

# Clinical utility of tafenoquine in the prevention of relapse of *Plasmodium vivax* malaria: a review on the mode of action and emerging trial data

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**Abstract:** Tafenoquine is an 8-aminoquinoline with activity against all human life cycle stages of *Plasmodium vivax*, including dormant liver stages – so called hypnozoites. Its long half-life of ~15 days is allowing for a single exposure regimen. It has been under development since 1980 and received approval by the US Food and Drug Administration in summer 2018 as an anti-relapse drug for *P. vivax* malaria in patients aged 16 years and older and for prophylaxis of malaria caused by any *Plasmodium* species in adults. Prior to tafenoquine administration, glucose-6-phosphate dehydrogenase (G6PD) deficiency needs to be excluded by testing. Individuals with a deficient G6PD activity are at risk of tafenoquine-induced hemolysis – as is the case for primaquine, the mainstay drug for *P. vivax* radical cure.

A wealth of clinical studies have been conducted and are still ongoing to assess the safety, tolerability, and efficacy of tafenoquine. This review focuses on data emerging from the latest clinical trials on *P. vivax* radical cure with tafenoquine, the key studies for regulatory approval of tafenoquine, and elucidates the latest hypothesis on the mode of action.

**Keywords:** hypnozoite, 8-aminoquinoline, WR238605, radical cure

## Introduction

Tafenoquine (TQ) is an 8-aminoquinoline derivative that had just received approval by the US Food and Drug Administration (FDA, July 2018) and the Australian Therapeutic Goods Administration (TGA, September 2018) for a radical cure of *Plasmodium vivax* malaria (US/Australia brand name Krintafel/Kozenis, developed by GlaxoSmithKline [GSK, London, UK]) together with Medicines for Malaria Venture (MMV, Geneva, Switzerland) and for prophylaxis of malaria (US/Australia brand name Arakoda/Kodatef, developed by 60 Degrees Pharmaceuticals (Washington DC, USA) together with the US Army).<sup>1</sup> TQ passed more than four decades of development as an antimalarial drug, and was initially under investigation as a prophylactic antimalarial agent for preventing *Plasmodium falciparum* malaria but without final submission of the dossier for market authorization. Clinical development slowed down and only gained pace again in the last 10 years when containment and treatment of *P. vivax* malaria appeared on the WHO agenda.<sup>2</sup> Previously a neglected pathogen, *P. vivax* has received more attention in recent years. Due to its unique biologic features, *P. vivax* is nowadays considered a huge challenge for the control and elimination of malaria.<sup>3</sup> *P. vivax* is globally the most widespread human malaria parasite species, and indeed causes more significant morbidity and mortality than previously thought.<sup>4</sup> Unlike *P. falciparum*, *P. vivax* develops undetectable dormant liver stages (hypnozoites) in the infected host. These hypnozoites are spontaneously activated

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by unknown mechanisms weeks (3–6 weeks) to several months (6–12 months) after the primary infection and cause blood stage infections called relapses, resulting in recurrent disease.<sup>5,6</sup> As hypnozoites are not affected by standard antimalarial treatments, eg, chloroquine (CQ) or artemisinin based combination therapies (ACTs), the treatment is a particular challenge to *P. vivax* malaria control.

Until FDA approval of TQ this summer, the only licensed drug for treatment of hypnozoites was primaquine (PQ), also an 8-aminoquinoline (8-AQ) known to act against dormant liver stages. It is given together with a 3-day treatment of CQ to provide radical cure, ie, curing the acute asexual blood stage infection and additionally clearing hypnozoites, thus preventing *P. vivax* relapses.<sup>7–9</sup> PQ side effects include gastrointestinal disturbances (GID), leukopenia, and methemoglobinemia (MHb).<sup>9</sup> Of special concern is hemolysis in people with glucose-6-phosphate-dehydrogenase (G6PD)-deficiency, a genetic disorder frequently found in populations of malaria-endemic regions.<sup>7–10</sup> This impedes PQ to be given without prior testing of the G6PD-status. In addition, PQ has to be metabolized by liver enzymes (CYP2D) to exert its action and will not be fully active in low metabolizers, leading to treatment failure.<sup>7,8</sup> A major limitation is the short biological half-life (3–6 hours) of PQ, implying daily administration for 14 days, presenting a major issue for compliance.<sup>11</sup>

GSK supported by MMV were spearheading the recent TQ development program for a radical cure of *P. vivax*. These efforts resulted into FDA approval of TQ as a single-dose (300 mg) oral treatment for *P. vivax* hypnozoites in patients older than 16 years given together with appropriate acute *P. vivax* antimalarial treatment (full course CQ or ACT).

