be required for pregnant women when azithromycin is given in combination with chloroquine or sulphadoxine-pyrimethamine.

<u>Meta-Analysis</u>
In addition to the literature search which was focused primarily on the identification of publications involving children and pregnant women, the MAH has also summarized the results of a meta-analysis authored by van Eijk and Terlouw published in 2011 by the Cochrane group which pooled results from 15 clinical trials involving 2,284 participants (16%) children. The 15 trials were conducted in malaria endemic areas of Asia, Africa and South America.
- Three-day azithromycin (AZ) monotherapy did not perform well for *P. vivax* or *P. falciparum*

- Thailand
    - *P. vivax* failure rate with 0.5 g daily, 56% (95% CI = 31 to 78)
- India
    - *P. vivax* failure rate with 1 g daily,12% (95% CI = 7 to 21)
    - *P. falciparum* failure rate with 1 g daily, 64% (95% CI = 36 to 86)

- A 1 g azithromycin and 0.6 g chloroquine combination daily for three days for uncomplicated *P. falciparum* infections was associated with increased treatment failure in India and Indonesia compared with the combination of sulphadoxine-pyrimethamine and chloroquine (pooled RR 2.66, 95% CI = 1.25 to 5.67), and compared with the combination atovaquone-proguanil in a multicentre trial in Columbia and Surinam (RR 24.72, 95% CI = 6.16 to 99.20).

- No increased risk of treatment failure was seen in two studies in Africa with mefloquine as the comparator drug (pooled RR 2.02, 95% CI = 0.51 to 7.96, P = 0.3); the pooled RR for PCR-corrected data for the combination versus mefloquine was 1.01, 95% CI 0.18 to 5.84 (P = 1.0). An increased treatment failure risk was seen when comparing azithromycin in a dose of 1.2 to 1.5 g in combination with artesunate (200 mg per day for three days) with artemether + lumefantrine (pooled RR 3.08, 95% CI 2.09 to 4.55; PCR-corrected pooled RR 3.63, 95% CI 2.02 to 6.52).

- Serious adverse events and treatment discontinuation were similar across treatment arms.

The authors felt based on the results of the meta-analysis that there is no evidence for the superiority or equivalence of azithromycin monotherapy or azithromycin as part of a combination therapy for the treatment of *P. falciparum* or *P. vivax* compared with the current first-line antimalarial combinations. The authors go on to state that the available evidence suggests that azithromycin is a "weak antimalarial with some appealing safety characteristics."

Although azithromycin monotherapy was equivalent to chloroquine monotherapy in the treatment of children with uncomplicated *P. falciparum*, azithromycin combination therapy regimens were inferior to regimens which included artemether + doxycycline, artesunate + mefloquine and dihydroartemisinin + mefloquine. The azithromycin + artesunate combination was equivalent to an artemether + lumefantrine regimen at 42 days (94.6% vs 97%); however there were a larger number of late treatment failures reported associated with the azithromycin combination.

The current UK [11], and WHO guidelines[12] for the treatment of malaria do not include azithromycin either as a 1st line or alternative therapy for children, pregnant women or adults. Moreover, azithromycin is not indicated for the treatment or for the prevention of malaria.

Conclusion

In summary, the results of the literature review and the meta- analysis published by the Cochrane Group in 2011 do not provide support for the use of azithromycin either as monotherapy or in combination therapy for treatment of children or for pregnant women with *P falciparum* malaria. Based this review, the MAH has concluded there are no clinically relevant results that would warrant inclusion in Section 5.1 of the SmPC for this indication.

Rapporteur's comments

The results of this literature revision (with almost all studies having been conducted in Asia and Africa) and Cochrane Group revision are welcomed. It seems clear that currently available results, as the ones from the studies being revised in this procedure, do not provide support for

the use of azithromycin as monotherapy nor in combination schemes for the treatment of children and pregnant women with *P falciparum* malaria.
These studies are considered a strong evidence for the non-use of azithromycin either as monotherapy or part of combine scheme for treating malaria.
This information, even being on a non-indication, could be included in the SmPC.
This inclusion should be considered if the risk of off-label use would be reasonable.
All available guidelines and the standard of care do not recommend its use, but the risk of off-label use still exists.

Consultation with the SmPC Advisory Group and Paediatric Committee

The SmPC Advisory Group and Paediatric Committee where consulted regarding inclusion in section 5.1 of non-use in children with malaria taking in account that azithromycin is not approved for treatment of malaria in the SmPC.

The SmPC Advisory Group considered that, as advised in the SmPC guideline, the results of all pharmacodynamics or efficacy studies conducted in children should be presented in Section 5.1, even if there is no authorised indication in any subset of the population (adult and paediatric populations), if the information is considered relevant to prescribers. The relevance of communicating results from completed paediatric studies and the need to warn healthcare professionals, depend on available evidence and expertise in the treatment of malaria. In this case, it may be useful to consider if the information may be of benefit to healthcare professionals when managing paediatric patients with malaria or to prevent misuse.

PDCO agreed with the inclusion of the information in the SmPC in this specific case, based on the evidence / robustness of the data being analysed and considering the current and continued investigational activity in the field evaluating azithromycin used in malaria.

VI. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

From the assessed studies that led to this procedure a new text should be included in section 5.1 of the SmPC:

5.1 Pharmacodynamic properties

"*Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.*"

A Type IB variation, usually, should be submitted within 30 days after the end of the procedure, in order to update the SmPC, with the text proposed in section 5.1.
However, the Rapporteur has agreed with the Applicant request for submission of the Type IB variation until 31st January 2019, to allow the submission as a worksharing.

