# THE LANCET

## Supplementary appendix

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Supplement to: Taylor WRJ, Thriemer K, von Seidlein L, et al. Short-course primaquine for the radical cure of *Plasmodium vivax* malaria: a multicentre, randomised, placebo-controlled non-inferiority trial. *Lancet* 2019; published online July 18. http://dx.doi.org/10.1016/S0140-6736(19)31285-1.

## **Supplementary Appendices**

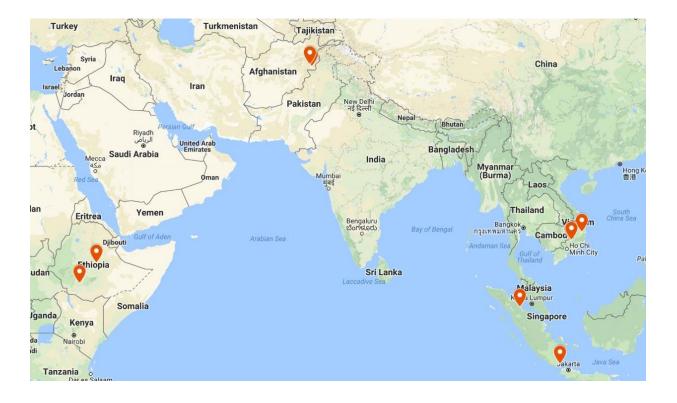
Supplement to: Short course primaquine for the radical cure of Plasmodium vivax malaria: a randomised placebo-controlled multicentre trial

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## 1. Map of Study Sites



### 2. Information About Study Sites

	Afgha	nistan	Ethiopia		Indonesia		Vietnam	
Site Name	Jalalabad	Laghman	Arba Minch	Metahara	Hanura	Tanjung Leidong	Dak O & Bu Gia Map	Krong Pa
Site Code	AF001	AF008	ET001	ET002	ID004	ID005	VN001	VN002
Name of study center	Speen-Ghar Teaching Hospital	Laghman, Mihterlam hospital	Arba Minch Hospital	Metehara Sugar Factory Hospital	Hanura Primary Health Center	Tanjung Leidong	Dak-O & Bu Gia Map Commune Health Stations	Krong Pa Medical Center
Study center GPS coordinates	34.4344/ 70.4612	34.6891/         6.025204/           70.1467         37.556696		8.8875/ 39.9169444	-5.320619/ 105.622958	2.698056/ 99.901667	12.047594/ 107.093178	13.221819/ 108.682475
Altitude above sea level	575 m	779m	1285m	946 m	15 – 65 m	5m	338-408 m	136 m
Treatment policy (incl. G6PD testing)	Pf: AL+PQ (single dose 0.25 mg/kg) Pv: CQ+PQ (0.25 mg/kg for 14 days) G6Pd testing recommended. If not available, weekly PQ course recommended		Pf: AL+PQ (single dose 0.25 mg/kg) Pv: CQ+PQ (0.25 mg/kg for 14 days) G6PD testing not explicitly recommended		<ul> <li>Pf: DHP+PQ (single dose 0.25 mg/kg)</li> <li>Pv: DHP+PQ (0.25 mg/kg for 14 days).</li> <li>G6PD testing not explicitly recommended</li> </ul>		<ul> <li>Pf: DHP+PQ (single dose 0.25 mg/kg)</li> <li>Pv: CQ+PQ</li> <li>(0.25 mg/kg for 14 days)</li> <li>G6PD testing not explicitly recommended</li> </ul>	
G6PD prevalence and variants	Mediterranean variant 7% in many ethnic groups <sup>1</sup>	Mediterranean variant 7% in many ethnic groups <sup>1</sup>	Unknown, likely A- and Mediterranean	Unknown, likely A- and Mediterranean	Unknown	2.7%, Mahidol variant <sup>2</sup>	Vientiane & Mahidol (Kinh = 2% Ethnic minorities: 10%) <sup>3</sup>	Vientiane & Mahidol (Kinh = 2% Ethnic minorities: 10%) <sup>3</sup>

<sup>&</sup>lt;sup>1</sup> Jamornthanyawat N, Awab GR, Tanomsing N, *et al* A Population Survey of the Glucose-6-Phosphate Dehydrogenase (G6PD) 563C>T (Mediterranean) Mutation in Afghanistan. *PLoS One* 2014; 9(2):e88605.

<sup>&</sup>lt;sup>2</sup> Pasaribu AP, Chokejindachai W, Sirivichayakul C, *et al.* A randomised comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine for radical treatment of vivax malaria in Sumatera, Indonesia. *J Infect Dis* 2013 ;208(11):1906-13. doi: 10.1093/infdis/jit407.

<sup>&</sup>lt;sup>3</sup> Personal communication Hien Tran Tinh

Approx. catchment population of study center	356,274	100,000	164,529	22,0259 <sup>7</sup>	35,692	21,191	22,000	70,000
Seasonality of malaria	May to Nov (peak in summer /July), Pf is confined to Oct-Nov)	May to Nov (peak in summer /July), Pf is confined to Oct-Nov)	Year round with peak at Dec- Feb	Peak malaria Sept-October, smaller season April	Peak season November and march	Year round, peak between July- December	Peak malaria season October to April	Peak malaria season October to January
P.v./ P.f. ratio	95:5	90:10	30:70	40:60 <sup>7</sup>	40:60 <sup>4</sup>	95:5	40:60	40:60
Relapse periodicity			3-5 months <sup>5</sup>	3-5 months <sup>5</sup>	3 months	3 months	45 days	3 months
Vectors	An. stephensi An. culicifacies An. fluviatilus An. Annularis An. Pulcherrimus An. superpictus An. hycranus <sup>6</sup>	A. stephensi A. subpictusand A. culicifacies	A.arabiensis <sup>7</sup>	A.arabiensis <sup>7</sup>	A. sundaicus <sup>8</sup>	Not known, probably A. sundaicus	A. dirus A. minimus <sup>9</sup>	A. dirus A. minimus <sup>9</sup>
ΑΡΙ	3.5 per 1,000 per year <sup>10</sup>	1.62 per 1,000 per year	unknown	unknown	43.9 per 1,000 per year	49 per 1,000 per year <sup>11</sup>	50 per 1,000 year <sup>12</sup>	8.5 per 1,000 year <sup>12</sup>

<sup>4</sup> Based on screening data from within IMPROV study

<sup>&</sup>lt;sup>5</sup> Abreha T, Hwang J, Thriemer K, *et al*. Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of Plasmodium vivax infection in Ethiopia: A randomised controlled trial. *PLoS Med* 2017;14(5):e1002299. doi: 10.1371/journal.pmed.1002299

<sup>&</sup>lt;sup>6</sup> Rowland M, Mohammad N, Rehman H, et al. Anopheline vectors and malaria transmission in eastern Afghanistan. Trans. R. Soc. Trop. Med. Hyg. 2002; 15 (11): 17530-9.

<sup>&</sup>lt;sup>7</sup> Based on Federal democratic republic of Ethiopia population census commission, summary and statistical report of the 2007 population and housing census. 2008

<sup>&</sup>lt;sup>8</sup> Sukowati S, Shinta, Suwito, *et al*. Some aspect of behavior of Malaria vector Anopheles sundaicus (Theobald) in Lampung, Sumatera. *J Ekol Kesehat.* 2011;10(4):267–78.

<sup>&</sup>lt;sup>9</sup> Son DH, Thuy-Nhien N, von Seidlein L, *et al.* The prevalence, incidence and prevention of Plasmodium falciparum infections in forest rangers in Bu Gia Map National Park, Binh Phuoc province, Vietnam: a pilot study. *Malar J.* 2017; 16: 444.

<sup>&</sup>lt;sup>10</sup> Based on the national strategic plan for malaria control to elimination in Afghanistan 2018-2022 by the Ministry of Public Health, Afghanistan

<sup>&</sup>lt;sup>11</sup> Based on data from the Ministry of Health on annual parasite incidence (API) in 2016

<sup>&</sup>lt;sup>12</sup> Based on reports of the National Malaria Control Program (NMCP of Vietnam) in 2017

## 3. List of Ethics Review Boards and Regulatory Agencies

Australia	The Human Research Ethics Committee of the Northern Territory Department of
	Health (HREC)
	John Mathews Building (Bldg 58)
	Royal Darwin Hospital Campus, Rock
	PO Box: 41096, Casuarina NT 0811, Australia
	Website: www.menzies.edu.au
United	The Oxford Tropical Research Ethics Committee (OxTREC)
Kingdom	University of Oxford
Kinguom	Research Services, University Offices
	Willington Square, Oxford OX1 2JD
	Tel: +44 (0) 1865 (2) 82106
	E-mail: oxtrec@admin.ox.ac.uk
	Website: www.admin.ox.ac.uk/rso/
Afghanistan	Islamic Republic of Afghanistan, Ministry of Public Health, Institutional Review
Ū	Board
	3 <sup>rd</sup> floor of Main Building of Ministry of Public Health
	Masoud Circle, Wazir Akbar Khan, Kabul-Afghanistan
	Tel: +93(0) 20 29 22 435
	email: anphi@moph.gov.af
Ethiopia	The National Research Ethics Review Committee (NRERC)
•	Addis Ababa, Ethiopia
	PO Box: 2490
	Tel: +251 114-674-353
	E-mail: most@ethionet.et
	Fax: +251 114-660-241
	Website: www.most.gov.et
	Scientific & Ethical Review Committee (SERC)
	Ethiopian Public Health Institute
	Addis Ababa, Ethiopia
	PO Box: 1242/5654
	E-mail: ephi@ethionet.et
	Tel: +251 11 2133499, +251 11 2751522
	Fax: +251 11 2758634
	Website: www.ephi.gov.et
	The Food Medicine and Health Care Administration and Control Authority
	(FMHACA)
	Addis Ababa, Ethiopia
	Tel: 251-11-552 41 22/552 41 23
	E-mail: regulatory@fmaca.gov.et
	Fax: 251-11-552 13 92
	PO Box: 5681

Indonesia	The Health Research Ethics Committee of the Faculty of Medicine University of Indonesia
	Cipto Mangunkusumo Hospital
	Jalan Salemba Raya No. 6, Jakarta Pusat 10430
	Tel: 021-3157008
	E-mail: ec_fkui@yahoo.com
	Indonesian Food and Drug Agency (BPOM)
	Jl, Percetakan Negara No. 23 Jakarta Pusat 10560 Indonesia
	E-mail: infopom@indo.net.id;
	Tel: (021) 4244691, 4209221, 4263333, 4244755, 4241781, 4244819
	Fax: (02) 4245139
	Website: www.pom.go.id
Vietnam	The Ministry of Health Evaluation Committee on Ethics in Biomedical Research
	138A Giang Vo Street, Ba Dinh District, Ha Noi, Viet Nam
	Email: iecmoh@gmail.com
	Tel: +84 4 6273 2156

### 4. Sample Size and Power Calculation

The primary aim of this trial was to demonstrate non-inferiority of a 7-day primaquine regimen to the standard 14-day primaquine regimen with respect to incidence rate of symptomatic vivax parasitaemia over 12 months. The sample size calculation was based on an assumed incidence rate of 0.2 infections per person-year in both arms, a non-inferiority margin of 0.07 infections per person-year and a one-sided significance level of 2.5%. Based on these assumptions, a total sample size of 1200 evaluable patients, randomly allocated to receive a primaquine regimen (600 patients in each treatment arm), followed for one year were calculated to provide a power of 80% to show non-inferiority or, equivalently, that the two-sided 95% confidence interval for the difference in incidence rate of malaria between the two arms excludes an excess rate of 0.07 infections per person-year or more in favour of the 14-day regimen.

A further 300 patients in the control arm were also followed for one year. With 300 patients in the control arm and 600 patients in each treatment arm (i.e. 75 controls and 150 patients in each treatment arm at each of the five study sites), the study had 95% power and 95% confidence to detect a difference (i.e. a superiority comparison of either regimen) at each of the study sites assuming an incidence rate of 0.2 infections per person-year in each of the treatment arms and 0.6 infections per person-year in the control arm (ranging from 0.2 in the Indian subcontinent and 1.0 in Vietnam and Indonesia). The combined proportion of losses to follow-up and major protocol violations was expected to be no more than 20%, so to account for this, a total of 1875 G6PD normal patients (750 per treatment arm; 375 in the control arm) were aimed to be randomised in this trial.

The inclusion of two additional sites in Ethiopia increased the sample size by 25% and increased the power to detect non-inferiority between the PQ7 and PQ14 arms to 86%, and the power to detect superiority between PQ7/PQ14 and placebo to 99.8%.

## 5. Primaquine Dosing of Tablets

Patient weight was rounded to the nearest integer

Weight Band	Weight/kg	PQ7	,	PQ14		
		1 mg/kg/day	mg/kg	0.5 mg/kg/day	mg/kg	
А	5 to 22	see suspension	dosing chart	see suspension dosing chart		
А	23-34	30	0.88 - 1.3	15	0.44 - 0.65	
В	35-45	45	1 - 1.29	22.5	0.5 - 0.64	
С	≥ 46	60	≤1.33	30	≤0.67	

## 6. Primaquine Suspension Dosing of Children Under 23 kgs

Weight	ml/day			ne Regimen ( red in 5ml syrup	-	<b>14 day Primaquine regimen (PQ14)</b> One 15mg tablet dissolved in 5ml syrup (1ml=3mg)				
		Daily dose in mg/day	Daily dose in mg/kg/day	Total dose in mg/kg	Total dose in mg	Daily dose in mg/day	Daily dose in mg/kg/day	Total dose in mg/kg	Total dose in mg	
5	0.8	4.8	0.96	6.72	33.6	2.4	0.48	6.72	33.6	
6	1	6	1	7	42	3	0.5	7	42	
7	1.2	7.2	1.03	7.2	50.4	3.6	0.51	7.2	50.4	
8	1.3	7.8	0.98	6.83	54.6	3.9	0.49	6.83	54.6	
9	1.5	9	1	7	63	4.5	0.5	7	63	
10	1.7	10.2	1.02	7.14	71.4	5.1	0.51	7.14	71.4	
11	1.8	10.8	0.98	6.87	75.6	5.4	0.49	6.87	75.6	
12	2	12	1	7	84	6	0.5	7	84	
13	2.2	13.2	1.02	7.11	92.4	6.6	0.51	7.11	92.4	
14	2.3	13.8	0.99	6.9	96.6	6.9	0.49	6.9	96.6	
15	2.5	15	1	7	105	7.5	0.5	7	105	
16	2.5	15	0.94	6.56	105	7.5	0.47	6.56	105	
17	3	18	1.06	7.41	126	9	0.53	7.4	126	
18	3	18	1	7	126	9	0.5	7	126	
19	3	18	0.95	6.63	126	9	0.47	6.63	126	
20	3	18	0.9	6.3	126	9	0.45	6.3	126	
21	3.5	21	1	7	147	10.5	0.5	7	147	
22	3.5	21	0.95	6.68	147	10.5	0.48	6.68	147	

## 7. Microscopy Quality Control Results

Standard thick (using 6  $\mu$ l blood on a 12 mm diameter template) and thin malaria films were prepared at each visit for Giemsa staining (3%, 40-50 min) according to procedures based on the Research Malaria Microscopy Standards.<sup>13</sup>

All sites	Readable slides with available data	4361	
combined	Slides with asexual parasitaemia	2603	59.7%
	P. falciparum	112	2.6%
	<i>P. falciparum</i> - mixed	26	0.6%
	Non-P. falciparum	2465	56.5%
	Negative (no asexual parasitaemia)	1480	33.9%
	Accuracy (%)	4281/4361	98.6%
	Parasite density discordance	1625	62.4%
	Overall sensitivity	2531/2603	97.2%
	Overall specificity	1471/1480	99.4%
	Kappa statistics for asexual parasite detection & species	0.93	[0.92 - 0.94]
AF001 Jalalabad	Readable slides with available data	447	
Jalalabaŭ	Slides with asexual parasitaemia	223	49.9%
	P. falciparum	4	0.9%
	P. falciparum - mixed	2	0.4%
	Non-P. falciparum	217	48.5%
	Negative (no asexual parasitaemia)	224	50.1%
	Accuracy (%)	415/447	92.8%
	Parasite density discordance	140	62.8%
	Overall sensitivity	192/223	86.1%
	Overall specificity	222/224	99.1%
	Kappa statistics for asexual parasite detection & species	0.82	[0.76 - 0.87]
AF008	Readable slides with available data	329	
Laghman	Slides with asexual parasitaemia	197	59.9%
	P. falciparum	0	0.0%
	<i>P. falciparum</i> - mixed	0	0.0%

<sup>&</sup>lt;sup>13</sup> WHO Special Programme for Research and Training in Tropical Diseases. Microscopy for the detection, identification and quantification of malaria parasites on stained thick and thin blood films in research settings, 2015. <u>https://www.who.int/tdr/publications/microscopy\_detec\_ident\_quantif/en/</u>