TQ (2,6-dimethoxy-4-methyl-5-[[3(trifluoromethyl)phenoxy]–8-[[4-amino-1-methylbutyl]amino] quinoline) (Figure 1) is a long-acting PQ analog active against both blood and liver stages of *P. vivax* developed in the 1980s as an alternative to PQ by the Walter Reed Army Institute of Research in the USA, under the identifier WR238605.<sup>12,13</sup>

In total, 33 clinical studies with TQ as an anti-malarial agent have been conducted until October 2018. Results of the first TQ clinical trial in humans were published in 1998, showing that TQ was safe and well tolerated.<sup>14</sup> The molecule's promising half-life of 15 days initiated a series of clinical studies that led to established and consolidated safety, tolerability, and efficacy data.<sup>12,15–23</sup>

Three key studies with promising efficacy outcomes encouraged/fueled the current TQ anti-hypnozoite development program: DETECTIVE Part 1<sup>15</sup> (phase II study) and Part 2 (NCT01376167, phase III study) and GATHER

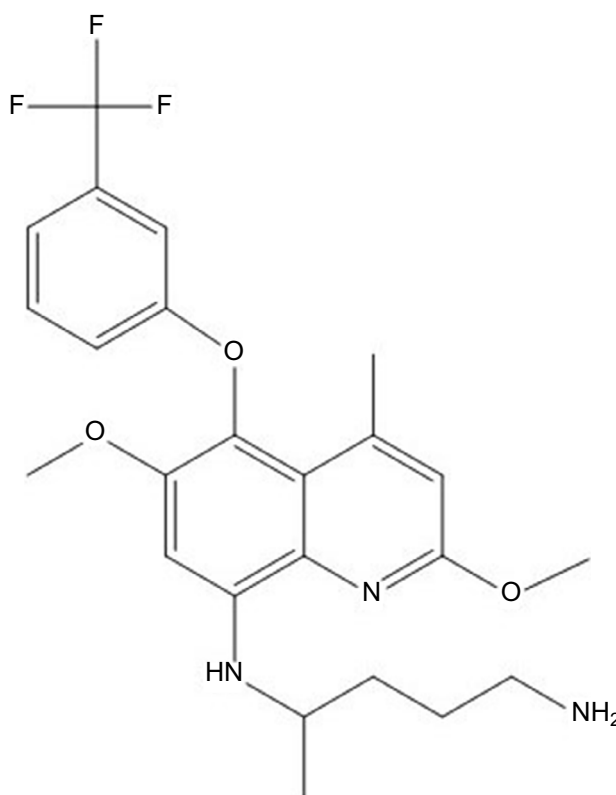


Figure 1 Chemical structure of tafenoquine.

(NCT02216123, phase III study). Overall, TQ at a 300 mg single dose was highly efficacious in preventing *P. vivax* recurrences until 6 months after treatment. In DETECTIVE Part 2, recurrence-free efficacy was 63% (95% CI = 55–69) for CQ + TQ, compared to 28% (95% CI = 20–36) for CQ alone. When CQ + TQ was compared to CQ + PQ, recurrence-free efficacy was 73% (95% CI = 65–79), compared to 75% (95% CI = 64–83), respectively.<sup>24</sup>

The aim of this review is to provide an update on what is known about the mode of action of TQ and to give an overview of the data emerging from the latest clinical trials conducted/being conducted in *P. vivax* infected patients. Studies leading to approval of TQ as a prophylactic antimalarial drug against all *Plasmodium* species are beyond the scope of this review, and will only be briefly summarized.

## Methods

The literature databases NCBI PubMed and Cochrane Library, as well as the clinical trial registry databases ClinicalTrials.gov, FDA homepage [fda.gov](http://fda.gov), and the WHO International Clinical Trial Registry Platform were searched. Search terms included tafenoquine, mode of action, clinical trials, human, *P. vivax* malaria, and malaria in combination. The

last search was done in October 2018. Any clinical trial on TQ was included, irrespective of study type. Data on two key studies (Detective Part II and Gather) are not yet published in peer-reviewed journals, but results were available through the FDA Application Review files available on the FDA webpage.

