Study Summary Report
'Sample Vivax Study'

Automated report generated
by WWARN

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Vivax Report

Contents

List of Tables

List of Figures

Introduction

The emergence and spread of antimalarial drug resistance is one of the most important factors undermining malaria control programmes in most of the malaria endemic world. Following World Health Organization (WHO) recommendations, more than 80 countries have now adopted artemisinin-based combination therapies (ACT) as first line treatment policy for uncomplicated malaria. Changing national policy in resource-poor settings has huge financial and practical implications and the debate continues as to which are the most suitable combinations and how these new treatments should be deployed and funded. In this context, it becomes of paramount importance to policy makers, funding bodies and researchers alike, to document the clinical efficacy of older drugs now being combined with artemisinins and to monitor the continued efficacy of newly deployed antimalarial regimens.

The Worldwide Antimalarial Resistance Network (WWARN) is establishing a comprehensive clinical database from which standardised estimates of antimalarial efficacy can be derived and monitored over time from diverse geographical and endemic regions.

The data generated from this study were uploaded into WWARN's online resource transformed and analysed using standardised methodology and an automated process. The aim of this system is to ensure that the estimates of clinical drug efficacy are derived in uniform manner so that they can be compared over time with studies conducted at the same site and with other studies conducted at different locations.

Most clinical efficacy studies follow the design laid out in the WHO guidelines (World Health Organization (WHO), Methods for surveillance of antimalarial drug efficacy, 2009), although some studies modify the design to address local logistical or research considerations. The application of a standard approach to manage deviations helps to minimise the bias of original study design when comparing between different studies. Full details of this approach are available in the Clinical Module Data management and statistical analytical plan (DMSAP) available at www.wwarn.org/research/clinical/methodology.

Variables in the submitted data were extracted and transformed into a standard format. Specific details of data extraction and transformation are available in the DMSAP. Data were checked for inconsistencies, unexpected values and missing values. These data points were corrected from source documents or if this was not possible the inconsistencies and unexpected values were transformed to missing.

The study population defined for the efficacy analysis was restricted to patients with uncomplicated malaria. Hence any patients with the following criteria were excluded:

- Hb <5g/dL on day 0
- Ht < 15% on day 0
- Severe anaemia variable labelled as "Yes" on day 0
- Hyperparasitaemia, defined as parasite density > $250000/\mu L$

PCR-correct and uncorrected cure rates at different time points were assessed. Time to failure was estimated with the Kaplan-Meier method. Patients with incomplete follow up or more than

18 days between consecutive blood smear results were censored on the last day of follow up. If a patient had multiple deviations at different times the first deviation to occur was used in survival analysis. Parasite clearance was reported as the proportion of patients with parasitaemia on days 1-4 following the start of treatment.

In the analysis of P. falciparum treatment failure, all patients enrolled with P. falciparum infection (either alone or mixed species infection) were included in the analysis. The unadjusted and adjusted risk of treatment failure of P. falciparum is presented for each drug regimen studied.

In the **unadjusted analysis** the following are considered as treatment failures:

- Early treatment failures according to the WHO guidelines
- Any recurrent P. falciparum parasitaemia after day 4 until the end of the follow-up period

In the **adjusted analysis** the following are considered as treatment failures:

- Early treatment failures according to the WHO guidelines
- P. falciparum parasitaemia between 4 and 6 days after treatment.
- Late treatment failure (late clinical failure or late parasitological failure) after day 6 with P. falciparum (alone or mixed) with PCR-confirmation of recrudescence.

Where mixed infections were included in a study, efficacy estimates were derived from patient data according to the following table when 0=censored, 1=failure and -=not included in the analysis.

P.*falciparum* efficacy estimates:

Table 1: P.*falciparum* efficacy estimates

Day 0 species	Day of failure species	PCR	PfAdj*	PfUnadj*
Pf	Pf	Recrudescence	1	1
Pf	Pf	Reinfection	0	1
Pf	Pf	No PCR	-	1
Pf	Pf + Other	Recrudescence	1	1
Pf	Pf + Other	Reinfection	0	1
Pf	Pf + Other	No PCR	-	1
Pf	No Pf	-	0	0
Pf + Other	Pf	Recrudescence	1	1
Pf + Other	Pf	Reinfection	0	1
Pf + Other	Pf	No PCR	-	1
Pf + Other	Pf + Other	Recrudescence	1	1
Pf + Other	Pf + Other	Reinfection	0	1
Pf + Other	Pf + Other	No PCR	-	1
Pf + Other	No Pf	-	0	0

P.*vivax* efficacy estimates:

Table 2: P.*vivax* efficacy estimates

Day 0 species	Day of failure species	Pv*
Pv	Pv	1
Pv	Pv + other	1
Pv	No Pv	0
Pv + other	Pv	1
Pv + other	Pv + other	1
Pv + other	No Pv	0

1 Study design, description of datasets and key variables

This study was conducted in [Asia]. This study started on 2012-06-01 and ended on 2012-12-31.