	Non-P. falciparum	197	59.9%
	Negative (no asexual parasitaemia)	132	40.1%
	Accuracy (%)	320/329	97.3%
	Parasite density discordance	152	77.2%
	Overall sensitivity	188/197	95.4%
	Overall specificity	132/132	100.0%
	Kappa statistics for asexual parasite detection & species	0.94	[0.90 - 0.98]
ET001	Readable slides with available data	826	
Arba Minch	Slides with asexual parasitaemia	335	40.6%
	P. falciparum	15	1.8%
	<i>P. falciparum</i> - mixed	3	0.4%
	Non-P. falciparum	317	38.4%
	Negative (no asexual parasitaemia)	224	27.1%
	Accuracy (%)	817/826	99.0%
	Parasite density discordance	158	47.2%
	Overall sensitivity	326/335	97.3%
	Overall specificity	224/224	100.0%
	Kappa statistics for asexual parasite detection & species	0.96	[0.93 - 0.98]
	_		
ET002	Readable slides with available data	340	
Metahara	Slides with asexual parasitaemia	211	62.1%
	P. falciparum	5	1.5%
	<i>P. falciparum</i> - mixed	0	0.0%
	Non-P. falciparum	206	60.6%
	Negative (no asexual parasitaemia)	118	34.7%
	Accuracy (%)	332/340	97.6%
	Parasite density discordance	80	37.9%
	Overall sensitivity	198/211	93.8%
	Overall specificity	118/118	100.0%
	Kappa statistics for asexual parasite detection & species	0.90	[0.85 - 0.95]
		1	
D004	Readable slides with available data	1117	
lanura	Slides with asexual parasitaemia	716	64.1%
	P. falciparum	37	3.3%
	P. falciparum - mixed	10	0.9%
	Non-P. falciparum	669	59.9%
	Negative (no asexual parasitaemia)	401	35.9%
	Accuracy (%)	1107/1117	99.1%

	Parasite density discordance	500/716	69.8%
	Overall sensitivity	709/716	99.0%
	Overall specificity	398/401	99.3%
	Kappa statistics for asexual parasite detection & species	0.92	[0.90 - 0.94]
	•		
ID005	Readable slides with available data	630	
Tanjung	Slides with asexual parasitaemia	376	59.7%
Leidong	P. falciparum	0	0.0%
	P. falciparum - mixed	0	0.0%
	Non-P. falciparum	376	59.7%
	Negative (no asexual parasitaemia)	254	40.3%
	Accuracy (%)	616/630	97.8%
	Parasite density discordance	295/376	78.5%
	Overall sensitivity	366/376	97.3%
	Overall specificity	250/254	98.4%
	Kappa statistics for asexual parasite detection & species	0.95	[0.93 - 0.98]
VN001	Readable slides with available data	485	
Dak O & Bu	Slides with asexual parasitaemia	295	60.8%
Gia Map	P. falciparum	26	5.4%
	<i>P. falciparum</i> - mixed	3	0.6%
	Non-P. falciparum	266	54.8%
	Negative (no asexual parasitaemia)	190	39.2%
	Accuracy (%)	484/485	99.8%
	Parasite density discordance	25	8.5%
	Overall sensitivity	295/295	100.0%
	Overall specificity	189/190	99.5%
	Kappa statistics for asexual parasite		
	detection & species	0.96	[0.94 - 0.98]
		1	
VN002	Readable slides with available data	187	
Krong Pa	Slides with asexual parasitaemia	109	58.3%
	P. falciparum	0	0.0%
	<i>P. falciparum</i> - mixed	0	0.0%
	Non-P. falciparum	109	58.3%
	Negative (no asexual parasitaemia)	78	41.7%
	Accuracy (%)	185/187	98.9%
	Parasite density discordance	27	24.8%
	Overall sensitivity	107/109	98.2%
	Overall specificity	78/78	100.0%
	Kappa statistics for asexual parasite	0.98	[0.95 - 1.00]
	detection & species		-

### 8. Statistical Methods

Full details of the Statistical Analysis Plan are available in the published protocol and associated supplementary files<sup>14</sup>.

All statistical analyses were performed using Stata v14 (StataCorp, College Station, TX, USA).

#### **Baseline characteristics**

Patient and disease characteristics at baseline were summarised by study arm using means [SD], medians (25<sup>th</sup> – 75<sup>th</sup> percentile), geometric mean [SD (log scale), 95% reference range] and frequencies (proportion).

#### Summary of efficacy endpoints

Efficacy endpoints including early treatment failure (recurrent parasitaemia within 3 days), and recurrence within 28, 42, and 365 days were summarised by treatment arm. The primary efficacy endpoint, incidence rate of symptomatic *P. vivax* recurrence, was calculated as the number of symptomatic *P. vivax* recurrences per person-year, with censoring at 365 days. This approach was also followed for the incidence rate of any (and symptomatic) *P. falciparum* and *P. spp* infections, and any *P. vivax* recurrences. Incidence risks of *P. vivax* considered only the first *P. vivax* recurrence (regardless of symptoms) and were calculated using the Kaplan-Meier method with censoring at the time of failure or a non-vivax infection, or at 28 days, 42 days, or 365 days. The same approach was applied for the incidence risks of symptomatic) *P. falciparum* recurrence, and any (and symptomatic) *P. spp* recurrence. The proportion of patients with patent *P. vivax* parasitaemia or fever on day one, two, and three following the initial enrolment treatment on day 0, and the proportion of patients with patent *P. falciparum* recurrence, was calculated by treatment arm.

#### **Efficacy endpoints**

To assess the primary efficacy endpoint for radical cure, the absolute incidence rate difference in symptomatic *P. vivax* recurrences (mono-infection or mixed) per person-year between the 7-day arm and the 14-day arm was estimated using weighted least squares regression with a robust standard error<sup>15</sup> [Xu et al. 2010], and a non-inferiority margin of 0.07 recurrences per person-year. To assess the secondary efficacy endpoints, incidence rate ratios were estimated using negative binomial regression (analysis of all recurrences), and cumulative incidence risks and hazard ratios were estimated using the Kaplan-Meier method and Cox regression (analysis of time to the first recurrence), with comparisons between the 7-day and control arms, the 14-day and control arms, and the 7-day and 14-day arms. The main analysis was done in the ITT (Intention to Treat) population; analyses were repeated in the PP (Per Protocol) population.

#### Further details on incidence rate analyses, including sensitivity analyses:

In the analysis of incidence rates (both differences and ratios), follow-up time began at enrolment and patients were censored at 365 days. The effect of post-treatment prophylaxis was assessed in a sensitivity

<sup>&</sup>lt;sup>14</sup> Improv Study Group. Improving the radical cure of vivax malaria (IMPROV): a study protocol for a multicentre randomised, placebo-controlled comparison of short and long course primaquine regimens. *BMC Infect Dis*, 2015; **15**: 558

<sup>&</sup>lt;sup>15</sup> Xu Y, Cheung YB, Lam KF, *et al.* A simple approach to the estimation of incidence rate difference. *Am J Epidemiol*. 2015; **172**(3):334-43.

analysis subtracting 28 days from a patient's follow-up time for each antimalarial treatment, irrespective of the drug. To determine the effect of providing open primaquine to all patients after the  $3^{rd}$  symptomatic *P. vivax* recurrence in Vietnam rather than after the  $4^{th}$  at other sites, two sensitivity analyses were performed – 1) excluding Vietnam; and 2) including Vietnam but censoring all patients at the time point of the  $3^{rd}$  recurrence at other sites.

#### Censoring

All analyses censored patients at the time of their last visit if they were lost to follow-up or if the intervention was discontinued. Patients were also censored from risk analyses on the day of initial parasitaemia (regardless of species or symptoms), on the day preceding a period of absence of 18 consecutive days prior to 42 days' follow-up, or two consecutive monthly visits after 42 days of follow-up. Additionally, schizontocidal efficacy analyses to 28 or 42 days censored patients at the day of the last blood smear prior to 25 or 39 days if no blood smear was taken between 25-31 or 39-45 days, respectively.

#### Heterogeneity between sites

For all efficacy endpoints within 365 days (radical cure), coefficients and their standard errors were first estimated within each study arm using the statistical methods described above (see **Efficacy Endpoints**) and heterogeneity was assessed visually using Forrest plots. Random effects meta-analysis was used to estimate the I<sup>2</sup> value for heterogeneity across sites, and the pooled measure of association across sites was presented unless there was substantial heterogeneity. There were too few events to assess heterogeneity between study sites in the analysis of secondary efficacy endpoints within 28 days and 42 days (schizontocidal efficacy).

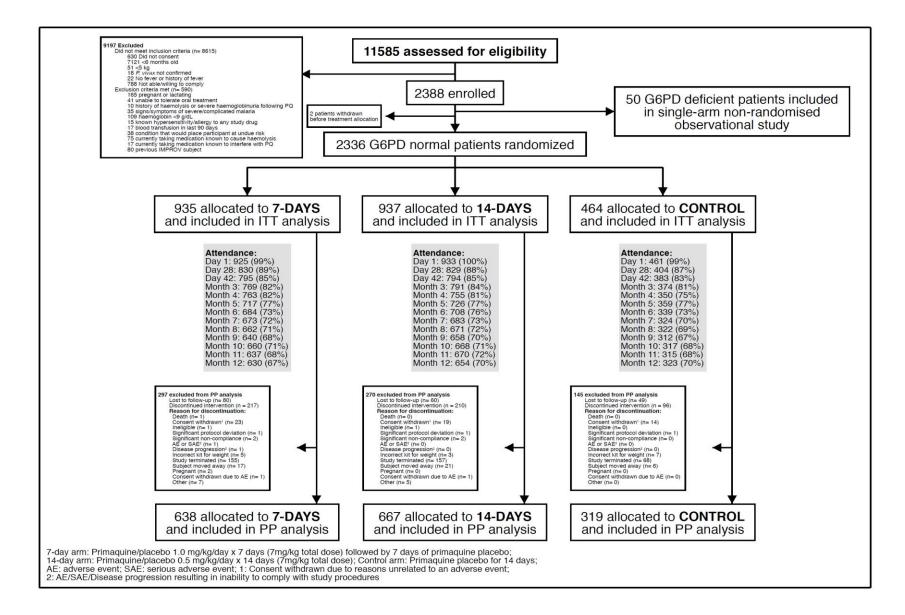
#### Safety analysis - haemolysis

The incidence risk of severe anaemia or transfusion within 365 days of follow-up was calculated using the Kaplan-Meier method within each treatment arm. Patients were censored at the time of failure, at the time of the last visit, or at the last visit immediately prior to missing two or more scheduled haemoglobin measurements. There were too few outcomes for comparison between arms. The nadir of haemoglobin within 28 days and the time to nadir was summarised within treatment arms; patients who missed two or more consecutive scheduled haemoglobin measurements were excluded. Nadirs were compared between arms using linear regression adjusting for site. The median day of nadir was compared between study arms using a nonparametric K-sample test on the equality of medians. The mean and standard deviation of haemoglobin on day 0, 3, 7, and 13 (or 14 in the G6PD arm), and the mean [SD] change in haemoglobin from day 0 to days 3, 7, and 13 (or 14 in the G6PD arm), was calculated within each arm. Additionally, the proportion of patients whose haemoglobin dropped more than 5 g/dL or more than 25% from day 0 to days 3, 7, and 13 (or 14 in the G6PD arm) was calculated within each arm. Comparisons in mean changes between arms was done using linear-mixed effects modelling adjusting for site, with random effects for the intercept and slope, and an interaction parameter between the day of measurement and the study arm.

#### Safety analysis – adverse events

Adverse events (AEs) within 42 days of initial treatment were summarised within each treatment arm, by severity (only grade 3 and 4) and in relation to primaquine. The number of patients with AEs within 7, 14, 28, and 42 days of initial treatment was calculated within each arm, by relation to primaquine, to assess trends in the incidence of adverse events over time. All serious adverse events (SAEs) are reported and presented by relation to study drug and severity.

#### 9. Consort Flow Chart



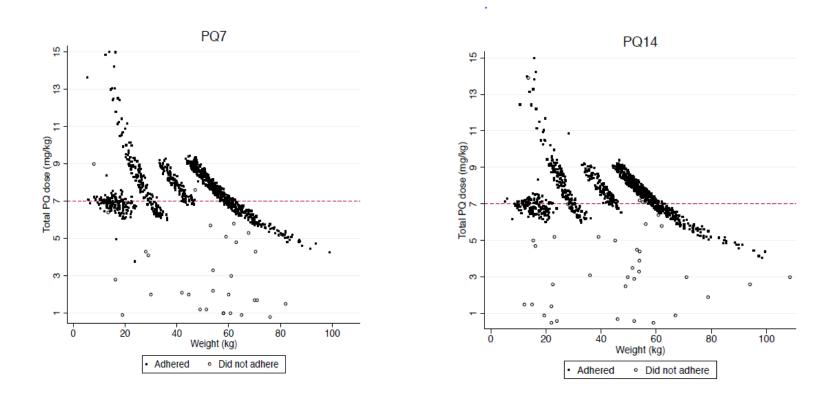
## **10.** Site-specific Baseline Tables

		Afghanistan		Ethi	opia	Indo	nesia	Viet	nam	
		AF001 Jalalabad	AF008 Laghman	ET001 Arba Minch	ET002 Metahara	ID004 Hanura	ID005 Tanjung Leidong	VN001 Dak O & Bu Gia Map	VN002 Krong Pa	Total
		N=311	N=120	N=371	N=209	N=575	N=425	N=219	N=106	N=2,336
Age (years),		14.0	11.0	16.0	16.0	14.0	17.0	22.0	25.0	16.0
median (IQR)		(9.0 - 22.0)	(7.5 - 16.0)	(10.0 - 20.0)	(11.0 - 27.0)	(8.0 - 27.0)	(11.0 - 30.0)	(16.0 - 32.0)	(22.0 - 30.0)	(10.0 - 26.0)
	6-12	1	1	0	0	1	0	0	0	3
	months	(0.3%)	(0.8%)	(0.0%)	(0.0%)	(0.2%)	(0.0%)	(0.0%)	(0.0%)	(0.1%)
	>=1 & <5	22	5	43	11	50	19	1	0	151
	yrs	(7.1%)	(4.2%)	(11.6%)	(5.3%)	(8.7%)	(4.5%)	(0.5%)	(0.0%)	(6.5%)
	>=5 & <15	135	79	119	72	264	144	40	3	856
	yrs	(43.4%)	(65.8%)	(32.1%)	(34.4%)	(45.9%)	(33.9%)	(18.3%)	(2.8%)	(36.6%)
Age category		153	35	209	126	260	262	178	103	1,326
N (%)	>=15 yrs	(49.2%)	(29.2%)	(56.3%)	(60.3%)	(45.2%)	(61.6%)	(81.3%)	(97.2%)	(56.8%)
		234	71	195	136	300	251	184	96	1,467
	Male	(75.2%)	(59.2%)	(52.6%)	(65.1%)	(52.2%)	(59.1%)	(84.0%)	(90.6%)	(62.8%)
		77	49	176	73	275	174	35	10	869
Sex N (%)	Female	(24.8%)	(40.8%)	(47.4%)	(34.9%)	(47.8%)	(40.9%)	(16.0%)	(9.4%)	(37.2%)
Weight (kg)		41.0 (22.5 -	31.9 (21.8 -	47.0 (24.0 -	47.1 (29.0 -	38.0 (21.3 -	49.0 (27.4 -	52.0 (45.0 -	55.0 (52.0 -	46.6 (26.0 -
median (IQR)		61.3)	46.9)	58.0)	55.5)	52.0)	58.1)	60.0)	60.0)	57.0)
Weight		2	1	7	0	5	2	0	0	17
category N	5-9.9 kg	(0.6%)	(0.8%)	(1.9%)	(0.0%)	(0.9%)	(0.5%)	(0.0%)	(0.0%)	(0.7%)
(%)		78	34	69	28	158	69	13	0	449
	10-22.9 kg	(25.1%)	(28.3%)	(18.6%)	(13.4%)	(27.5%)	(16.2%)	(5.9%)	(0.0%)	(19.2%)
		55	33	47	38	95	63	14	1	346
	23-34.9 kg	(17.7%)	(27.5%)	(12.7%)	(18.2%)	(16.5%)	(14.8%)	(6.4%)	(0.9%)	(14.8%)
		31	21	56	32	95	47	29	9	320
	35-45.9 kg	(10.0%)	(17.5%)	(15.1%)	(15.3%)	(16.5%)	(11.1%)	(13.2%)	(8.5%)	(13.7%)
		145	31	192	111	222	244	163	96	1,204
	46+ kg	(46.6%)	(25.8%)	(51.8%)	(53.1%)	(38.6%)	(57.4%)	(74.4%)	(90.6%)	(51.5%)