In total, 33 clinical studies on TQ were done or are still ongoing (Table 1). To date (October 2018) TQ has been evaluated in more than 4,000 individuals enrolled in ten phase I, nine phase II, eleven phase II/III, and three phase III clinical studies.

## Mechanism of action

As is true for many antimalarial compounds, neither the exact mechanism of antiplasmodial activity of TQ nor of the much longer available/licensed drug PQ is well understood. TQ is active against both liver stages and blood stages of *P. vivax* and *P. falciparum*. Current hypotheses claim that different compound metabolites and, hence, different modes of action account for TQ's parasite stage specific activity. As identified for PQ, CYP/CYP450 metabolism of TQ plays a crucial role for *P. vivax* liver stage activity, but seems not to be relevant for its blood schizonticidal activity.<sup>25</sup> For PQ's liver stage and anti-relapse activity liver enzyme CYP/CYP450 2D6 (CYP-2D6) metabolism is crucial. This was shown in transgenic mice that had a knockout of the P450 2D isozyme gene

cluster. PQ was only active against *P. berghei* liver stages if the knockout was rescued with human CYP-2D6.<sup>26</sup> This finding is completed by a report from a *P. vivax* human challenge trial, where two study participants experienced *P. vivax* relapses after CQ and PQ treatment, who were retrospectively identified as poor CYP-2D6 metabolizer genotypes.<sup>27</sup>

The most likely mechanism of PQ's antiplasmodial activity is its metabolism via CYP-2D6 generating hydroxyl PQ metabolites. Redox cycling of these metabolites results in formation of reactive oxygen species leading to parasite death.<sup>28,29</sup> The CYP-2D6 enzyme is highly polymorphic in human populations, and activity of the enzyme can be categorized in ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, and poor metabolizer.<sup>30,31</sup> Frequencies of poor metabolizers vary between populations, but can be as high as 19% , in addition to poor metabolizers, also intermediate metabolizers might not be able to sufficiently metabolize the drug.<sup>25,27,32,33</sup> Studies in the CYP-2D/human CYP-2D6 mice model indicated that CYP-2D metabolism is also crucial for TQ activation, although the extent of CYP-2D6 involvement in TQ liver stage efficacy is not clear.<sup>25,32</sup> Indeed, evidence from human studies suggested that the mechanisms of TQ activation might be different. Retrospective analysis of CYP-2D6 genotypes in a phase IIb TQ trial did not reveal an effect on the anti-relapse efficacy of TQ nor

**Table 1** List of studies with a primary focus on safety, tolerability, and pharmacokinetics of TQ

Title of publication or clinical trial	Study date	Reference
Assessment of any potential retinal effects of TQ	2016–2017	NCT02658435
Application of the stable isotope label approach in clinical development-supporting dissolution specifications for a commercial tablet product with tafenoquine, a long half-life compound	2016	78
Pharmacokinetic interactions between tafenoquine and dihydroartemisinin-piperaquine or artemether-lumefantrine in healthy adult subjects	2014–2015	55
Hemolytic potential of tafenoquine in female volunteers heterozygous for G6PD deficiency (G6PD mahidol variant) vs G6PD-normal volunteers	2009–2013	49
Tafenoquine at therapeutic concentrations does not prolong fridericia-corrected QT interval in healthy subjects	2011–2012	39
Exposure-response analyses for tafenoquine after administration to patients with <i>Plasmodium vivax</i> malaria	2011–2013	56
Pharmacokinetic interactions and safety evaluations of coadministered tafenoquine and chloroquine in healthy subjects	2009	45
Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects	n.i.	54
Gender differences in gastrointestinal disturbances and plasma concentrations of tafenoquine in healthy volunteers after tafenoquine administration for post-exposure <i>vivax</i> malaria prophylaxis	1999	43
Comparative ophthalmic assessment of patients receiving tafenoquine or chloroquine/primaquine in a randomized clinical trial for <i>P. vivax</i> malaria radical cure	1999–2000	41
Plasma concentrations of tafenoquine, a new long-acting antimalarial agent, in Thai soldiers receiving monthly prophylaxis	1998–1999	79
Population pharmacokinetics of the new antimalarial agent tafenoquine in Thai soldiers	1998–1999	53
First-time-in-humans safety and pharmacokinetics of WVR 238605, a new antimalarial	n.i.	14