In the submitted dataset(s), 335 patients were treated with AS3+AQ and DHA+PQP with a follow-up period of 42 days. 168 patients were allocated AS3+AQ and 167 patients were allocated DHA+PQP .

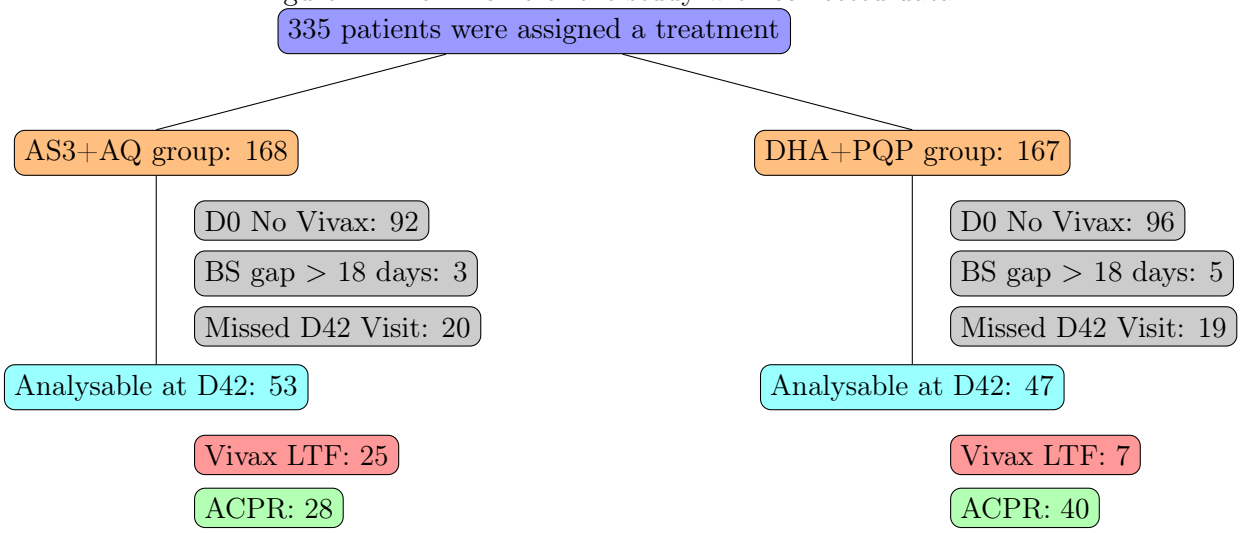
2 Outputs

The following outputs have been produced from the submitted data using the WWARN standard analysis procedures (please refer to the WWARN DMSAP in our website at www.wwarn.org/research/clinical/methodology).

2.1 Trial Profile

The trial profile summarizes participant flow, with numbers of randomization assignment, treatment group, and outcomes for each randomized group.

Figure 1: Trial Profile of the study with corrected data



2.2 Baseline Characteristics

The baseline characteristic tables below summarise key features of the trial population in the submitted dataset(s).

Table 3: Baseline Characteristics without data correction

	AS3+AQ (n=168)	DHA+PQP (n=167)
Median Age (IQR)	$14.0 years (21.5)$	$17.0 years (23.0)$
Gender (% Male)	56.50%	59.80%
Fever* (%)	30.30%	33.50%
Median weight (IQR)	$43.1 kg (36.0)$	$46.4 kg (35.8)$
Geom. Mean P.*falc* (IQR)	$4187/\mu L (7837)$	$4928/\mu L (9600)$
Geom. Mean P.*vivax* (IQR)	$1743/\mu L (1650)$	$986/\mu L (690)$
Proportion $\geq$ 100,000 para/μL	0.60%	0.60%
Gametocyte Carriage	10.10%	10.70%
Mean Hb (SD)	$10.80 g/dL (2.60)$	$11.10 g/dL (2.60)$

*Fever defined as temperature $\geq$37.5 ° C

2.3 Treatment Outcome

The parasite clearance rate measures the percentage of remaining parasites at Day1, Day2 and Day3. Missing parasitaemia were considered negative if they were negative earlier . The parasitaemia clearance were as follows:

- For 'AS3+AQ':
  - 13.41 % (22/ 164) on Day1
  - 0.61 % (1/ 163) on Day2
  - 0.00 % (0/ 163) on Day3

- For 'DHA+PQP':
  - 17.83 % (28/ 157) on Day1
  - 0.64 % (1/ 156) on Day2
  - 0.62 % (1/ 162) on Day3

The following treatment outcomes were classified on the basis of an assessment of the parasitological and clinical outcome of antimalarial treatment according to the latest WHO guidelines (WHO Methods for surveillance of antimalarial drug efficacy, 2009)