The IMPROV Study – Supplementary Appendices

							INFROV Study	- Supplement	/ !!
P. vivax	1347	1830	12090	2237	1379	6334	7639	6952	3440
parasites/uL	(278 -	(221 -	(722 -	(45 - 77500)	(52 -	(1615 -	(749 -	(593 -	(140 -
- geometric	17500)	10935)	135000)		13833)	17896)	32500)	52500)	53037)
mean (95%									-
normal									
range)									
Gametocytes	311	1	371	207	574	425	219	106	2,214
present N	(100.0%)	(0.8%)	(100.0%)	(99.0%)	(99.8%)	(100.0%)	(100.0%)	(100.0%)	(94.8%)
(%)									
Gametocytes	441	56	664	499	38	141	109	403	201
/uL -	(74-17500)	()	(56 - 3093)	(30 - 9701)	(3.7 - 307)	(30 - 578)	(15 - 734)	(19 - 15000)	(15 - 3037)
geometric									
mean (95%									
normal									
range)									
Temperature	37.6 [0.8]	37.7 [0.8]	37.3 [1.1]	37.4 [0.8]	37.7 [1.4]	38.0 [1.2]	38.7 [1.0]	39.0 [0.9]	37.8 [1.2]
(°C) mean									
[SD]									
Fever	177	72	138	107	288	271	193	96	1,342
(Axillary	(59.4%)	(60.0%)	(37.2%)	(51.2%)	(50.1%)	(63.8%)	(88.1%)	(90.6%)	(57.8%)
>37.5C or									
Oral >38C) N									
(%)									
Haemoglobi	13.3 [1.7]	12.5 [1.4]	13.2 [1.7]	13.0 [1.7]	12.4 [1.7]	12.9 [1.8]	13.5 [1.6]	13.6 [1.3]	13.0 [1.7]
n (g/dL)									
mean [SD]									
Anemia	6	4	10	4	48	15	2	0	89
(Hb <10	(1.9%)	(3.4%)	(2.7%)	(1.9%)	(8.3%)	(3.5%)	(0.9%)	(0.0%)	(3.8%)
g/dL) N (%)									

## **11.** Scatterplots of Total Dose of PQ Received by Weight



	Control	PQ7	PQ14
	N=464	N=935	N=937
Number of patients (%) with incomplete treatment until day 7 <sup>1,2</sup>	11 (2.4%)	30 (3.2%)	19 (2.0%)
Number of patients (%) with incomplete treatment until day 14 <sup>1,3</sup>	14 (3.0%)	53 (5.7%)	37 (3.9%)
Number of patients with interrupted treatment (> 1 day) <sup>1</sup>		125 (13.8%)	218 (24.2%)
Total Dose PQ received (mg/kg) – all patients <sup>1</sup>		7.39 [SD: 1.53] (range: 0.80 - 15.00)	7.39 [SD 1.48] (range: 0.50 - 15.00)
Total Dose PQ received (mg/kg) – only patients who received full course <sup>1</sup>		7.53 [SD: 1.28] (range: 3.80 - 15.00)	7.54 [SD: 1.19] (range: 4.20 - 15.00)
Total Dose PQ received (mg/kg) – only patients who received incomplete course <sup>1, 2, 3</sup>		3.16 [SD: 2.22], (range: 0.80- 9.00)	3.74 [SD 2.71] (range: 0.50-13.90)
<sup>1</sup> only recruitment episode <sup>2</sup> incomplete treatment wa <sup>3</sup> incomplete treatment wa	s defined as less than 3		

## 12. Adherence and Total Dose of Drug Received

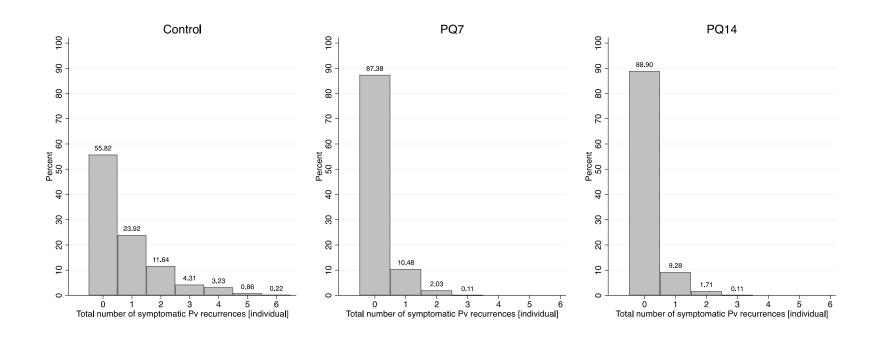
	Control	PQ7	PQ14
	N=464	N=935	N=937
Asexual <i>P. vivax</i> parasitaemia on Day 1	231/461 (50.1%)	431/926 (46.5%)	426/934 (45.6%)
Asexual <i>P. vivax</i> parasitaemia on Day 2	24/458 (5.2%)	34/919 (3.7%)	35/933 (3.8%)
Asexual <i>P. vivax</i> parasitaemia on Day 3	1/457 (0.2%)	4/916 (0.4%)	3 /929(0.3%)
Fever on Day 1	30/460 (6.5%)	75/918 (8.2%)	59/931 (8.2%)
Fever on Day 2	5/458 (1.1%)	10/916 (1.1%)	5/931 (0.5%)
Fever on Day 3	3/451 (0.7%)	3/909 (0.3%)	4/919 (0.4%)
The denominator is the num	•	nded on the respective day.	

### 13. Parasite and Fever Clearance

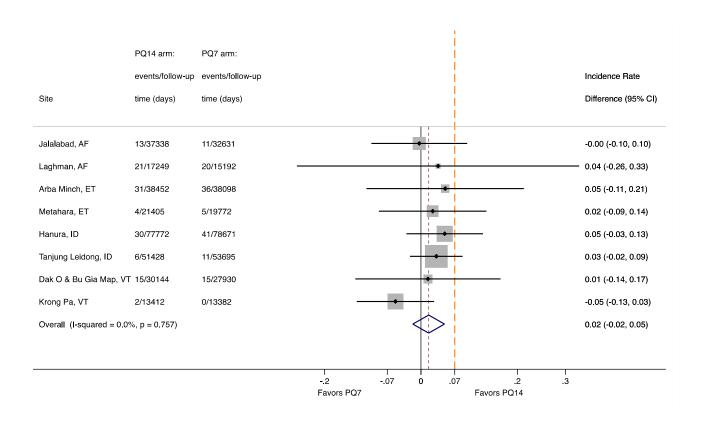
Patients with missing temperature were excluded from the fever denominators, but patients without a blood smear were not excluded from the parasitaemia denominators.

Fever was defined as either an axillary temperature >37.5°C or an oral temperature > 38.0 °C.

### 14. Histogram of the number of symptomatic *P. vivax* recurrences in each treatment arm



## **15.** Site Specific Results for the Primary Endpoint – Incidence Rate of Recurrent Symptomatic Episodes of *P. vivax* within 12 months Follow up



AF = Afghanistan; ET = Ethiopia; ID = Indonesia; VT = Vietnam

Absolute difference in incidence rates of symptomatic P. vivax between the 7-day and 14-day treatment arms: assessment of heterogeneity between study sites. The dashed orange line indicates the non-inferiority margin (incidence rate difference of 0.07 events per person-year). The incidence rate difference was estimated for each site using weighted least squares regression with a robust standard error; random effects meta-analysis was used to estimate the I<sup>2</sup> value for heterogeneity and the overall incidence rate difference across all sites.

### 16. Per protocol Analysis

Excludes patients who discontinued treatment and were lost to follow up.

Time point	Outcome	Measure of association	PQ7 vs Control	PQ14 vs Control	PQ7 vs PQ14
12	Symptomatic P.	Pooled IRD*, (95%CI); p-			0.02 (-0.02 - 0.05);
months	vivax	value, [l <sup>2</sup> ]			0.4162, [l <sup>2</sup> = 0.00]
	parasitaemia	Pooled IRR, (95%CI); p-	0.26 (0.20 - 0.35);	0.23 (0.17 - 0.29);	1.18 (0.90 - 1.55);
		value, [l <sup>2</sup> ]	<0.0001, [l <sup>2</sup> = 15.56]	<0.0001, [l <sup>2</sup> = 5.18]	0.2320, [l <sup>2</sup> = 0.00]
		Pooled HR, (95%Cl); p-	0.22 (0.15 - 0.34);	0.17 (0.11 - 0.26);	1.19 (0.77 - 1.83);
		value, [l <sup>2</sup> ]	<0.0001, [l <sup>2</sup> = 39.11]	<0.0001, [I <sup>2</sup> = 40.66]	0.4332, [l <sup>2</sup> = 26.55]
	Any P. vivax	Pooled IRR, (95%CI); p-	0.24 (0.18 - 0.33);	0.21 (0.15 - 0.29);	1.15 (0.88 - 1.49);
	parasitaemia	value, [l <sup>2</sup> ]	<0.0001, [l <sup>2</sup> = 32.50]	<0.0001, [l <sup>2</sup> = 41.69]	0.2980, [l <sup>2</sup> = 0.00]
		Pooled HR, (95%CI); p-	0.21 (0.14 - 0.31);	0.17 (0.12 - 0.25);	1.16 (0.86 - 1.58);
		value, [l <sup>2</sup> ]	<0.0001, [l <sup>2</sup> = 44.79]	<0.0001, [I <sup>2</sup> = 38.48]	0.3399, [l <sup>2</sup> = 0.00]
	Symptomatic P.	Pooled IRR, (95%CI); p-	1.08 (0.67 - 1.73); 0.7540,	0.85 (0.53 - 1.38); 0.5180,	1.24 (0.83 - 1.84);
	falciparum	value, [l <sup>2</sup> ]	$[I^2 = 0.00]$	$[l^2 = 0.00]$	0.2950, [l <sup>2</sup> = 0.00]
	parasitaemia	Pooled HR, (95%Cl); p-	0.67 (0.38 - 1.20); 0.1814,	0.56 (0.31 - 1.01); 0.0560,	1.15 (0.71 - 1.86);
		value, [l <sup>2</sup> ]	$[I^2 = 0.00]$	$[I^2 = 0.00]$	0.5589, [l <sup>2</sup> = 0.00]
	Any P. falciparum	Pooled IRR, (95%CI); p-	1.09 (0.69 - 1.73); 0.7230,	0.93 (0.58 - 1.48); 0.7560,	1.14 (0.78 - 1.66);
	parasitaemia	value, [l <sup>2</sup> ]	$[I^2 = 0.00]$	$[l^2 = 0.00]$	0.5050, [l <sup>2</sup> = 0.00]
		Pooled HR, (95%Cl); p-	0.77 (0.46 - 1.29); 0.3292,	0.65 (0.39 - 1.09); 0.1043,	1.16 (0.76 - 1.75);
		value, [l <sup>2</sup> ]	$[I^2 = 0.00]$	$[I^2 = 0.00]$	0.4970, [l <sup>2</sup> = 0.00]
*Non-Infe	riority analysis				
HR= Haza	rd ratio				
IRR= Incid	ence rate ratio				
IRD= Incid	ence rate difference				

## **17.** Sensitivity Analyses in the ITT Population

Exclusio	on of data from th	e Vietnam sites <sup>1</sup>			
Time point	Outcome	Measure of association	PQ7 vs Control	PQ14 vs Control	PQ7 vs PQ14
12 months	Symptomatic P. vivax parasitaemia	Pooled IRD*, (95%CI); p- value, [I <sup>2</sup> ] Pooled IRR, (95%CI); p-	0.23 (0.17 - 0.30);	0.19 (0.13 - 0.26);	0.03 (-0.01 - 0.07); 0.1031 [l <sup>2</sup> = 0.00] 1.24 (0.95 - 1.63);
	Anna Daviana	value, [l <sup>2</sup> ] Pooled IRR, (95%CI); p-	<pre>0.23 (0.17 + 0.30); &lt;0.0001 [l<sup>2</sup> = 31.81] 0.21 (0.16 - 0.28);</pre>	<0.0001 [l <sup>2</sup> = 46.51] 0.18 (0.13 - 0.25);	$\begin{array}{c} 1.24 (0.53 - 1.05), \\ 0.1150 [l^2 = 0.00] \\ 1.20 (0.93 - 1.55); \end{array}$
	Any <i>P.vivax</i> parasitaemia	value, [l <sup>2</sup> ]	<pre>0.21 (0.16 - 0.28); &lt;0.0001 [l<sup>2</sup> = 33.21]</pre>	<0.18 (0.13 - 0.25); <0.0001 [l <sup>2</sup> = 46.35]	0.1702 [l <sup>2</sup> = 0.00]
	Symptomatic P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.03 (0.65 - 1.64); 0.8882 [l <sup>2</sup> = 0.00]	0.72 (0.45 - 1.17); 0.1852 [l <sup>2</sup> = 0.00]	1.45 (0.97 - 2.15); 0.0703 [l <sup>2</sup> = 0.00]
	Any P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.12 (0.71 - 1.75); 0.6347 [l <sup>2</sup> = 0.00]	0.82 (0.51 - 1.30); 0.3935 [l <sup>2</sup> = 0.00]	1.39 (0.95 - 2.02); 0.0861 [l <sup>2</sup> = 0.00]
Exclusio	n of data from th	e Indonesian sites <sup>2</sup>			
12 months	Symptomatic <i>P. vivax</i> parasitaemia	Pooled IRD*, p-value (95%CI); p-value, [I <sup>2</sup> ]			-0.01 (-0.06 - 0.04); 0.7250 [l <sup>2</sup> = 0.00]
		Pooled IRR, (95%Cl); p- value, [l <sup>2</sup> ]	0.18 (0.12 - 0.28); <0.0001 [l <sup>2</sup> = 48.36]	0.17 (0.11 - 0.26); <0.0001 [l <sup>2</sup> = 51.14]	1.07 (0.78 - 1.46); 0.6807 [l <sup>2</sup> = 0.00]
	Any <i>P.vivax</i> parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	0.17 (0.11 - 0.26); <0.0001 [l <sup>2</sup> = 57.05]	0.16 (0.10 - 0.24); <0.0001 [I <sup>2</sup> = 59.23]	1.07 (0.79 - 1.44); 0.6772 [l <sup>2</sup> = 0.00]
	Symptomatic P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.10 (0.62 - 1.96); 0.7495 [l <sup>2</sup> = 0.00]	0.81 (0.45 - 1.48); 0.5017 [l <sup>2</sup> = 0.00]	1.36 (0.85 - 2.18); 0.1986 [l <sup>2</sup> = 0.00]

	Any P. falciparum parasitaemia	Pooled IRR, (95%Cl); p- value, [l <sup>2</sup> ]	1.23 (0.70 - 2.17); 0.4686 [l <sup>2</sup> = 0.00]	1.01 (0.57 - 1.79); 0.9661 [I <sup>2</sup> = 0.00]	1.22 (0.79 - 1.89); 0.3684 [l <sup>2</sup> = 0.00]
Censorir	ng patients after t	heir 3 <sup>rd</sup> Recurrence <sup>3</sup>			
12 months	Symptomatic P.vivax parasitaemia	Pooled IRD*, (95%CI); p- value, [I <sup>2</sup> ]			0.02 (-0.02 - 0.05); 0.3396 [I <sup>2</sup> = 0.00]
		Pooled IRR, (95%Cl); p- value, [l <sup>2</sup> ]	0.21 (0.15 - 0.29); <0.0001 [l <sup>2</sup> = 45.80]	0.18 (0.13 - 0.25); <0.0001 [l <sup>2</sup> = 39.93]	1.19 (0.92 - 1.53); 0.1884 [l <sup>2</sup> = 0.00]
	Any <i>P.vivax</i> parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	0.20 (0.14 - 0.27); <0.0001 [l <sup>2</sup> = 49.64]	0.17 (0.12 - 0.23); <0.0001 [l <sup>2</sup> = 47.84]	1.17 (0.92 - 1.48); 0.2102 [l <sup>2</sup> = 0.00]
	Symptomatic P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.12 (0.70 - 1.81); 0.6386 [l <sup>2</sup> = 0.00]	0.92 (0.56 - 1.54); 0.7621 [I <sup>2</sup> = 0.00]	1.28 (0.87 - 1.90); 0.2126 [l <sup>2</sup> = 0.00]
	Any <i>P.</i> <i>falciparum</i> parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.06 (0.70 - 1.62); 0.7768 [l <sup>2</sup> = 0.00]	0.88 (0.56 - 1.37); 0.5645 [I <sup>2</sup> = 0.00]	1.24 (0.87 - 1.76); 0.2309 [l <sup>2</sup> = 0.00]
Excludin	g the influence o	 f post treatment prophylax	is <sup>4</sup>		
Time point	Outcome	Measure of association			
12 months	Symptomatic P. vivax parasitaemia	Pooled IRD*, (95%Cl); p- value, [l <sup>2</sup> ]			-0.01 (-0.06 - 0.04); 0.7250 [l <sup>2</sup> = 0.00]
		Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	0.18 (0.12 - 0.28); <0.0001 [l <sup>2</sup> = 48.36]	0.17 (0.11 - 0.26); <0.0001 [l <sup>2</sup> = 51.14]	1.07 (0.78 - 1.46); 0.6807 [l <sup>2</sup> = 0.00]
	Any <i>P. vivax</i> parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	0.17 (0.11 - 0.26); <0.0001 [l <sup>2</sup> = 57.05]	0.16 (0.10 - 0.24); <0.0001 [l <sup>2</sup> = 59.23]	1.07 (0.79 - 1.44); 0.6772 [l <sup>2</sup> = 0.00]

Symptomatic P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.10 (0.62 - 1.96); 0.7495 [l <sup>2</sup> = 0.00]	0.81 (0.45 - 1.48); 0.5017 [I <sup>2</sup> = 0.00]	1.36 (0.85 - 2.18); 0.1986 [l <sup>2</sup> = 0.00]
Any P. falciparum parasitaemia	Pooled IRR, (95%CI); p- value, [I <sup>2</sup> ]	1.23 (0.70 - 2.17); 0.4686 [l <sup>2</sup> = 0.00]	1.01 (0.57 - 1.79); 0.9661 [l <sup>2</sup> = 0.00]	1.22 (0.79 - 1.89); 0.3684 [l <sup>2</sup> = 0.00]

\* Non-inferiority analysis

[1] All sites except the sites in Vietnam provided the same treatment as originally randomized for up to 4 repeated episodes of *P. vivax* during follow up. The sites in Vietnam only provided the same treatment until the 3rd episode and thereafter treated patients with open primaquine for the subsequent episodes. This sensitivity analysis excludes the sites in Vietnam to accommodate for this difference in procedures.