**Abbreviations:** G6PD, glucose-6-phosphate dehydrogenase; n.i., not indicated; TQ, tafenoquine.

on TQ pharmacokinetics, whereas these data further support the liability of CYP-2D6 metabolism of PQ for efficacy against hypnozoites.<sup>34</sup> Despite its well described activity against *P. falciparum* and *P. vivax* blood stages, forming the rationale for the prophylaxis development program, the mechanism of action is not known, but seems to be independent from the CYP-2D6 status.<sup>35</sup> Potential mechanisms include interference with heme polymerization or oxidative mechanisms. In contrast to PQ, TQ is highly active against *Plasmodium* blood stages.<sup>34,36</sup> Indeed in the mouse malaria model, TQ was 9-times more active than PQ against blood stages of drug-sensitive *P. berghei* strains.<sup>37</sup> However, TQ is less active than CQ regarding the activity against blood stages of CQ-sensitive parasites.<sup>35</sup> Currently the most likely explanation for PQ failures after a full treatment course (14 days) is rather based on polymorphisms of CYP-2D6 and mostly not resistance of the parasite to PQ.<sup>32</sup>

## Safety and tolerability

More than 4,000 participants received at least one dose of TQ, and safety and tolerability profiles were generally good. See Table 1 for an overview of studies with a particular focus on safety, tolerability, and pharmacokinetics, although safety was also studied and reported within efficacy trials (phase II and phase III). All studies were conducted in adults, except one that included children and young adults aged 12–20 years.<sup>17</sup> The adverse event (AE) profile was similar between single dose and weekly or monthly treatments. Most of the AEs reported were mild and transient. Low doses of TQ (200 mg) were associated with fewer AEs compared to high doses (400, 500, and 600 mg).<sup>38</sup> The most frequently reported AE was GIT with diarrhea and abdominal pain.<sup>39–43</sup>

Pooled data of the three key studies for registration revealed that pruritus was the most frequent AE in participants exposed to CQ + TQ 300 mg single dose (37/317) followed by dizziness and nausea.<sup>44</sup>

AEs of special interest (AESIs) include cardiac, ophthalmic, and hematologic side effects, in addition to neurologic and psychiatric side effects, as these are known to be prevalent at various degrees for related drugs.

### Cardiac side effects

Cardiac effects of TQ were assessed in two studies with different doses (300, 450, 600, and 1,200 mg) given as monotherapy<sup>39,45</sup> or in combination with CQ.<sup>45</sup> No major clinical significant effect of TQ up to 1,200 mg on the QTcF was detected, and co-administration of TQ + CQ did not prolong the QT interval more than CQ monotherapy.

### Ophthalmic side effects

Eye disorders (mild vortex keratopathy, photophobia) were reported from one study in 69/74 (93%) Australian soldiers who received weekly TQ 200 mg for 6 months as a prophylactic regimen.<sup>40</sup> The ophthalmic changes were not associated with visual disturbances or impaired acuity/color vision. The keratopathy resolved within 1 year in all cases (incidence at 3 month 39% and at 6 month 10%). Fundoscopic assessments were made 3 months after the end of prophylactic treatment, and abnormalities were found in 27/69 individuals who took TQ and 4/17 individuals who took mefloquine. An independent group of experts investigated these findings and concluded that there is no sign of TQ-induced retinal toxicity. Induced ophthalmic changes are also known from other drugs, including the 4-aminoquinoline antimalarial CQ.<sup>46,47</sup> Results of three following studies aimed to provide further evidence of the ophthalmic effects of TQ and did not find a clinically significant effect of TQ on ophthalmic function,<sup>19,41,45</sup> even so a mild keratopathy was also observed with TQ when given for a short course (3 days).<sup>41</sup> One unpublished study (NCT02658435) submitted with the dossier to FDA was a phase I study designed to investigate ophthalmic safety of the 300 mg TQ dose for radical cure. The study did not find a signal for retinal toxicity of this TQ dose.<sup>24</sup> Ophthalmic safety will remain of special interest in future studies.

