Incidence of Adverse Events

The incidence of CNS AEs over the full study period were similar in the TQ+chloroquine (TQ+CQ) and PQ+CQ treatment groups and lower than in the CQ alone group in these trials. This difference was driven primarily by AEs of headache, probably associated with malaria recurrence in this treatment group.

CNS AEs by System Organ Class and Preferred Term in the PC and AP Groupings (Safety Populations)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	**TQ+CQ (N=317) n (%)**	**PQ+CQ (N=179) n (%)**	**TQ+CQ (N=483) N (%)**	**PQ+CQ (N=264) N (%)**
Nervous System Disorders, any event	**50 (27)**	**58 (18)**	**35 (20)**	**105 (22)**	**60 (23)**
Headache	39 (21)	37 (12)	24 (13)	64 (13)	40 (15)
Dizziness	16 (9)	30 (9)	14 (8)	59 (12)	30 (11)
Migraine	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Syncope	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Somnolence	0	1 (<1)	0	1 (<1)	0
Burning sensation	0	0	1 (<1)	0	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Balance disorder	0	0	0	1 (<1)	0
Hypoaesthesia	0	0	0	0	1 (<1)
Psychiatric Disorders, any event	**5 (3)**	**13 (4)**	**8 (4)**	**15 (3)**	**12 (5)**
Insomnia	5 (3)	13 (4)	8 (4)	15 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	3 (1)
Depression	0	0	0	0	1 (<1)

PC: Placebo controlled studies in the radical cure program
AP: All primary studies in the radical cure program

Given this confounding factor, CNS events with onset during the first 29 days of the study are considered a better reflection of the AE profile for the active arms (TQ+CQ and PQ+CQ) compared to placebo (CQ only group).

Central Nervous System AEs with Onset On or Prior to Day 29 by System Organ Class and Preferred Term (PC and AP Safety Populations)

	PC Grouping			AP Grouping	
System Organ Class Preferred Term	**CQ alone (N=187) n (%)**	**TQ+CQ (N=317) n (%)**	**PQ+CQ (N=179) n (%)**	**TQ+CQ (N=483) n (%)**	**PQ+CQ (N=264) n (%)**
Nervous System Disorders, any event	**19 (10)**	**36 (11)**	**18 (10)**	**75 (16)**	**35 (13)**
Dizziness	6 (3)	25 (8)	10 (6)	52 (11)	23 (9)
Headache	12 (6)	15 (5)	9 (5)	34 (7)	19 (7)
Syncope	0	2 (<1)	0	2 (<1)	0
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Migraine	1 (<1)	0	0	0	0
Somnolence	0	1 (<1)	0	1 (<1)	0
Psychiatric Disorders, any event	**5 (3)**	**12 (4)**	**8 (4)**	**14 (3)**	**9 (3)**
Insomnia	5 (3)	12 (4)	8 (4)	14 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	1 (<1)

Using this more stringent analysis, the overall incidence of dizziness was higher for both TQ+CQ and PQ+CQ versus for CQ alone. This is consistent with the current labelling for primaquine. However, the overall incidences of other CNS events were similar across the treatment groups. In the TQ+CQ group, the events of anxiety and somnolence were Grade 1 or Grade 2 in severity and transient. None of the events were considered to be related to study treatment by the investigator.