[2] All sites except the sites in Indonesia used CQ as schizontocidal treatment, the Indonesian sites used DHAP, therefore this sensitivity analysis excludes the sites in Indonesia to accommodate for this difference in schizontocidal treatment regimen. This sensitivity analysis wasn't planned for a priori in the Statistical Analysis Plan, but added post hoc as it was perceived to be important additional information.
[3] All sites except the sites in Vietnam provided the same treatment as originally randomised for up to 4 repeated episodes of *P. vivax* during follow up. The sites in Vietnam only provided the same treatment until the 3rd episode and thereafter treated patients with open primaquine for the subsequent episodes. This sensitivity analysis includes all sites but censors all patients at the time point of the third episode in all countries to accommodate for this difference in procedures.

[4] The effect of post-treatment prophylaxis on the time of observation was assessed using sensitivity analyses by subtracting 28 days from a patient's follow-up time for each antimalarial treatment, irrespective of the drug.

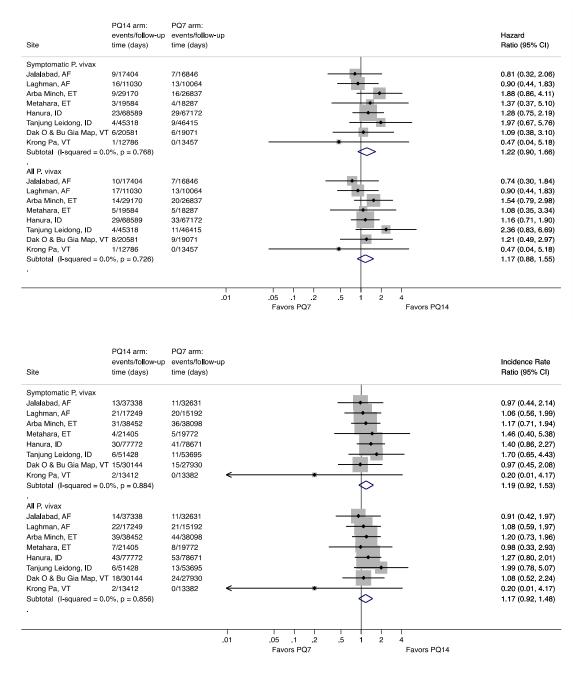
IRR= Incidence rate ratio

IRD= Incidence rate difference

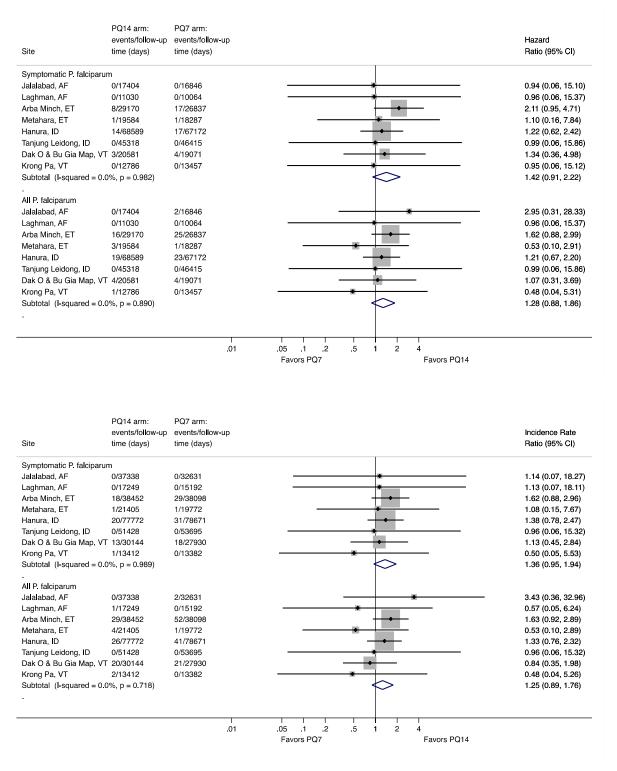
### 18. Site-Specific ITT Hazard Ratios (HR) and Incidence Rate Ratios (IRR)

The hazard ratios (HRs) were estimated using Cox regression (analysis of time to the first event). Incidence rate ratios (IRRs) were estimated using negative binomial regression (analysis of all events). Random effects meta-analysis was used to estimate the I<sup>2</sup> value for heterogeneity across sites. The pooled measure of association is presented across all sites.

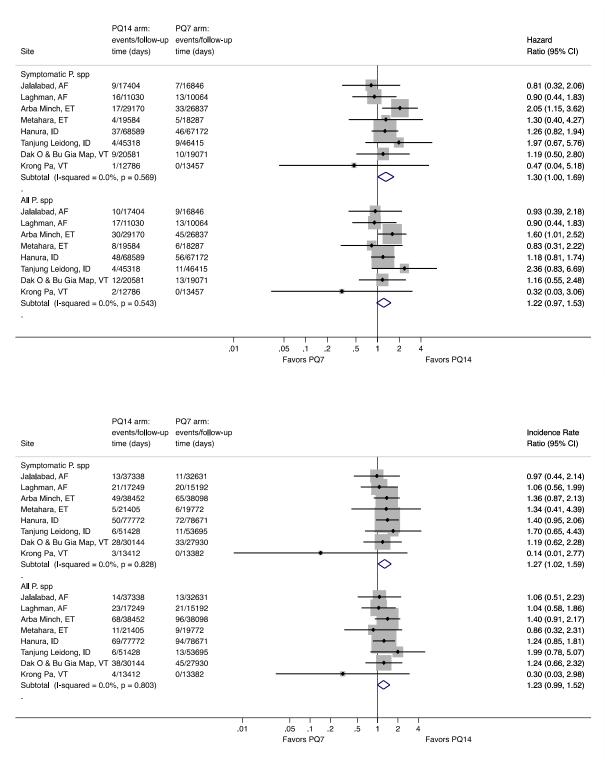
## a) <u>PQ7 vs PQ14:</u> Risks and rates for recurrent parasitemia due to symptomatic and any infection due to *P. vivax*



## b) <u>PQ7 vs PQ14:</u> Risks and rates for recurrent parasitemia due to symptomatic and any infection due to *P. falciparum*



## c) <u>PQ7 vs Pq14</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due to all *Species*



## d) <u>PQ7 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due to *P. vivax*

Site	Control arm: events/follow-up time (days)	PQ7 arm: events/follow-up time (days)		Hazard Ratio (95% CI)
Symptomatic P. vivax				
Jalalabad, AF	17/6354	7/16846		0.18 (0.08, 0.4
_aghman, AF	14/3327	13/10064	<b>•</b>	0.29 (0.14, 0.6
Arba Minch, ET	29/7937	16/26837		0.18 (0.10, 0.32
vetahara, ET	16/5485	4/18287		0.09 (0.03, 0.25
	38/26756	29/67172		
Hanura, ID				0.30 (0.19, 0.49
Fanjung Leidong, ID	19/20151	9/46415		0.22 (0.10, 0.48
Dak O & Bu Gia Map, VT	21/5079	6/19071		0.10 (0.04, 0.23
Krong Pa, VT	9/3380	0/13457 🗧 🗲		0.03 (0.00, 0.24
Subtotal (I-squared = 44	.5%, p = 0.082)		$\diamond$	0.18 (0.13, 0.2
All P vivax				
lalalabad, AF	17/6354	7/16846		0.18 (0.08, 0.4
_aghman, AF	14/3327	13/10064		0.29 (0.14, 0.6
Arba Minch, ET	42/7937	20/26837		0.16 (0.09, 0.23
Vetahara, ET	22/5485	5/18287		0.08 (0.03, 0.2
Hanura, ID	59/26756	33/67172		0.23 (0.15, 0.3
Fanjung Leidong, ID	21/20151	11/46415		0.24 (0.12, 0.4
Dak O & Bu Gia Map, VT		9/19071	•	0.09 (0.05, 0.19
Krong Pa, VT	9/3380	0/13457 🗧 🗲	*	0.03 (0.00, 0.24
Subtotal (I-squared = 44	.2%, p = 0.084)		$\diamond$	0.17 (0.12, 0.2
			.01 .05 .1 .2 .5 1 2 4 Favors PQ7 Favo	rs Control
74.	Control: events/follow-up			Incidence Rate
Symptomatic P. vivax	events/follow-up time (days)	events/fo <b>ll</b> ow-up time (days)		Incidence Rate Ratio (95% CI)
Symptomatic P. vivax Jalalabad, AF	events/follow-up time (days) 28/15969	events/follow-up time (days) 11/32631		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4;
Symptomatic P. vivax Ialalabad, AF .aghman, AF	events/follow-up time (days) 28/15969 28/7978	events/follow-up time (days) 11/32631 20/15192		Incidence Rate Ratio (95% Cl) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6/
Symptomatic P. vivax Ialalabad, AF aghman, AF Arba Minch, ET	events/follow-up time (days) 28/15969 28/7978 99/18752	events/follow-up time (days) 11/32631 20/15192 36/38098		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4 0.38 (0.21, 0.6 0.20 (0.13, 0.3)
Symptomatic P. vivax Ialalabad, AF .aghman, AF Arba Minch, ET Metahara, ET	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4 0.38 (0.21, 0.6 0.20 (0.13, 0.3 0.09 (0.03, 0.2
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.64 0.20 (0.13, 0.36 0.09 (0.03, 0.2 0.28 (0.19, 0.44
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Wetahara, ET Hanura, ID Fanjung Leidong, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6/ 0.20 (0.13, 0.3/ 0.09 (0.03, 0.2' 0.28 (0.19, 0.4/ 0.20 (0.10, 0.3/
Symptomatic P. vivax Ialalabad, AF a.ghman, AF Arba Minch, ET Metahara, ET 4anura, ID Fanjung Leidong, ID Dak O & Bu Gia Map, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6/ 0.20 (0.13, 0.3/ 0.09 (0.03, 0.2' 0.28 (0.19, 0.4/ 0.20 (0.10, 0.3/ 0.17 (0.09, 0.3/ 0.17 (0.09, 0.3/
Symptomatic P. vivax Ialalabad, AF aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239 48/14540 20/5284	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4 0.38 (0.21, 0.6 0.20 (0.13, 0.3 0.09 (0.03, 0.2 0.28 (0.19, 0.4 0.20 (0.10, 0.3 0.17 (0.09, 0.3 0.03 (0.00, 0.2
Symptomatic P. vivax Ialalabad, AF aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239 48/14540 20/5284	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6/ 0.20 (0.13, 0.3/ 0.29 (0.13, 0.3/ 0.29 (0.19, 0.4/ 0.20 (0.10, 0.3/ 0.17 (0.09, 0.3/ 0.03 (0.00, 0.2'
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Fanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056)	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6( 0.20 (0.13, 0.3( 0.09 (0.03, 0.2) 0.28 (0.19, 0.4/ 0.20 (0.10, 0.3( 0.17 (0.09, 0.3) 0.03 (0.00, 0.2) 0.20 (0.15, 0.2)
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Fanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239 48/14540 20/5284	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4/ 0.38 (0.21, 0.6( 0.20 (0.13, 0.3( 0.09 (0.03, 0.2) 0.28 (0.19, 0.4/ 0.20 (0.10, 0.3( 0.17 (0.09, 0.3) 0.03 (0.00, 0.2) 0.20 (0.15, 0.2)
Symptomatic P. vivax Jalalabad, AF Aaghman, AF Arba Minch, ET Vetahara, ET Hanura, ID Fanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056)	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382		Incidence Rate
Symptomatic P. vivax Jalalabad, AF arba Minch, ET Metahara, AF Tanura, ID Jak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF Laghman, AF	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 00%, p = 0.056) 28/15969	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 —		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.33 0.09 (0.03, 0.27 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.17 (0.09, 0.34 0.03 (0.00, 0.27 0.20 (0.15, 0.26 0.21 (0.10, 0.44
Symptomatic P. vivax Jalalabad, AF _aghman, AF Arba Minch, ET Hetahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF _aghman, AF Arba Minch, ET	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056) 28/15969 30/7978	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 -	Favors PQ7 Favo	Incidence Rate Ratio (95% Cl) 0.21 (0.10, 0.42 0.38 (0.21, 0.63 0.20 (0.13, 0.33 0.09 (0.03, 0.2 <sup>-</sup> 0.28 (0.19, 0.42 0.20 (0.10, 0.33 0.17 (0.09, 0.33 0.03 (0.00, 0.2 <sup>-</sup> 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.67
Site Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056) 28/15969 30/7978 133/18752	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 11/32631 21/15192 44/38098 8/19772	Favors PQ7 Favo	Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.30 0.09 (0.03, 0.2 <sup>-</sup> 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.03 (0.00, 0.2 <sup>-</sup> 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.66 0.18 (0.12, 0.26 0.09 (0.04, 0.2 <sup>-</sup>
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 00%, p = 0.056) 28/15969 30/7978 133/18752 44/9788 129/40698	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 11/32631 21/15192 44/38098 8/19772 53/78671		Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.30 0.09 (0.03, 0.2 <sup>-</sup> 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.17 (0.09, 0.33 0.03 (0.00, 0.2 <sup>-</sup> 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.67 0.18 (0.12, 0.26 0.09 (0.04, 0.2 <sup>-</sup> 0.24 (0.16, 0.35
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Fanjung Leidong, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 00%, p = 0.056) 28/15969 30/7978 133/18752 44/9798 132/18752 44/9798 129/40698 30/26239	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 11/32631 21/15192 44/38098 8/19772 53/78671 13/53695	Favors PQ7 Favo	Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.33 0.09 (0.03, 0.27 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.17 (0.09, 0.33 0.03 (0.00, 0.27 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.67 0.18 (0.12, 0.24 0.09 (0.04, 0.27 0.24 (0.16, 0.33 0.24 (0.12, 0.44)
Symptomatic P. vivax Jalalabad, AF arba Minch, ET Metahara, ET Hanura, ID Janjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9788 82/40698 28/26239 48/14540 20/5284 00%, p = 0.056) 28/15969 30/7978 133/18752 44/9788 129/40698 30/26239 90/14540	events/follow-up time (days)	Favors PQ7 Favo	Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.3 0.09 (0.03, 0.2 <sup>-</sup> 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.17 (0.09, 0.33 0.03 (0.00, 0.2 <sup>-</sup> 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.67 0.18 (0.12, 0.24 0.09 (0.44, 0.2 <sup>-</sup> 0.24 (0.16, 0.33 0.24 (0.12, 0.44 0.13 (0.07, 0.24
Symptomatic P. vivax Jalalabad, AF _aghman, AF Arba Minch, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF _aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056) 28/15969 30/7978 133/18752 44/9798 129/40698 129/40698 30/26239 90/14540 20/5284	events/follow-up time (days) 11/32631 20/15192 36/38098 5/19772 41/78671 11/53695 15/27930 0/13382 11/32631 21/15192 44/38098 8/19772 53/78671 13/53695	Favors PQ7 Favo	Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.4; 0.38 (0.21, 0.6; 0.20 (0.13, 0.3; 0.09 (0.03, 0.2; 0.28 (0.19, 0.4; 0.20 (0.10, 0.3; 0.17 (0.09, 0.3; 0.33 (0.00, 0.2; 0.20 (0.15, 0.24; 0.37 (0.21, 0.6; 0.18 (0.12, 0.24; 0.09 (0.04, 0.2; 0.24 (0.12, 0.4; 0.13 (0.07, 0.24; 0.13 (0.07, 0.24; 0.33 (0.00, 0.2;
Symptomatic P. vivax Jalalabad, AF arba Minch, ET Metahara, ET Hanura, ID Janjung Leidong, ID Dak O & Bu Gia Map, VT Krong Pa, VT Subtotal (I-squared = 49 All P. vivax Jalalabad, AF aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 48/14540 20/5284 0%, p = 0.056) 28/15969 30/7978 133/18752 44/9798 129/40698 129/40698 30/26239 90/14540 20/5284	events/follow-up time (days)	Favors PQ7 Favo	Incidence Rate Ratio (95% CI) 0.21 (0.10, 0.44 0.38 (0.21, 0.66 0.20 (0.13, 0.33 0.09 (0.03, 0.27 0.28 (0.19, 0.44 0.20 (0.10, 0.33 0.17 (0.09, 0.33 0.03 (0.00, 0.27 0.20 (0.15, 0.26 0.21 (0.10, 0.44 0.37 (0.21, 0.67 0.18 (0.12, 0.24 0.09 (0.04, 0.27 0.24 (0.16, 0.33 0.24 (0.12, 0.44)