### Hematologic side effects

The main safety concern of TQ, like with other 8-AQ, is hemolysis in patients with G6PD-deficiency. G6PD-deficiency is frequently found in malaria endemic areas and is a hereditary, X-linked genetic defect so that males have either deficient G6PD activity (<30% of normal) or normal (>70% activity), whereas females can have intermediate (30%–60% activity) in addition to deficient and normal activity.<sup>48</sup>

One study assessed the hemolytic risk of different doses of TQ (100, 200, and 300 mg) vs the standard 14-day regimen of PQ in healthy G6PD-deficient females with a G6PD enzyme activity of 40%–60% of the site median normal value in comparison to G6PD “normal” control individuals.<sup>49</sup> Dose-limiting toxicity ( $\geq 2.5$  g/dL decline in hemoglobin and  $\geq 7.5\%$  decrease in hematocrit vs pre-treatment) was reached in 3/3 individuals receiving TQ 300 mg and 3/5 individuals receiving PQ. Following these results, further female individuals with a higher enzyme activity (61%–80%) were recruited to receive a 200 mg dose of TQ. Only two individuals could be identified (six planned), both had lower hemolysis compared to the individuals with

lower enzyme activity. Overall, hemolysis induced by TQ was higher in individuals with low G6PD-activity levels and increased with TQ dose. A TQ 300 mg single dose had similar hemolytic potential as PQ 15 mg for 14 days. All other clinical studies with TQ excluded individuals with a G6PD-activity <70%. Despite of this, eight incorrectly typed G6PD-deficient individuals were included in five clinical studies, all recovered without sequelae, but one individual experienced a serious adverse event (SAE), she was hospitalized and needed blood transfusion.<sup>24</sup> These results further supported the contraindication of giving TQ to individuals with G6PD-activity <70%.

### Neurologic/psychiatric side effects

Other clinical AEs that occurred with TQ administration were nervous and psychiatric disorders: insomnia, anxiety, depression, and mainly headache and dizziness. AEs were mild-to-moderate and transitional<sup>14,15,17,40,50</sup> DETECTIVE-Part 2 and GATHER. A limited number of serious psychiatric adverse reactions, such as depression, suicidal behaviour, and psychosis, have been reported, mainly in relation with multiples doses and in individuals with a prior history of psychiatric disorders.<sup>24</sup> Many participants of these trials were military personal that were in a “psychologically hostile environment”, however, prescription is contraindicated in people with a history of psychotic disorders.<sup>24</sup>

### Serious adverse events

In the three key studies, a total of 29 SAEs occurred in 483 individuals receiving CQ + TQ. Of those, hemoglobin (Hb) decrease was the most frequent SAE. An Hb decrease  $\geq 30\%$  or >39 g/L from baseline or a drop in Hb below 60 g/L was a predefined SAE described in the study protocol.

The safety profile led to the addition of the following points to the prescribing information of TQ. G6PD testing has to be done in all individuals before prescription of the drug. Contraindications include unknown G6PD status, G6PD deficiency (<70% activity), pregnancy, breastfeeding in cases where the G6PD deficiency of the child is unknown/child is G6PD deficient, and individuals with a history of psychotic disorders. Mothers should not breastfeed infants of unknown/deficient G6PD status for 3 months after the last dose of TQ.<sup>51</sup>

### Pharmacokinetics

The pharmacokinetic profile of TQ was evaluated in several studies.<sup>14,20,42,43,52–54</sup> TQ is slowly absorbed, with maximum

plasma concentrations reached 12–16 hour post-administration. TQ has a large volume of distribution (~1,600 L), a long elimination half-life of 13–19 days, and is enriched in erythrocytes vs plasma. Administration of TQ with food increases adsorption and minimizes gastrointestinal side-effects.<sup>42</sup> A population modeling approach combined data from different studies and showed that body weight, age, gender, and ethnicity did not have a large impact on pharmacokinetics.<sup>52</sup> TQ pharmacokinetics were not affected by co-administration of commonly prescribed antimalarial drugs such as CQ or ACTs (dihydroartemisinin-piperazine [DHA-PQP] or artemether-lumefantrine) so that TQ as well as the co-administered drug can be given without dose adjustment.<sup>55</sup> The area under the curve (AUC) of TQ after a single dose of 300 mg TQ in adults is ~100  $\mu\text{g}\cdot\text{h}/\text{mL}$  and a  $C_{\text{max}}$  of ~200 ng/mL.<sup>55,56</sup> Modeling revealed that this dose (300 mg) would provide in 90% of individuals an AUC greater than 56.4  $\mu\text{g}\cdot\text{h}/\text{mL}$  – a concentration that was a significant breakpoint as a predictor of relapse to infection, so that individuals with a higher AUC have a high probability of being relapse-free at 6 months.<sup>56</sup>