[i] Krudsood S, Buchachart K, Chalermrut K, et al. A comparative clinical trial of combinations of dihydroartemisinin plus azithromycin and dihydroartemisinin plus mefloquine for treatment of multidrug resistant falciparum malaria. Southeast Asian J Trop Med Public Health 2002;33(3):525-31.

[ii] Krudsood S, Silachamroon U, Wilairatana P, et al. A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated plasmodium falciparum malaria in Thailand. Southeast Asian J Trop Med Public Health 2000;31(4):801-7.

[iii] Thriemer K, Starzengruber P, Khan WA, et al. Azithromycin combination therapy for the treatment of uncomplicated falciparum malaria: Preliminary results from an open label randomized controlled trial in Bangladesh. Am J Trop Med Hyg 2007;77(5):182.

[iv] Thanh NX, Trung TN, Phong NC, et al. Efficacy of artesunate and artesunate-azithromycin for the treatment of uncomplicated *Plasmodium falciparum* malaria in Vietnam. Am J Trop Med Hyg 2012;87(5 Suppl 1):97.

[v] Marko JL, Pandey SP, Chourishi A. A comparative study of efficacy of azithromycin and chloroquine for the treatment of uncomplicated falciparum malaria. Int J Pharm Pharm Sci 2011;3(3):221-4.

[vi] Marko JL, Chourishi A, Pandey SP. Comparison of efficacy of chloroquine alone, azithromycin alone, and chloroquine azithromycin combination for the treatment of uncomplicated *Plasmodium falciparum* malaria. Int J Pharm Sci Rev Res 2011;11(1):7-12.

[vii] Chandra R, Ansah P, Samara I, et al. Comparison of azithromycin plus chloroquine versus artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in children in Africa: A randomized, open-label study. Malar J 2015;14(108):1-10.

[viii] Zhao Q, Tensfeldt TG, Chandra R, et al. Population pharmacokinetics of azithromycin and chloroquine in healthy adults and paediatric malaria subjects following oral administration of fixed-dose azithromycin and chloroquine combination tablets. Malar J 2014;13:36.

[ix] Kalilani L, Mofolo I, Chaponda M, et al. A randomized controlled pilot trial of azithromycin or artesunate added to sulfadoxine-pyrimethamine as treatment for malaria in pregnant women. PLoS ONE [Electronic Resource] 2007;2(11):e1166.

[x] Salman S, Rogerson SJ, Kose K, et al. Pharmacokinetic properties of azithromycin in pregnancy. Antimicrob Agents Chemother 2010;54(1):360-6.

[11] UK malaria treatment guidelines David G. Lalloo et al British Infection Society Journal of Infection (2007) 54, 111-121 December 2008

[12] GUIDELINES FOR THE TREATMENT OF MALARIA: WORLD HEALTH ORGANISATION (WHO) 3rd Edition 2015

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC).EUROPEAN COMMISSION ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL.September 2009. http://ec.europa.eu/health/files/eudralex/vol2/c/smpc_guideline_rev2_en.pdf

UK malaria treatment guidelines David G. Lalloo et al British Infection Society Journal of Infection (2007) 54, 111-121 December 2008

1. SUMMARY

The table below provides a detailed break-up of the relevant publications included in the literature review.

Author Name (Year of Publication)	Title	Journal Name	
Paediatric Patients With *P. falciparum* Malaria			
Na-Bangchang et al (1996)	Activity of artemether-azithromycin versus artemether-doxycycline in the treatment of multiple drug resistant falciparum malaria.	The Southeast Asian journal of Tropical Medicine and Public Health	
Krudsood et al (2000)	A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated plasmodium falciparum malaria in Thailand.	The Southeast Asian journal of Tropical Medicine and Public Health	
Krudsood et al (2002)	A comparative clinical trial of combinations of dihydroartemisinin plus azithromycin and dihydroartemisinin plus mefloquine for treatment of multidrug resistant falciparum malaria.	The Southeast Asian Journal of Tropical Medicine and Public Health	

Thriemer et al (2007 and 2010)	Azithromycin combination therapy for the treatment of uncomplicated falciparum malaria: Preliminary results from an open label randomized controlled trial in Bangladesh.	American Journal of Tropical Medicine & Hygiene	
Marko et al (2011)	A comparative study of efficacy of azithromycin and chloroquine for the treatment of uncomplicated falciparum malaria.	International Journal of Pharmaceutical Sciences Review and Research	
Marko et al (2011)	Comparison of efficacy of chloroquine alone, azithromycin alone, and chloroquine azithromycin combination for the treatment of uncomplicated Plasmodium Falciparum Malaria.	International Journal of Pharmaceutical Sciences Review and Research	
Thanh et al (2012)	Efficacy of artesunate and artesunate-azithromycin for the treatment of uncomplicated plasmodium falciparum malaria in Vietnam.	American Journal of Tropical Medicine and Hygiene	
Zhao et al (2014)	Population pharmacokinetics of azithromycin and chloroquine in healthy adults and paediatric malaria subjects following oral administration of fixed-dose azithromycin and chloroquine combination tablets.	Malaria Journal	

Chandra et al (2015)	Comparison of azithromycin plus chloroquine versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in children in Africa: a randomized, open-label study.	Malaria Journal	
Pregnant Women With *P. falciparum* Malaria			
Kalilani et al (2007)	A randomized controlled pilot trial of azithromycin or artesunate added to sulfadoxine-pyrimethamine as treatment for malaria in pregnant women.	PLoS ONE	
Salman et al (2010)	Pharmacokinetic Properties of Azithromycin in Pregnancy.	Antimicrobial Agents & Chemotherapy	