## e) <u>PQ7 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due to *P. falciparum*

Site	Control arm: events/follow-up time (days)	∕Q7 arm: vents/follow-up me (days)	Hazard Ratio (95% CI)
Symptomatic P. falcipar	um		
lalalabad, AF	0/6354	/16846	0.31 (0.02, 4.89)
aghman, AF	0/3327	/10064	0.27 (0.02, 4.30)
Arba Minch, ET	5/7937	7/26837	1.29 (0.51, 3.27)
/letahara, ET	0/5485	/18287	0.68 (0.06, 7.62)
lanura, ID	8/26756	7/67172	- 0.83 (0.37, 1.86)
anjung Leidong, ID	0/20151	/46415	0.39 (0.02, 6.16)
ak O & Bu Gia Map, \	/T 0/5079	/19071	0.77 (0.09, 6.60)
frong Pa, VT	0/3380	/13457	0.16 (0.01, 2.59)
Subtotal (I-squared = C	0.0%, p = 0.820)	$\Leftrightarrow$	0.80 (0.47, 1.36)
II P. falciparum			
alalabad, AF	0/6354	/16846	1.19 (0.12, 11.59
aghman, AF	0/3327	/10064	0.27 (0.02, 4.30)
rba Minch, ET	7/7937	5/26837	1.38 (0.62, 3.06)
letahara, ET	0/5485	/18287	0.68 (0.06, 7.62)
lanura, ID	9/26756	3/67172	1.05 (0.50, 2.19)
anjung Leidong, ID	0/20151	/46415	0.39 (0.02, 6.16)
ak O & Bu Gia Map, ∖	/T 1/5079	/19071	
rong Pa, VT	0/3380	/13457	0.16 (0.01, 2.59)
Subtotal (I-squared = C	0.0%, p = 0.674)	$\diamond$	0.93 (0.58, 1.49)
Subtotal (I-squared = C	0.0%, p = 0.674)	$\diamond$	0.93 (0.58
		.01 .05 .1 .2 .5 1	2 4
		Favors PQ7	Favors Control

Site	Control: events/follow-up time (days)	PQ7 arm: events/fo <b>ll</b> ow-up time (days)		Incidence Rate Ratio (95% CI)
Symptomatic P. falciparur	n			
Jalalabad, AF	0/15969	0/32631		- 0.50 (0.03, 7.91)
Laghman, AF	0/7978	0/15192		- 0.54 (0.03, 8.57)
Arba Minch, ET	8/18752	29/38098		1.62 (0.76, 3.44)
Metahara, ET	1/9798	1/19772		0.50 (0.07, 3.58)
Hanura, ID	13/40698	31/78671		1.09 (0.57, 2.12)
Tanjung Leidong, ID	0/26239	0/53695		- 0.49 (0.03, 7.87)
Dak O & Bu Gia Map, VT	4/14540	18/27930		1.65 (0.45, 6.07)
Krong Pa, VT	0/5284	0/13382		- 0.41 (0.03, 6.57)
Subtotal (I-squared = 0.0	%, p = 0.855)		$\diamond$	1.16 (0.75, 1.78)
All P. falciparum				
Jalalabad, AF	0/15969	2/32631	•	1.49 (0.15, 14.28
Laghman, AF	0/7978	0/15192		
Arba Minch, ET	11/18752	52/38098		1.76 (0.84, 3.71)
Metahara, ET	1/9798	1/19772		0.50 (0.07, 3.58)
Hanura, ID	16/40698	41/78671		1.09 (0.57, 2.06)
Tanjung Leidong, ID	0/26239	0/53695		- 0.49 (0.03, 7.87)
Dak O & Bu Gia Map, VT	10/14540	21/27930		1.59 (0.43, 5.87)
Krong Pa, VT	0/5284	0/13382	*	- 0.41 (0.03, 6.57)
Subtotal (I-squared = 0.0	%, p = 0.848)		$\diamond$	1.22 (0.80, 1.85)
		.01	.05 .1 .2 .5 1 2 4	
				vors Control

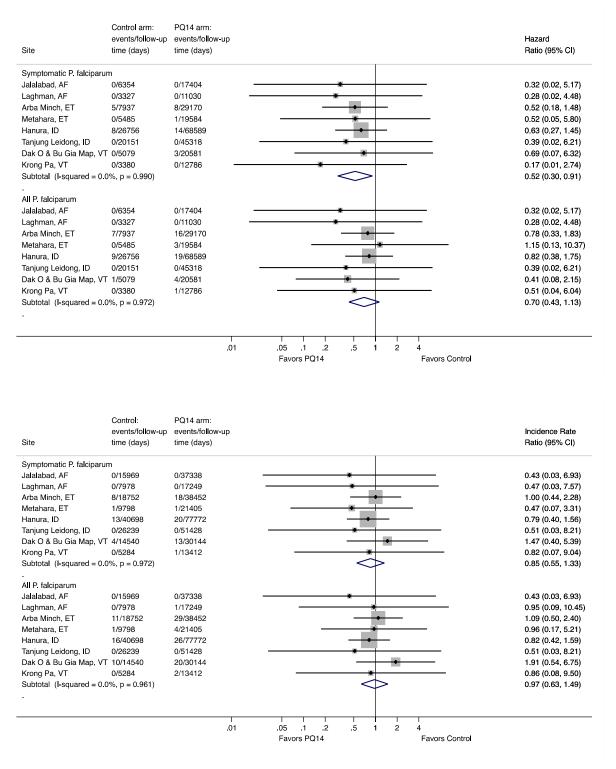
## f) <u>PQ7 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due to all *species*

Laghman, AF         14           Arba Minch, ET         34           Metahara, ET         16           Hanura, ID         46           Tanjung Leidong, ID         19           Dak O & Bu Gia Map, VT         21           Krong Pa, VT         97           Subtotal (I-squared = 57.8%           AII P. spp	3380	7/16846 13/10064 33/26837 5/18287 46/67172 9/46415 10/19071 0/13457 <b>&lt;</b>		0.18 (0.08, 0.4 0.29 (0.14, 0.6 0.34 (0.21, 0.5 0.11 (0.04, 0.2 0.40 (0.27, 0.6 0.22 (0.10, 0.4 0.14 (0.07, 0.2
Laghman, AF         14           Arba Minch, ET         34           Metahara, ET         16           Hanura, ID         46           Franjura, ID         46           Dak O & Bu Gia Map, VT 21         9/           Subtotal (I-squared = 57.8%         41	4/3327 4/7937 5/5485 5/26756 9/20151 1/5079 3380	13/10064 33/26837 5/18287 46/67172 9/46415 10/19071		0.29 (0.14, 0.6 0.34 (0.21, 0.5 0.11 (0.04, 0.2 0.40 (0.27, 0.6 0.22 (0.10, 0.4
Avin Aminch, ET         34           Aletahara, ET         16           Hanura, ID         46           Tanjung Leidong, ID         19           Dak O & Bu Gia Map, VT         21           Krong Pa, VT         97           Subtotal (I-squared = 57.8%           VII P. spp	4/7937 6/5485 6/26756 6/20151 1/5079 3380	33/26837 5/18287 46/67172 9/46415 10/19071		0.34 (0.21, 0.5 0.11 (0.04, 0.2 0.40 (0.27, 0.6 0.22 (0.10, 0.4
Metahara, ET         16           Ianura, ID         46           Anjung Leidong, ID         19           Dak O & Bu Gia Map, VT 21         17           Irong Pa, VT         97           Jubtotal         (I-squared = 57.8%)           III P. spp	5/5485 5/26756 5/20151 1/5079 3380	5/18287 46/67172 9/46415 10/19071		0.11 (0.04, 0.2 0.40 (0.27, 0.6 0.22 (0.10, 0.4
Ianura, ID         46           anjung Leidong, ID         19           Jak O & Bu Gia Map, VT 21         10           irong Pa, VT         9/           Jubtotal         (I-squared = 57.8%)           III P. spp         11	6/26756 9/20151 1/5079 3380	46/67172 9/46415 10/19071		0.40 (0.27, 0.6 0.22 (0.10, 0.4
anjung Leidong, ID 19 Dak O & Bu Gia Map, VT 21 (rong Pa, VT 9/ Subtotal (I-squared = 57.8%	9/20151 1/5079 3380	9/46415 10/19071		0.22 (0.10, 0.4
Dak O & Bu Gia Map, VT 21 (rong Pa, VT 9/: Subtotal (I-squared = 57.8%) VII P. spp	/5079 3380	10/19071		
Dak O & Bu Gia Map, VT 21 (rong Pa, VT 9/: Subtotal (I-squared = 57.8%) VII P. spp	3380			
Krong Pa, VT 9/3 Subtotal (I-squared = 57.8%	3380			· · ·
All P. spp	b, p = 0.020)		$\diamond$	0.03 (0.00, 0.2
			$\sim$	0.22 (0.15, 0.3
alalabau, Ar 17	7/6354	9/16846		0.22 (0.10, 0.5
A T d A				0.23 (0.10, 0.5
•	1/3327	13/10064		0.29 (0.14, 0.6
	9/7937	45/26837		0.33 (0.22, 0.4
	2/5485	6/18287		0.10 (0.04, 0.2
	3/26756	56/67172		0.34 (0.24, 0.4
	/20151	11/46415	<b>.</b>	0.24 (0.12, 0.4
Dak O & Bu Gia Map, VT 32	2/5079	13/19071		0.12 (0.06, 0.2
Krong Pa, VT 9/3	3380	0/13457 🗧 🗲		0.03 (0.00, 0.2
Subtotal (I-squared = 62.4%	o, p = 0.009)		$\diamond$	0.22 (0.15, 0.3
ev	ontrol: /ents/follow-up ne (days)	PQ7 arm: events/follow-up time (days)		Incidence Rate Ratio (95% CI
Symptomatic P. spp Jalalabad, AF 28	3/15969	11/32631		0.21 (0.10, 0.4
	3/7978	20/15192	-	0.38 (0.21, 0.6
•	)7/18752	65/38098		0.30 (0.21, 0.4
	3/9798	6/19772		
,				0.10 (0.04, 0.2
	5/40698	72/78671 11/53695		0.40 (0.28, 0.5
, 0	3/26239			0.20 (0.10, 0.3
	2/14340	33/27930		0.29 (0.16, 0.5 0.03 (0.00, 0.2
	1004			0.03 (0.00, 0.2
Krong Pa, VT 20		0/13382 —		0.25 (0.18, 0.3
Krong Pa, VT 20 Subtotal (I-squared = 60.3%		0/13382 —	 ◇	
Subtotal (I-squared = 60.3%	b, p = 0.014)		 ◇	0.25 (0.18, 0.3
Krong Pa, VT 20 Subtotal (I-squared = 60.3% NII P. spp Ialalabad, AF 28	b, p = 0.014) 8/15969	13/32631	 _+	0.25 (0.18, 0.3
Krong Pa, VT 20 Subtotal (I-squared = 60.3% NI P. spp Ialalabad, AF 28 .aghman, AF 30	6, p = 0.014) 8/15969 0/7978	13/32631 21/15192	 	0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6
Krong Pa, VT 20 Subtotal (I-squared = 60.3% VII P. spp Ialalabad, AF 28 aghman, AF 30 Vrba Minch, ET 14	6, p = 0.014) 8/15969 9/7978 14/18752	13/32631 21/15192 96/38098	  	0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4
Krong Pa, VT 20 Subtotal (I-squared = 60.3% VII P. spp alalabad, AF 28 aghman, AF 30 vrba Minch, ET 14 Aetahara, ET 45	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798	13/32631 21/15192 96/38098 9/19772		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4 0.10 (0.04, 0.2
Krong Pa, VT 20 Subtotal (I-squared = 60.3% VII P. spp alalabad, AF 28 aghman, AF 30 vrba Minch, ET 14 Aetahara, ET 45 fanura, ID 14	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698	13/32631 21/15192 96/38098 9/19772 94/78671	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4
Krong Pa, VT     20       Subtotal (I-squared = 60.3%       NI P. spp       Ialalabad, AF     28       .aghman, AF     30       Arba Minch, ET     14       Aletahara, ET     45       Hatanura, ID     14       Yanjung Leidong, ID     30	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698 0/26239	13/32631 21/15192 96/38098 9/19772 94/78671 13/53695		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4 0.24 (0.12, 0.4
Krong Pa, VT 20 Subtotal (I-squared = 60.3% VII P. spp Ialalabad, AF 28 aghman, AF 30 Vrba Minch, ET 14 Metahara, ET 45 Ianura, ID 14 anjung Leidong, ID 30 Dak O & Bu Gia Map, VT 10	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698 0/26239 00/14540	13/32631 21/15192 96/38098 9/19772 94/78671 13/53695 45/27930		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.4 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4 0.24 (0.12, 0.4 0.21 (0.13, 0.3
Krong Pa, VT         20           Subtotal (I-squared = 60.3%           VII P. spp           Ialalabad, AF         28           aghman, AF         30           Vrba Minch, ET         14           Aletahara, ET         45           Hanura, ID         14           Dak O & Bu Gia Map, VT         10           Krong Pa, VT         20	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698 15/40698 0/26239 00/14540 0/5284	13/32631 21/15192 96/38098 9/19772 94/78671 13/53695		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4 0.24 (0.12, 0.4 0.21 (0.13, 0.3 0.03 (0.00, 0.2
Krong Pa, VT 20 Subtotal (I-squared = 60.3% VII P. spp Ialalabad, AF 28 aghman, AF 30 Vrba Minch, ET 14 Metahara, ET 45 Ianura, ID 14 anjung Leidong, ID 30 Dak O & Bu Gia Map, VT 10	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698 15/40698 0/26239 00/14540 0/5284	13/32631 21/15192 96/38098 9/19772 94/78671 13/53695 45/27930		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.4 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4 0.24 (0.12, 0.4 0.21 (0.13, 0.3
irong Pa, VT 20 ubtotal (I-squared = 60.3% II P. spp alalabad, AF 28 aghman, AF 30 rba Minch, ET 14 letahara, ET 45 lanura, ID 14 anjung Leidong, ID 30 lak O & Bu Gia Map, VT 10 irong Pa, VT 20	5, p = 0.014) 3/15969 0/7978 14/18752 5/9798 15/40698 15/40698 0/26239 00/14540 0/5284	13/32631 21/15192 96/38098 9/19772 94/78671 13/53695 45/27930		0.25 (0.18, 0.3 0.24 (0.12, 0.4 0.37 (0.21, 0.6 0.30 (0.21, 0.4 0.10 (0.04, 0.2 0.33 (0.23, 0.4 0.24 (0.12, 0.4 0.21 (0.13, 0.3 0.03 (0.00, 0.2