2.3.1 At D28

Table 4: Outcome table, PCR-unadjusted and with data correction at day 28

	AS3+AQ (n=168)	DHA+PQP (n=167)
ACPR	46	50
BS gap > 18 days	3	4
D0 No Vivax	92	96
Missed D28 Visit	15	14
Vivax LTF	12	3

2.3.2 At D42

Table 5: Outcome table, PCR-unadjusted and with data correction at day 42

	AS3+AQ (n=168)	DHA+PQP (n=167)
ACPR	28	40
BS gap > 18 days	3	5
D0 No Vivax	92	96
Missed D42 Visit	20	19
Vivax LTF	25	7

2.4 Kaplan Meier Curves and Lifetables

Cure rates are described by Kaplan Meier estimates where the y-axis represents cumulative risk of recurrent parasitemia calculated by survival analysis. The WHO recommends the Kaplan Meier method for deriving estimates of clinical drug efficacy (WHO Methods for surveillance of antimalarial drug efficacy, 2009, pg. 7.). In the PCR adjusted results recurrent infections are only regarded as treatment failures when the infection has been confirmed to be a recrudescence based on PCR result (see WHO methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations). In this method new infections are censored on the day of recurrence. When PCR results are unavailable recurrent P. falciparum infections are censored.
The life tables presented below each survival curve summarize the survival analysis results.

Figure 2: Kaplan Meier curve, PCR-unadjusted and with data correction

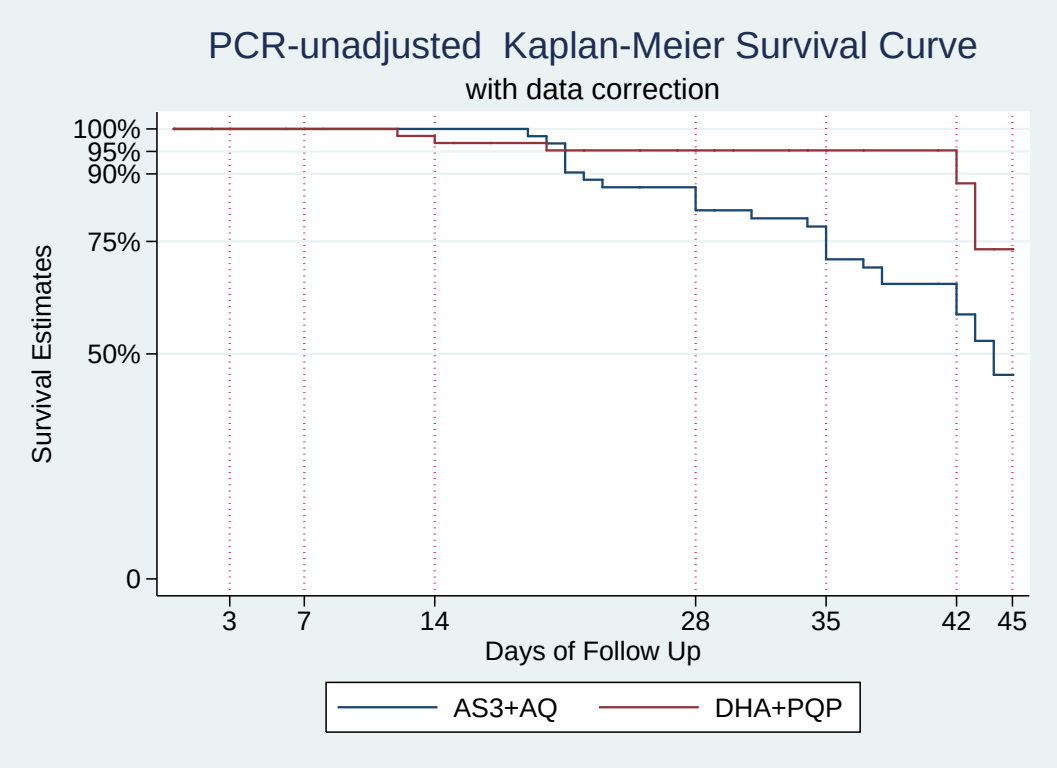


Table 6: PCR unadjusted outcomes with data correction

Day	Population	Estimate	95% CI
AS3+AQ (N=168)			
Day28	51	**0.819**	(0.697-0.896)
Day42	29	**0.588**	(0.444-0.706)
DHA+PQP (N=167)			
Day28	52	**0.952**	(0.859-0.984)
Day42	39	**0.879**	(0.746-0.945)

3 Conclusion

The following conclusions are at Day 42. Using WWARN analytical methods the Kaplan-Meier survival estimates are 58.8% (95% CI (44.4-70.6)) in the AS3+AQ group (N=168), 87.9% (95% CI (74.6-94.5)) in the DHA+PQP group (N=167).