## g) <u>PQ14 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due *P. vivax*

Site	Control arm: events/follow-up time (days)	PQ14 arm: events/follow-up time (days)	Hazard Ratio (95% Cl)
Symptomatic P. vivax			
Jalalabad, AF	17/6354	9/17404	0.21 (0.10, 0.46
_aghman, AF	14/3327	16/11030	0.36 (0.18, 0.72
Arba Minch, ET	29/7937	9/29170	0.09 (0.04, 0.19
letahara, ET	16/5485	3/19584	0.03 (0.04, 0.13
lanura, ID	38/26756	23/68589	0.24 (0.14, 0.40
anjung Leidong, ID	19/20151	4/45318	0.11 (0.04, 0.30
0ak O & Bu Gia Map, V		6/20581	0.08 (0.03, 0.19
Grong Pa, VT	9/3380	1/12786	0.06 (0.01, 0.29
Subtotal (I-squared = 5	8.9%, p = 0.017)	$\langle \rangle$	0.14 (0.09, 0.22
All P. vivax			
lalalabad, AF	17/6354	10/17404	0.24 (0.11, 0.50
.aghman, AF	14/3327	17/11030	0.36 (0.18, 0.72
-			
Arba Minch, ET	42/7937		0.10 (0.06, 0.18
Metahara, ET	22/5485	5/19584	0.08 (0.03, 0.20
Hanura, ID	59/26756	29/68589	0.20 (0.13, 0.30
Tanjung Leidong, ID	21/20151	4/45318	0.10 (0.04, 0.27
Dak O & Bu Gia Map, V	T 31/5079	8/20581	0.07 (0.03, 0.16
Krong Pa, VT	9/3380	1/12786	0.06 (0.01, 0.29
Subtotal (I-squared = 5	9.7%, p = 0.015)	$\diamond$	0.14 (0.09, 0.2
		.01 .05 .1 .2 .5 1 2 Favors PQ14	4 Favors Control
Site	Control: events/follow-up	Favors PQ14 PQ14 arm: events/follow-up	Favors Control
Site		Favors PQ14 PQ14 arm:	Favors Control
Symptomatic P. vivax	events/follow-up time (days)	Favors PQ14 PQ14 arm: events/follow-up time (days)	Favors Control Incidence Rate Ratio (95% CI)
Symptomatic P. vivax Jalalabad, AF	events/follow-up time (days) 28/15969	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.39
Symptomatic P. vivax Jalalabad, AF aghman, AF	events/follow-up time (days) 28/15969 28/7978	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.38 0.36 (0.20, 0.63
Symptomatic P. vivax Ialalabad, AF .aghman, AF Arba Minch, ET	events/follow-up time (days) 28/15969 28/7978 99/18752	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27
Symptomatic P. vivax Ialalabad, AF Laghman, AF Arba Minch, ET Metahara, ET	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 13/3738 13/37452 1/17249 31/38452 1/21405	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.63 0.17 (0.11, 0.27 0.06 (0.02, 0.18
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 	Favors Control Incidence Rate Ratio (95% CI) 0.21 (0.11, 0.36 0.36 (0.20, 0.63 0.17 (0.11, 0.27 0.06 (0.22, 0.14 0.21 (0.13, 0.33
Symptomatic P. vivax Jalalabad, AF aghman, AF Arba Minch, ET Metahara, ET Hanura, ID Fanjung Leidong, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.30
Symptomatic P. vivax Ialalabad, AF .aghman, AF Arba Minch, ET Aetahara, ET Ianura, ID Tanjung Leidong, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.22, 0.18 0.21 (0.13, 0.35 0.12 (0.05, 0.33 0.17 (0.09, 0.37
Symptomatic P. vivax Ialalabad, AF .aghman, AF Vrba Minch, ET Aletahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.36 0.36 (0.20, 0.66 0.17 (0.11, 0.27 0.06 (0.02, 0.18 0.21 (0.13, 0.36 0.12 (0.05, 0.33 0.17 (0.09, 0.37
Symptomatic P. vivax alalabad, AF aghman, AF vrba Minch, ET Aetahara, ET fahura, ID anjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 15/30144 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.30
Symptomatic P. vivax Ialalabad, AF .aghman, AF Mrba Minch, ET Aetahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 15/30144 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.30 0.17 (0.09, 0.37 0.08 (0.02, 0.28
Symptomatic P. vivax Jalalabad, AF Laghman, AF Vrba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Jak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 15/30144 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.30 0.17 (0.09, 0.37 0.08 (0.02, 0.28
Symptomatic P. vivax Ialalabad, AF .aghman, AF Arba Minch, ET Actahara, ET Hanura, ID Tanjung Leidong, ID Jak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 VII P. vivax Ialalabad, AF	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 15/30144 2/13412 14/37338 	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.66 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.30 0.17 (0.09, 0.37 0.08 (0.02, 0.24 0.18 (0.13, 0.24 0.22 (0.12, 0.47
Symptomatic P. vivax Ialalabad, AF .aghman, AF Arba Minch, ET Metahara, ET Fanjung Leidong, ID Dak O & Bu Gia Map, V Grong Pa, VT Subtotal (I-squared = 4 All P. vivax Ialalabad, AF .aghman, AF	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 13/3738 13/38452 14/21405 30/77772 6/51428 15/30144 2/13412 14/37338 14/3738 14/37 14	Favors Control Incidence Rate Ratio (95% CI) 0.21 (0.11, 0.36 0.36 (0.20, 0.66 0.17 (0.11, 0.27 0.06 (0.02, 0.16 0.21 (0.13, 0.30 0.12 (0.05, 0.30 0.17 (0.09, 0.37 0.08 (0.02, 0.26 0.18 (0.13, 0.24 0.22 (0.12, 0.47 0.35 (0.20, 0.66
Symptomatic P. vivax Ialalabad, AF .aghman, AF Metahara, ET Ianura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 VII P. vivax Ialalabad, AF .aghman, AF Vrba Minch, ET	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 1/17249 31/38452 4/21405 30/77772 6/51428 15/30144 2/13412 14/37338	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.36 0.36 (0.20, 0.63 0.17 (0.11, 0.27 0.06 (0.02, 0.18 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.09, 0.37 0.08 (0.02, 0.28 0.18 (0.13, 0.24 0.22 (0.12, 0.47 0.35 (0.20, 0.66 0.16 (0.10, 0.25
Symptomatic P. vivax Ialalabad, AF .aghman, AF Mrba Minch, ET Aratanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 NI P. vivax Ialalabad, AF .aghman, AF wha Minch, ET Aretahara, ET	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 15/30144 2/13412 13/30144 2/13412	Favors Control           Incidence Rate Ratio (95% CI)           0.21 (0.11, 0.36 0.36 (0.20, 0.63 0.17 (0.11, 0.27 0.06 (0.22, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.09, 0.33 0.08 (0.02, 0.28 0.18 (0.13, 0.24           0.22 (0.12, 0.44 0.35 (0.20, 0.66 0.16 (0.10, 0.22 0.08 (0.04, 0.15
Symptomatic P. vivax Ialalabad, AF .aghman, AF Vrba Minch, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 VII P. vivax Ialalabad, AF .aghman, AF Vrba Minch, ET Hetahara, ET Hanura, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 129/40698	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 13/37452 1/17249 30/77772 6/51428 15/30144 2/13412 14/37338 14/37338 14/37338 14/37338 14/37338 14/37338 14/3733 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/373 14/37	Favors Control Incidence Rate Ratio (95% Cl) 0.21 (0.11, 0.35 0.36 (0.20, 0.63 0.17 (0.11, 0.27 0.06 (0.02, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.09, 0.37 0.08 (0.02, 0.24 0.18 (0.13, 0.24 0.22 (0.12, 0.47 0.35 (0.20, 0.66 0.16 (0.10, 0.24 0.08 (0.04, 0.11 0.19 (0.13, 0.25
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Tanjung Leidong, ID Jak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 All P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Metahara, ET Hanura, ID Fanjung Leidong, ID	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 139/18752	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 14/37338 22/17249 33/38452 14/37338 14/37737 6/51428	Favors Control           Incidence Rate Ratio (95% Cl)           0.21 (0.11, 0.38 0.36 (0.20, 0.66 0.17 (0.11, 0.27 0.06 (0.22, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.36 0.17 (0.09, 0.3² 0.08 (0.02, 0.24 0.18 (0.13, 0.24           0.22 (0.12, 0.4² 0.35 (0.20, 0.66 0.16 (0.10, 0.25 0.08 (0.04, 0.18 0.13 (0.13, 0.24
Site Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Vletahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 All P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Vletahara, ET Hanura, ID Fanjung Leidong, ID Dak O & Bu Gia Map, V Crong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 129/40698 30/26239 T 90/14540	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 14/37338 22/17249 39/38452 7/21405 30/377772 6/51428 18/30144	Favors Control           Incidence Rate Ratio (95% Cl)           0.21 (0.11, 0.36 0.36 (0.20, 0.65 0.17 (0.11, 0.27 0.06 (0.02, 0.16 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.90, 0.37 0.08 (0.02, 0.26 0.18 (0.13, 0.24 0.18 (0.13, 0.24 0.18 (0.10, 0.25 0.08 (0.04, 0.15 0.13 (0.05, 0.33 0.11 (0.06, 0.21
Symptomatic P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 All P. vivax Jalalabad, AF Laghman, AF Arba Minch, ET Wetahara, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 129/40698 30/26239 T 90/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 14/37338 22/17249 33/38452 14/37338 14/37737 6/51428	Favors Control Incidence Rate Ratio (95% CI) 0.21 (0.11, 0.36 0.36 (0.20, 0.63 0.17 (0.11, 0.37 0.06 (0.02, 0.13 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.09, 0.33 0.08 (0.02, 0.21 0.18 (0.13, 0.22 0.18 (0.13, 0.22 0.18 (0.10, 0.23 0.08 (0.04, 0.13 0.19 (0.13, 0.22 0.13 (0.55, 0.36 0.11 (0.06, 0.22 0.08 (0.02, 0.24
Symptomatic P. vivax Jalalabad, AF Jaghman, AF Arba Minch, ET Hatana, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V Krong Pa, VT Subtotal (I-squared = 4 All P. vivax Jalalabad, AF Jaghman, AF Arba Minch, ET Hetahara, ET Hanura, ID Tanjung Leidong, ID Dak O & Bu Gia Map, V	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 129/40698 30/26239 T 90/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 14/37338 22/17249 39/38452 7/21405 30/377772 6/51428 18/30144	Favors Control           Incidence Rate Ratio (95% Cl)           0.21 (0.11, 0.38 0.36 (0.20, 0.66 0.17 (0.11, 0.27 0.06 (0.22, 0.14 0.21 (0.13, 0.33 0.12 (0.05, 0.36 0.17 (0.09, 0.3² 0.08 (0.02, 0.24 0.18 (0.13, 0.24           0.22 (0.12, 0.4² 0.35 (0.20, 0.66 0.16 (0.10, 0.25 0.08 (0.04, 0.18 0.13 (0.13, 0.24
Symptomatic P. vivax alalabad, AF .aghman, AF Motahara, ET Aetahara, ET tanura, ID Ganjung Leidong, ID Dak O & Bu Gia Map, V Gubtotal (I-squared = 4 VI P. vivax alalabad, AF .aghman, AF vrba Minch, ET Aetahara, ID Tanjung Leidong, ID Jak O & Bu Gia Map, V Grong Pa, VT	events/follow-up time (days) 28/15969 28/7978 99/18752 32/9798 82/40698 28/26239 T 48/14540 20/5284 4.2%, p = 0.084) 28/15969 30/7978 133/18752 44/9798 129/40698 30/26239 T 90/14540 20/5284	Favors PQ14 PQ14 arm: events/follow-up time (days) 13/37338 21/17249 31/38452 4/21405 30/77772 6/51428 14/37338 22/17249 39/38452 7/21405 30/377772 6/51428 18/30144	Favors Control Incidence Rate Ratio (95% CI) 0.21 (0.11, 0.36 0.36 (0.20, 0.63 0.17 (0.11, 0.37 0.06 (0.02, 0.13 0.21 (0.13, 0.33 0.12 (0.05, 0.33 0.17 (0.09, 0.33 0.08 (0.02, 0.21 0.18 (0.13, 0.22 0.18 (0.13, 0.22 0.18 (0.10, 0.23 0.08 (0.04, 0.13 0.19 (0.13, 0.22 0.13 (0.55, 0.36 0.11 (0.06, 0.22 0.08 (0.02, 0.24

## h) <u>PQ14 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due *P. falciparum*

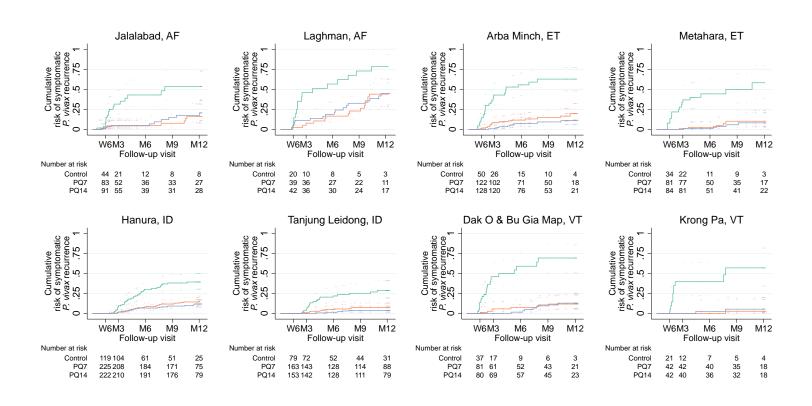


### i) <u>PQ14 vs Control</u>: Risks and rates for recurrent parasitemia due to symptomatic and any infection due all species

	Control arm:	PQ14 arm:			
	events/follow-up	events/follow-up			Hazard
Site	time (days)	time (days)			Ratio (95% CI)
Symptomatic P. spp					
Jalalabad, AF	17/6354	9/17404			0.21 (0.10, 0.46)
Laghman, AF	14/3327	16/11030	•		0.36 (0.18, 0.72)
Arba Minch, ET	34/7937	17/29170			0.15 (0.08, 0.27)
Metahara, ET	16/5485	4/19584			0.09 (0.03, 0.24)
Hanura, ID	46/26756	37/68589			0.32 (0.21, 0.49)
Tanjung Leidong, ID	19/20151	4/45318	•		0.11 (0.04, 0.30)
Dak O & Bu Gia Map, V	T 21/5079	9/20581 —	•		0.11 (0.05, 0.24)
Krong Pa, VT	9/3380	1/12786			0.06 (0.01, 0.29)
Subtotal (I-squared = 5	7.3%, p = 0.022)		$\diamond$		0.17 (0.11, 0.26)
All D					
All P. spp	17/0051	10/17404			0.04 (0.44, 0.56)
Jalalabad, AF	17/6354	10/17404			0.24 (0.11, 0.50)
Laghman, AF	14/3327	17/11030			0.36 (0.18, 0.72)
Arba Minch, ET	49/7937	30/29170			0.19 (0.12, 0.30)
Metahara, ET	22/5485	8/19584 —	•		0.12 (0.06, 0.27)
Hanura, ID	68/26756	48/68589	-•		0.28 (0.19, 0.41)
Tanjung Leidong, ID	21/20151	4/45318	•		0.10 (0.04, 0.27)
Dak O & Bu Gia Map, V		12/20581	•		0.10 (0.05, 0.19)
Krong Pa, VT	9/3380	2/12786	•		0.10 (0.03, 0.36)
Subtotal (I-squared = 5	3.5%, p = 0.035)		$\diamond$		0.18 (0.13, 0.26)
•					
		1 1		1 1	
		.01 .05	.1 .2 .5 1		
		Fav	ors PQ14	Favors Control	
	Control:	PQ14 arm:			
	events/follow-up	events/follow-up			Incidence Rate
Site	time (days)	time (days)			Ratio (95% CI)
Symptomatic P. spp					
Jalalabad, AF	28/15969	13/37338			0.21 (0.11, 0.39)
Laghman, AF	28/7978	21/17249			0.36 (0.20, 0.63)
Arba Minch, ET	107/18752	49/38452			0.22 (0.15, 0.33)
Metahara, ET	33/9798	5/21405			0.08 (0.03, 0.20)
Hanura, ID	95/40698	50/77772			0.28 (0.19, 0.41)
Tanjung Leidong, ID	28/26239	6/51428 —	•		0.12 (0.05, 0.30)
Dak O & Bu Gia Map, V		28/30144	I		0.24 (0.13, 0.43)
Krong Pa, VT	20/5284	3/13412	•		0.08 (0.02, 0.31)
Subtotal (I-squared = 4			$\diamond$		0.21 (0.15, 0.28)
All D. ann					
All P. spp	00/15000	14/07000			0.00 (0.10, 0.41)
Jalalabad, AF	28/15969	14/37338			0.22 (0.12, 0.41)
Laghman, AF	30/7978	23/17249			0.36 (0.21, 0.63)
Arba Minch, ET	144/18752	68/38452			0.21 (0.14, 0.32)
Metahara, ET	45/9798	11/21405 —			0.11 (0.05, 0.24)
Hanura, ID	145/40698	69/77772			0.26 (0.18, 0.36)

0.13 (0.05, 0.30) Tanjung Leidong, ID 30/26239 6/51428 Dak O & Bu Gia Map, VT 100/14540 38/30144 0.17 (0.10, 0.30) Krong Pa, VT 20/5284 4/13412 0.09 (0.02, 0.32) Subtotal (I-squared = 38.2%, p = 0.125) 0.21 (0.16, 0.27) .01 .05 .1 .2 .5 1 2 4 Favors PQ14 Favors Control

AF = Afghanistan; ET = Ethiopia; ID = Indonesia; VT = Vietnam



#### 19. Site-specific Kaplan Meier Curves for Symptomatic P. vivax Recurrence

Legend: W=week, M=month

AF = Afghanistan; ET = Ethiopia; ID = Indonesia; VT = Vietnam

95% CI	95% CI	95% CI
Control	PQ7	PQ14

#### 20. Details of SAEs

No	Age (yr.)	Sex	Site	Event/ diagnosis	Criteria for SAE reporting	G6PD status	Day of onset after last treatment	Duration (days)	Relation to study drug	Intensity	Outcome	Action taken to study drug
PQ7 1	Freatmer	nt Arm						<u>.</u>				•
1	9	F	ET001	Severe P. falciparum malaria	Hospitalization	Normal	46	1	Not related	Severe	Recovered	NA
2	2	M	ET001	Severe P. falciparum malaria	Hospitalization	Normal	221	3	Not related	Severe	Recovered	NA
3	2	F	ET001	Severe P. falciparum malaria	Hospitalization	Normal	57	2	Not related	Severe	Recovered	NA
4	11	F	ET002	Persistent vomiting	Hospitalization	Normal	10	4	Not related	Severe	Recovered	Temporarily discontinued for 4 days
5	25	F	ET002	Severe malaria (P. falciparum +P. vivax)	Hospitalization	Normal	2	5	Not related	Severe	Recovered	Continued
6	15	F	ET002	Persistent vomiting	Hospitalization	Normal	4	6	Probably related	Severe	Recovered	Temporarily discontinued for 3 days
7	13	F	ET002	Persistent vomiting	Hospitalization	Normal	2	4	Possibly related	Severe	Recovered	Temporarily discontinued for 6 days
8	25	Μ	ID004	Abdominal pain, fever of unexplained origin	Hospitalization	Normal	6	3	Not related	Severe	Recovered	Temporarily discontinued for 5 days
9	11	F	ID004	Haemolysis (Hb drop from 11.6 to 6.9 g/dl)	Hb fall <7g/dL	Normal	3	3	Possibly related	Moderate	Recovered	Temporarily discontinued for 1 day

10	23	F	ID004	Fever, abdominal pain, dyspnoea	Hospitalization	Normal	9	5	Possibly related	Severe	Recovered	Temporarily discontinued for 7 days
11	66	M	ID004	Sudden unexpected death due to myocardial infarction	Death	Normal	151	1	Not related	Life- threatenin g	Fatal	NA
12	11	F	ID004	Symptomatic methaemoglobin aemia & bronchopneumo nia	Hospitalization	Normal	10	7	Definitely related	Severe	Recovered	Temporarily discontinued for 2 days. 4 days later permanently discontinued
13	16	F	ID004	Acute appendicitis	Hospitalization	Normal	170	7	Not related	Moderate	Recovered	NA
14	13	М	ID004	Unilateral periorbital ecchymosis	Hospitalization	Normal	54	1	Not related	Moderate	Recovered	NA
15	19	F	ID004	Acute haemolysis (Hb drop from 13.7 to 9.5 g/dl)	Other important medical event	Normal	3	1	Definitely related	Severe	Recovered	Permanently discontinued
16	9	F	ID005	Epigastric pain	Hospitalization	Normal	4	1	Possibly related	Moderate	Recovered	Temporarily discontinued for 3 days
17	7	F	VN001	Diarrhoea	Hospitalization	Normal	7	4	Definitely related	Moderate	Recovered	Continued
18	20	М	VN001	Acute haemolysis (Hb drop from 15.3 to 6.4 g/dl)	Hospitalization and blood transfusion	Deficient*	5	6	Definitely related	Moderate	Recovered	Permanently discontinued
PQ14	4 Treatn	nent Ar	m									
19	3	М	ET002	Haemolysis (Hb drop from 10.2 to 6.8/dl)	Other important medical event	Normal	3	3	Probably related	Severe	Recovered	Permanently Discontinued
20	11	М	ET002	Acute exacerbation of bronchial asthma precipitated by pneumonia	Hospitalization	Normal	91	5	Not related	Severe	Recovered	NA

21	13	М	ID004	Complicated puncture wound	Hospitalization	Normal	129	5	Not related	Pot. life- threatenin g	Recovered	NA
22	46	М	ID004	Generalised peritonitis	Hospitalization	Normal	92	13	Not related	Severe	Recovered	NA
23	19	М	VN001	Undifferentiated carcinoma in nasopharynx	Life- threatening	Normal	147		Not related	Moderate	Improving	NA
Cont	rol Arm											
24	19	F	ET001	Soft tissue injury (car accident)	Hospitalization	Normal	5	3	Not related	Moderate	Recovered	Cont.
25	7	F	ID004	Bacterial enteritis	Hospitalization	Normal	12	4	Not related	Moderate	Recovered	Temporarily discontinued for 9 days
26	9	М	ID004	Dengue fever	Hospitalization	Normal	4	3	Not related	Moderate	Recovered	Temporarily discontinued for 3 days
27	22	М	VN001	Severe P. falciparum malaria	Hospitalization	Normal	14	3	Not related	Severe	Recovered	NA

#### 21. Site Specific Adverse Events

	Site	Outcome measure	Control	PQ7	PQ14
Afghanistan	AF001	Number enrolled	60	125	126
	Jalalabad	SAE PQ related - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
		SAE PQ unrelated - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
		AE - Grade 3 & 4	0 (0.0%)	1 (0.8%)	0 (0.0%)
		Event duration (days), median (IQR)		5.0 (5.0-5.0)	
		Treatment discontinued N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Vomited within 1hr of a study dose [initial episode]	1 (1.7%)	1 (0.8%)	1 (0.8%)
		,			
	AF008	Number enrolled	23	48	49
	Laghman	SAE PQ related - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
		SAE PQ unrelated - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
		AE - Grade 3 & 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event duration (days), median (IQR)			
		Treatment discontinued N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Vomited within 1hr of a study dose [initial episode]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethiopia	ET001	Number enrolled	74	149	148
	Arba Minch	SAE PQ related - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
		SAE PQ unrelated - All severities	1 (1.4%)	3 (2.0%)	0 (0.0%)
		AE - Grade 3 & 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event duration (days), median (IQR)	3.0 (3.0-3.0)		
		Treatment discontinued N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

		study dose [initial episode]	1 (1.2%)	4 (2.3%)	3 (1.8%)
		Vomited within 1hr of a	4 (4 20%)	4 (2, 200)	2 (4 00()
		Treatment discontinued N (%)	1 (1.2%)	1 (0.6%)	2 (1.2%)
		median (IQR)		(1.0-1.0)	
		AE - Grade 3 & 4 Event duration (days),	0 (0.0%)	0 (0.0%) 1.0	0 (0.0%)
		severities			0 (0.0%)
		SAE PQ unrelated - All	0 (0.0%)	0 (0.0%)	0 (0 0%)
	Tanjung Leidong	SAE PQ related - All severities	0 (0.0%)	1 (0.6%)	0 (0.0%)
	ID005	Number enrolled	85	171	169
		· · ·			
		Vomited within 1hr of a study dose [initial episode]	5 (4.2%)	11 (4.8%)	10 (4.4%)
		Treatment discontinued N (%)	2 (1.7%)	7 (3.1%)	2 (0.9%)
		median (IQR)	(3.0-3.0)	(3.0-6.0)	(1.0-1.0)
		AE - Grade 3 & 4 Event duration (days),	0 (0.0%) 3.0	4 (1.7%) 5.0	<u>1 (0.4%)</u> 1.0
		SAE PQ unrelated - All severities	2 (1.6%)	4 (1.7%)	2 (0.8%)
	Hanura	SAE PQ related - All severities	0 (0.0%)	4 (1.7%)	0 (0.0%)
Indonesia	ID004	Number enrolled	118	229	228
		episode]			
		Vomited within 1hr of a study dose [initial	0 (0.0%)	1 (1.2%)	0 (0.0%)
		Treatment discontinued	0 (0.0%)	4 (4.7%)	1 (1.2%)
		Event duration (days), median (IQR)		4.0 (3.0-5.0)	32.0 (32.0-32.0)
		AE - Grade 3 & 4	0 (0.0%)	1 (1.2%)	0 (0.0%)
		SAE PQ unrelated - All severities	0 (0.0%)	2 (2.4%)	1 (1.2%)
	Metahara	SAE PQ related - All severities	0 (0.0%)	2 (2.4%)	1 (1.2%)
	ET002	Number enrolled	40	85	84
		study dose [initial episode]	4 (5.4%)	2 (1.3%)	4 (2.7%)

Dak O & Bu Gia Map	SAE PQ related - All severities	0 (0.0%)	2 (2.3%)	0 (0.0%)
	SAE PQ unrelated - All severities	1 (2.3%)	0 (0.0%)	1 (1.1%)
	AE - Grade 3 & 4	0 (0.0%)	1 (1.1%)	0 (0.0%)
	Event duration (days), median (IQR)		4.0 (1.0-6.0)	
	Treatment discontinued N (%)	1 (2.3%)	6 (6.9%)	3 (3.4%)
	Vomited within 1hr of a study dose [initial episode]	0 (0.0%)	2 (2.3%)	1 (1.1%)
	· · · · · · · · · · · · · · · · · · ·			
VN002	Number enrolled	21	41	44
Krong Pa	SAE PQ related - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAE PQ unrelated - All severities	0 (0.0%)	0 (0.0%)	0 (0.0%)
	AE - Grade 3 & 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Event duration (days), median (IQR)			
	Treatment discontinued N (%)	0 (0.0%)	1 (2.4%)	1 (2.3%)
	Vomited within 1hr of a study dose [initial episode]	0 (0.0%)	0 (0.0%)	1 (2.3%)

#### 22. Details of AEs

No	Age	Sex	Site	Event/	Day of onset after last	Duration	Relation to study	Grade
	(yr.)			Diagnosis	treatment	(days)	drug	
PQ7 T	reatment /	Arm			•			·
1	38	Female	ID004	Dyspepsia	2	6	Possibly related	3
2	4	Male	AF001	Pneumonia	2	5	Possibly related	3
3	31	Male	VN001	Vomiting & Watery diarrhoea	4	1	Probably related	3
4	13	Female	ID004	Dyspepsia	5	6	Probably related	3
5	13	Female	ID004	Dyspepsia	5	4	Definitely related	3
6	13	Male	ID004	Dyspepsia	5	6	Probably related	3
7	15	Male	ET002	Gastritis	8	2	Possibly related	3
PQ14	Treatment	Arm						
1	40	Female	ID004	Fever & cold symptoms	10	1	Possibly related	3

## 23. Symptoms Elicited from Daily Questionnaires During Treatment between Days 1 and 3

The proportion of patients reporting each symptom at least once between days 1 and 3

	Site	Outcome measure	Control	PQ7	PQ14
Overall		Number [1]	N=461	N=927	N=934
		Vomiting	55 (11.9%)	137 (14.7%)	110 (11.7%)
		Headache	206 (44.4%)	424 (45.3%)	417 (44.5%)
		Nausea	144 (31.0%)	308 (32.9%)	292 (31.2%)
		Diarrhoea	15 (3.2%)	40 (4.3%)	18 (1.9%)
		Skin Rash	7 (1.5%)	12 (1.3%)	14 (1.5%)
		Poor appetite	166 (35.8%)	352 (37.6%)	347 (37.0%)
		Abdominal Pain	119 (25.6%)	259 (27.7%)	235 (25.1%)
		Myalgia / Arthralgia	112 (24.1%)	219 (23.4%)	205 (21.9%)
		Fever	121 (26.1%)	241 (25.8%)	260 (27.7%)
		Passing dark urine	17 (3.7%)	35 (3.7%)	38 (4.1%)
		Dizziness	66 (14.2%)	137 (14.7%)	133 (14.2%)
		Shortness of Breath	13 (2.8%)	19 (2.0%)	15 (1.6%)
		Itching	9 (1.9%)	16 (1.7%)	18 (1.9%)
		Any GI symptoms [2]	224 (48.3%)	461 (49.3%)	456 (48.7%)
	7			1	1
Afghanistan	AF001	Number [1]	N=59	N=124	N=125
	Jalalabad	Vomiting	1 (1.7%)	5 (4.0%)	6 (4.8%)
		Headache	13 (22.0%)	18 (14.5%)	28 (22.4%)
		Nausea	4 (6.8%)	11 (8.9%)	10 (8.0%)
		Diarrhoea	0 (0.0%)	5 (4.0%)	3 (2.4%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Poor appetite	3 (5.1%)	13 (10.5%)	14 (11.2%)
		Abdominal Pain	3 (5.1%)	11 (8.9%)	7 (5.6%)
		Myalgia / Arthralgia	8 (13.6%)	9 (7.3%)	19 (15.2%)
		Fever	6 (10.2%)	13 (10.5%)	16 (12.8%)
		Passing dark urine	0 (0.0%)	4 (3.2%)	2 (1.6%)
		Dizziness	4 (6.8%)	13 (10.5%)	8 (6.4%)
		Shortness of Breath	0 (0.0%)	1 (0.8%)	0 (0.0%)
		Itching	1 (1.7%)	0 (0.0%)	2 (1.6%)
		Any GI symptoms [2]	6 (10.2%)	23 (18.5%)	19 (15.2%)
		<u>, , , , , ,</u>	,	,	,
	AF008	Number [1]	N=23	N=47	N=49
	Laghman	Vomiting	0 (0.0%)	2 (4.3%)	1 (2.0%)
	_	Headache	1 (4.3%)	2 (4.3%)	9 (18.4%)
		Nausea	1 (4.3%)	3 (6.4%)	1 (2.0%)
		Diarrhoea	0 (0.0%)	1 (2.1%)	0 (0.0%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)

		Poor appetite	0 (0.0%)	4 (8.5%)	7 (14.3%)
		Abdominal Pain	0 (0.0%)	2 (4.3%)	2 (4.1%)
		Myalgia / Arthralgia	1 (4.3%)	1 (2.1%)	6 (12.2%)
		Fever	2 (8.7%)	8 (17.0%)	11 (22.4%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Dizziness	0 (0.0%)	1 (2.1%)	0 (0.0%)
		Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	1 (2.0%)
		Any GI symptoms [2]	1 (4.3%)	5 (10.6%)	8 (16.3%)
		Any di symptoms [2]	1 (4.576)	5 (10.078)	8 (10.376)
Ethiopia	ET001	Number [1]	N=72	N=146	N=147
-	Arba	Vomiting	21 (29.2%)	36 (24.7%)	39 (26.5%)
	Minch	Headache	38 (52.8%)	78 (53.4%)	80 (54.4%)
		Nausea	39 (54.2%)	81 (55.5%)	74 (50.3%)
		Diarrhoea	8 (11.1%)	18 (12.3%)	12 (8.2%)
		Skin Rash	5 (6.9%)	10 (6.8%)	11 (7.5%)
		Poor appetite	66 (91.7%)	132 (90.4%)	127 (86.4%)
		Abdominal Pain	35 (48.6%)	60 (41.1%)	61 (41.5%)
		Myalgia / Arthralgia	26 (36.1%)	47 (32.2%)	34 (23.1%)
		Fever	37 (51.4%)	73 (50.0%)	78 (53.1%)
		Passing dark urine	15 (20.8%)	29 (19.9%)	33 (22.4%)
		Dizziness	41 (56.9%)	80 (54.8%)	74 (50.3%)
		Shortness of Breath	11 (15.3%)	17 (11.6%)	15 (10.2%)
		Itching	8 (11.1%)	15 (10.3%)	11 (7.5%)
		Any GI symptoms [2]	68 (94.4%)	136 (93.2%)	135 (91.8%)
	57000	N	N 40	N 04	N 04
	ET002	Number [1]	N=40	N=84	N=84
	Metahara	Vomiting	1 (2.5%)	7 (8.3%)	5 (6.0%)
		Headache	14 (35.0%)	29 (34.5%)	30 (35.7%)
		Nausea	4 (10.0%)	11 (13.1%)	11 (13.1%)
		Diarrhoea	0 (0.0%)	1 (1.2%)	1 (1.2%)
		Skin Rash	0 (0.0%)	0 (0.0%)	1 (1.2%)
		Poor appetite	8 (20.0%)	14 (16.7%)	21 (25.0%)
		Abdominal Pain	2 (5.0%)	7 (8.3%)	5 (6.0%)
		Myalgia / Arthralgia	1 (2.5%)	8 (9.5%)	8 (9.5%)
		Fever	11 (27.5%)	19 (22.6%)	26 (31.0%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Dizziness	2 (5.0%)	0 (0.0%)	1 (1.2%)
				0 (0.0%)	0 (0.0%)
		Shortness of Breath	1 (2.5%)	. ,	
		Itching	0 (0.0%)	1 (1.2%)	1 (1.2%)
				. ,	
Indonesia	10004	Itching Any GI symptoms [2]	0 (0.0%) 11 (27.5%)	1 (1.2%) 26 (31.0%)	1 (1.2%) 29 (34.5%)
Indonesia	ID004 Hapura	Itching Any GI symptoms [2] Number [1]	0 (0.0%) 11 (27.5%) N=118	1 (1.2%) 26 (31.0%) N=228	1 (1.2%) 29 (34.5%) N=228
Indonesia	ID004 Hanura	Itching Any GI symptoms [2]	0 (0.0%) 11 (27.5%)	1 (1.2%) 26 (31.0%)	1 (1.2%) 29 (34.5%)

		Diarrhoea	4 (3.4%)	9 (3.9%)	2 (0.9%)
		Skin Rash	2 (1.7%)	1 (0.4%)	0 (0.0%)
		Poor appetite	35 (29.7%)	83 (36.4%)	73 (32.0%)
		Abdominal Pain	27 (22.9%)	65 (28.5%)	57 (25.0%)
		Myalgia / Arthralgia	29 (24.6%)	63 (27.6%)	60 (26.3%)
		Fever	39 (33.1%)	73 (32.0%)	76 (33.3%)
		Passing dark urine	2 (1.7%)	1 (0.4%)	3 (1.3%)
		Dizziness	14 (11.9%)	31 (13.6%)	36 (15.8%)
		Shortness of Breath	1 (0.8%)	1 (0.4%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Any GI symptoms [2]	68 (57.6%)	137 (60.1%)	132 (57.9%)
				(	(==================================
	ID005	Number [1]	N=85	N=170	N=169
	Tanjung	Vomiting	15 (17.6%)	43 (25.3%)	28 (16.6%)
	Leidong	Headache	70 (82.4%)	137 (80.6%)	134 (79.3%)
		Nausea	56 (65.9%)	110 (64.7%)	114 (67.5%)
		Diarrhoea	2 (2.4%)	4 (2.4%)	0 (0.0%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Poor appetite	53 (62.4%)	105 (61.8%)	103 (60.9%)
		Abdominal Pain	51 (60.0%)	110 (64.7%)	101 (59.8%)
		Myalgia / Arthralgia	47 (55.3%)	89 (52.4%)	78 (46.2%)
		Fever	6 (7.1%)	7 (4.1%)	9 (5.3%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Dizziness	5 (5.9%)	11 (6.5%)	14 (8.3%)
		Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	1 (0.6%)
		Any GI symptoms [2]	67 (78.8%)	125 (73.5%)	128 (75.7%)
Vietnam	VN001	Number [1]	N=43	N=87	N=89
	Dak O &	Vomiting	1 (2.3%)	2 (2.3%)	1 (1.1%)
	Bu Gia	Headache	7 (16.3%)	14 (16.1%)	10 (11.2%)
	Мар	Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Diarrhoea	1 (2.3%)	2 (2.3%)	0 (0.0%)
		Skin Rash	0 (0.0%)	1 (1.1%)	2 (2.2%)
		Poor appetite	1 (2.3%)	1 (1.1%)	2 (2.2%)
		Abdominal Pain	1 (2.3%)	3 (3.4%)	2 (2.2%)
		Myalgia / Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Fever	7 (16.3%)	17 (19.5%)	17 (19.1%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Dizziness	0 (0.0%)	1 (1.1%)	0 (0.0%)
		Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	2 (2.2%)
		Any GI symptoms [2]	3 (7.0%)	7 (8.0%)	5 (5.6%)
	VN002	Number [1]	N=21	N=41	N=43
	Krong Pa	Vomiting	0 (0.0%)	1 (2.4%)	0 (0.0%)

Headache	7 (33.3%)	21 (51.2%)	14 (32.6%)
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhoea	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
Poor appetite	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal Pain	0 (0.0%)	1 (2.4%)	0 (0.0%)
Myalgia / Arthralgia	0 (0.0%)	2 (4.9%)	0 (0.0%)
Fever	13 (61.9%)	31 (75.6%)	27 (62.8%)
Passing dark urine	0 (0.0%)	1 (2.4%)	0 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any GI symptoms [2]	0 (0.0%)	2 (4.9%)	0 (0.0%)
[1]: Number of patients with daily symptoms questio	•		·

[2]: Composite of any of the following: nausea, vomiting, anorexia, diarrhoea or abdominal pain

## 24. Symptoms elicited from daily questionnaires during treatment – Days 4 to 14

The proportion of patients reporting each symptom at least once between days 4 and 14

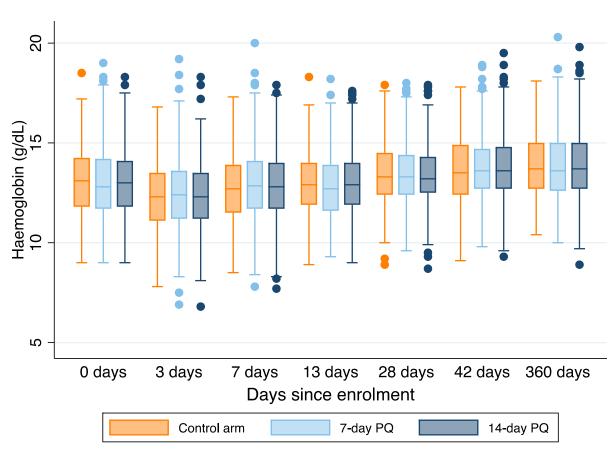
	Site	Outcome measure	Control	PQ7	PQ14
Overall		Number [1]	N=456	N=914	N=930
		Vomiting	14 (3.0%)	72 (7.7%)	47 (5.0%)
		Headache	93 (20.0%)	236 (25.2%)	201 (21.5%)
		Nausea	41 (8.8%)	143 (15.3%)	105 (11.2%)
		Diarrhoea	11 (2.4%)	67 (7.2%)	39 (4.2%)
		Skin Rash	8 (1.7%)	15 (1.6%)	16 (1.7%)
		Poor appetite	53 (11.4%)	179 (19.1%)	129 (13.8%)
		Abdominal Pain	45 (9.7%)	282 (30.2%)	172 (18.4%)
		Myalgia / Arthralgia	23 (5.0%)	71 (7.6%)	60 (6.4%)
		Fever	36 (7.8%)	80 (8.6%)	93 (9.9%)
		Passing dark urine	7 (1.5%)	27 (2.9%)	18 (1.9%)
		Dizziness	33 (7.1%)	77 (8.2%)	56 (6.0%)
		Shortness of Breath	6 (1.3%)	17 (1.8%)	14 (1.5%)
		Itching	8 (1.7%)	12 (1.3%)	9 (1.0%)
		Any GI symptoms [2]	92 (19.8%)	372 (39.8%)	259 (27.6%)
	• •			·	
Afghanistan	AF001	Number [1]	N=57	N=116	N=123
	Jalalabad	Vomiting	0 (0.0%)	7 (6.0%)	4 (3.3%)
		Headache	3 (5.3%)	12 (10.3%)	5 (4.1%)
		Nausea	0 (0.0%)	12 (10.3%)	3 (2.4%)
		Diarrhoea	0 (0.0%)	5 (4.3%)	2 (1.6%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Poor appetite	1 (1.8%)	14 (12.1%)	3 (2.4%)
		Abdominal Pain	0 (0.0%)	18 (15.5%)	8 (6.5%)
		Myalgia / Arthralgia	2 (3.5%)	5 (4.3%)	3 (2.4%)
		Fever	3 (5.3%)	1 (0.9%)	3 (2.4%)
		Passing dark urine	0 (0.0%)	3 (2.6%)	1 (0.8%)
		Dizziness	1 (1.8%)	8 (6.9%)	4 (3.3%)
		Shortness of Breath	0 (0.0%)	2 (1.7%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Any GI symptoms [2]	1 (1.8%)	23 (19.8%)	11 (8.9%)
				1	Γ
	AF008	Number [1]	N=23	N=46	N=49
	Laghman	Vomiting	0 (0.0%)	2 (4.3%)	1 (2.0%)
		Headache	0 (0.0%)	0 (0.0%)	1 (2.0%)
		Nausea	0 (0.0%)	1 (2.2%)	1 (2.0%)
		Diarrhoea	0 (0.0%)	2 (4.3%)	1 (2.0%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)

		Poor appetite	0 (0.0%)	2 (4.3%)	1 (2.0%)
		Abdominal Pain	0 (0.0%)	3 (6.5%)	2 (4.1%)
		Myalgia / Arthralgia	0 (0.0%)	0 (0.0%)	1 (2.0%)
		Fever	0 (0.0%)	1 (2.2%)	1 (2.0%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Shortness of Breath			
			0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Any GI symptoms [2]	0 (0.0%)	4 (8.7%)	3 (6.1%)
Ethiopia	ET001	Number [1]	N=71	N=143	N=146
•	Arba	Vomiting	9 (12.7%)	23 (16.1%)	14 (9.6%)
	Minch	Headache	16 (22.5%)	40 (28.0%)	36 (24.7%)
		Nausea	16 (22.5%)	39 (27.3%)	28 (19.2%)
		Diarrhoea	7 (9.9%)	27 (18.9%)	22 (15.1%)
		Skin Rash	5 (7.0%)	12 (8.4%)	10 (6.8%)
		Poor appetite	35 (49.3%)	69 (48.3%)	59 (40.4%)
		Abdominal Pain	17 (23.9%)	62 (43.4%)	49 (33.6%)
		Myalgia / Arthralgia	8 (11.3%)	19 (13.3%)	14 (9.6%)
		Fever	6 (8.5%)	16 (11.2%)	16 (11.0%)
		Passing dark urine	4 (5.6%)	16 (11.2%)	14 (9.6%)
		Dizziness	22 (31.0%)	37 (25.9%)	26 (17.8%)
		Shortness of Breath	3 (4.2%)	5 (3.5%)	3 (2.1%)
		Itching	5 (7.0%)	11 (7.7%)	6 (4.1%)
		Any GI symptoms [2]	43 (60.6%)	93 (65.0%)	90 (61.6%)
		Any di symptoms [2]	43 (00.076)	93 (03.078)	30 (01.078)
	ET002	Number [1]	N=39	N=84	N=84
Metah	Metahara	Vomiting	0 ( 0.0%)	8 ( 9.5%)	0 ( 0.0%)
		Headache	6 (15.4%)	12 (14.3%)	7 ( 8.3%)
		Nausea	0 ( 0.0%)	6 ( 7.1%)	0 ( 0.0%)
		Diarrhoea	0 ( 0.0%)	2 ( 2.4%)	2 ( 2.4%)
		Skin Rash	0 ( 0.0%)	1 ( 1.2%)	0 ( 0.0%)
		Poor appetite	1 ( 2.6%)	10 (11.9%)	1 ( 1.2%)
		Abdominal Pain	0 ( 0.0%)	13 (15.5%)	4 ( 4.8%)
		Myalgia / Arthralgia	0 ( 0.0%)	3 ( 3.6%)	1 ( 1.2%)
		Fever	2 ( 5.1%)	1 ( 1.2%)	2 ( 2.4%)
		Passing dark urine	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
		Dizziness	0 ( 0.0%)	0 ( 0.0%)	1 ( 1.2%)
		Shortness of Breath	0 ( 0.0%)	0 ( 0.0%)	1 ( 1.2%)
		Itching	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
		Any GI symptoms [2]	1 ( 2.6%)	21 (25.0%)	6 ( 7.1%)
ndonesia	ID004	Number [1]	N=118	N=228	N=228
	Hanura	Vomiting	4 (3.4%)	11 (4.8%)	21 (9.2%)
		Headache	36 (30.5%)	82 (36.0%)	80 (35.1%)
		Nausea	15 (12.7%)	35 (15.4%)	43 (18.9%)

		Diarrhoea	3 (2.5%)	10 (4.4%)	9 (3.9%)
		Skin Rash	3 (2.5%)	0 (0.0%)	5 (2.2%)
		Poor appetite	10 (8.5%)	44 (19.3%)	40 (17.5%)
		Abdominal Pain	18 (15.3%)	99 (43.4%)	61 (26.8%)
		Myalgia / Arthralgia	9 (7.6%)	20 (8.8%)	29 (12.7%)
		Fever	17 (14.4%)	41 (18.0%)	50 (21.9%)
		Passing dark urine	3 (2.5%)	7 (3.1%)	2 (0.9%)
		Dizziness	8 (6.8%)	21 (9.2%)	19 (8.3%)
		Shortness of Breath	3 (2.5%)	10 (4.4%)	10 (4.4%)
		Itching	3 (2.5%)	0 (0.0%)	1 (0.4%)
		Any GI symptoms [2]	30 (25.4%)	121 (53.1%)	90 (39.5%)
				(,	
	ID005	Number [1]	N=84	N=170	N=169
	Tanjung	Vomiting	1 (1.2%)	12 (7.1%)	6 (3.6%)
	Leidong	Headache	32 (38.1%)	89 (52.4%)	71 (42.0%)
		Nausea	10 (11.9%)	44 (25.9%)	30 (17.8%)
		Diarrhoea	1 (1.2%)	8 (4.7%)	1 (0.6%)
		Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Poor appetite	6 (7.1%)	32 (18.8%)	25 (14.8%)
		Abdominal Pain	10 (11.9%)	61 (35.9%)	41 (24.3%)
		Myalgia / Arthralgia	4 (4.8%)	24 (14.1%)	12 (7.1%)
		Fever	6 (7.1%)	11 (6.5%)	14 (8.3%)
		Passing dark urine	0 (0.0%)	0 (0.0%)	1 (0.6%)
		Dizziness	2 (2.4%)	11 (6.5%)	6 (3.6%)
		Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	0 (0.0%)	1 (0.6%)
		Any GI symptoms [2]	17 (20.2%)	78 (45.9%)	51 (30.2%)
Vietnam	VN001	Number [1]	N=43	N=86	N=89
	Dak O &	Vomiting	0 (0.0%)	7 (8.1%)	1 (1.1%)
	Bu Gia	Headache	0 (0.0%)	1 (1.2%)	1 (1.1%)
	Мар	Nausea	0 (0.0%)	5 (5.8%)	0 (0.0%)
		Diarrhoea	0 (0.0%)	11 (12.8%)	2 (2.2%)
		Skin Rash	0 (0.0%)	2 (2.3%)	1 (1.1%)
		Poor appetite	0 (0.0%)	5 (5.8%)	0 (0.0%)
		Abdominal Pain	0 (0.0%)	22 (25.6%)	6 (6.7%)
		Myalgia / Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Fever	2 (4.7%)	7 (8.1%)	7 (7.9%)
		Passing dark urine	0 (0.0%)	1 (1.2%)	0 (0.0%)
		Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Itching	0 (0.0%)	1 (1.2%)	1 (1.1%)
		Any GI symptoms [2]	0 (0.0%)	28 (32.6%)	7 (7.9%)
				1	
	VN002	Number [1]	N=21	N=41	N=42
	Krong Pa	Vomiting	0 (0.0%)	2 (4.9%)	0 (0.0%)

Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (2.4%)	0 (0.0%)
Diarrhoea	0 (0.0%)	2 (4.9%)	0 (0.0%)
Skin Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)
Poor appetite	0 (0.0%)	3 (7.3%)	0 (0.0%)
Abdominal Pain	0 (0.0%)	4 (9.8%)	1 (2.4%)
Myalgia / Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fever	0 (0.0%)	2 (4.9%)	0 (0.0%)
Passing dark urine	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shortness of Breath	0 (0.0%)	0 (0.0%)	0 (0.0%)
Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any GI symptoms [2]	0 (0.0%)	4 (9.8%)	1 (2.4%)

[2]: Composite of any of the following: nausea, vomiting, anorexia, diarrhoea or abdominal pain



# 25. Distribution of haemoglobin (g/dL) during follow up by treatment arm

Boxes represent 25<sup>th</sup> and 75<sup>th</sup> percentiles.

### 26. Haemoglobin Profile by Treatment Arm

	Control	PQ7	PQ14
Number of patients	464	935	937
Incidence risk of severe anaemia (<7 g/dL) or transfusion within 365		0.40 (0.13, 1.30)	0.11 (0.02, 0.77)
days (95% CI) [N]	[N = 0]	[N = 3]	[N = 1]
Hb drop >5g/dL within 7 days of initial treatment N (%)	0 (0.00)	0 (0.00)	1 (0.00)
Hb nadir within 28 days of treatment initiation, g/dL , mean[SD]	11.96 [1.6]	11.92 [1.6]	11.86 [1.6]
Time to Hb nadir, days, median (range)	3 (3 - 7)	3 (3 - 13)	3 (3 - 13)
Day 0			
Number of Patients	464	934	937
Hb on day 0, g/dL, mean[SD]	13.04 [1.7]	12.96 [1.8]	12.94 [1.7]
Day 3			
Number of Patients	432	891	895
Hb on day 3, g/dL , mean[SD]	12.31 [1.7]	12.41 [1.7]	12.30 [1.7]
Change in Hb between Day 0 and Day 3, g/dL, mean[SD]	-0.72 [1.12]	-0.52 [1.19]	-0.62 [1.09]
Absolute drop between Day 0 and Day 3 >5 g/dL, N (%)	0 (0.00)	0 (0.00)	1 (0.11)
Fractional change in Hb between Day 0 and Day 3, %, mean[SD]	-5.26 [8.64]	-3.60 [9.17]	-4.53 [8.47]
Fractional drop between Day 0 and Day 3 >25%, N (%)	3 (0.69)	8 (0.89)	8 (0.89)
Day 7			
Number of patients	447	882	888
Hb on day 7, g/dL , mean[SD]	12.72 [1.7]	12.91 [1.8]	12.81 [1.7]
Change in Hb between Day 0 and Day 7, g/dL, mean[SD]	-0.31 [1.20]	-0.01 [1.23]	-0.12 [1.09]
Absolute drop between Day 0 and Day 7 >5 g/dL, N (%)	0 (0.00)	0 (0.00)	0 (0.00)
Fractional change in Hb between Day 0 and Day 7, % , mean[SD]	-2.08 [9.01]	0.32 [9.58]	-0.62 [8.72]
Fractional drop between Day 0 and Day 7 >25%, N (%)	2 (0.45)	9 (1.02)	2 (0.23)
Day 13			
Number of patients	438	852	866
Hb on day 13, g/dL , mean[SD]	12.97 [1.6]	12.82 [1.6]	12.98 [1.5]
Change in Hb between Day 0 and Day 13, g/dL, mean[SD]	-0.07 [ 1.23]	-0.10 [ 1.26]	0.07 [ 1.15]
Absolute drop between Day 0 and Day 13 >5 g/dL, N (%)	0 (0.00)	1 (0.12)	0 (0.00)

Fractional change in Hb between Day 0 and Day 13, %, mean[SD]	-0.02 [ 9.48]	-0.08 [ 9.85]	1.08 [ 9.30]
Fractional drop between Day 0 and Day 13 >25%, N (%)	0 (0.00)	3 (0.35)	2 (0.23)
Day 28			
Number of patients	396	817	813
Hb on day 28, g/dL , mean[SD]	13.43 [1.6]	13.47 [1.5]	13.38 [1.5]
Day 42			
Number of patients	377	785	773
Hb on day 42, g/dL , mean[SD]	13.63 [1.7]	13.75 [1.5]	13.76 [1.6]