### Efficacy of TQ against *P. vivax* hypnozoites

In July/September 2018, FDA/TGA approved TQ (Krintafel/Kodatef) for radical cure of *P. vivax* malaria administered as a 300 mg single dose together with a standard *P. vivax* antimalarial to patients  $\geq 16$  years. Three key studies (DETECTIVE Parts 1 and 2, and GATHER) (NCT01376167, NCT02216123)<sup>24</sup> provided evidence for efficacy and safety of this dose and led to dossier submission applying for registration.<sup>1</sup>

In total, eight clinical studies investigated the anti-relapse efficacy of TQ in more than 2,700 adults  $\geq 16$  years with *P. vivax* malaria, of which more than 1,800 received TQ. Of these, 483 patients received a CQ (standard regimen)+TQ 300 mg single dose in three pivotal studies summarized below. All studies but one (7/8)<sup>57</sup> randomized study participants, and 5/8 were multicentric studies (NCT02216123, NCT01376167).<sup>15,19,57</sup> The anti-relapse efficacy of TQ was determined by assessing the proportion of overall recurrent *P. vivax* parasitemia in the Kaplan–Meier analysis at 6 months follow-up. All studies were conducted in malaria-endemic areas where *P. vivax* reinfections can occur. Unfortunately, for *P. vivax* no method is established to reliably distinguish relapses caused by hypnozoites from new infections. See Table 2 for an overview of clinical studies focusing on TQ efficacy for radical cure as well as for malaria prophylaxis.

**Table 2** List of clinical studies focusing on TQ efficacy

	Study drugs	Study type/endpoint(s)	Study period	RC/Pro	Location	No. of participants	Sex/age	Infected on inclusion
1	TQ PQ DHA/PQP	Randomized, active-controlled, double-blind Efficacy/superiority of DHA/PQP+TQ against DHA/PQP for <i>Plasmodium vivax</i> radical cure compared to CQ at 6 months after treatment	2018 – 2019	RC	Timor-Leste	150 planned	Males, females/≥18 years	Yes <i>P. vivax</i>
2	TQ PQ CQ <sup>a</sup>	<b>Active-controlled, double-blind</b> <b>Incidence of hemolysis, safety, and efficacy of TQ vs PQ for <i>P. vivax</i> radical cure at 6 months after treatment</b>	2015 – 2016	RC	Brazil Colombia Ethiopia Peru Thailand Vietnam	251 included	Males, females/≥16 years	Yes <i>P. vivax</i>
3	TQ PQ CQ <sup>a</sup>	Randomized, active-controlled, double-blind <b>Effectiveness and safety of 300 mg TQ + CQ for <i>P. vivax</i> radical cure compared to CQ at 6 months after treatment</b>	2014 – 2016	RC	Bangladesh Brazil Cambodia Ethiopia India Peru Philippines Thailand	522 included	Males, females/≥16 years	Yes <i>P. vivax</i>
4	TQ MQ PQ	Randomized, active-controlled, double-blind Efficacy of TQ for malaria prophylaxis for 6 months and for <i>P. vivax</i> post-exposure prophylaxis 3 months later	2000 – 2001	Pro, RC	Timor-Leste	654 included	Males, females/18–55 years	No
5	(Doxy) TQ PQ	Randomized, open-label, parallel-group Efficacy of TQ for <i>P. vivax</i> post-exposure prophylaxis for 12 months	1999 – 2000	Pro	Papua New Guinea Timor-Leste	1,512 included	Males, females/18–55 years	No
6	TQ	Randomized, placebo-controlled, double-blind, Long-term safety	2017 – 2020	Pro	Australia	600 planned	Males, females/18–55 years	NA
7	TQ CQ	Open-label, non-comparative, single arm Pharmacokinetics, safety and efficacy of TQ in pediatric patients for <i>P. vivax</i> radical cure	2017 – 2019	RC	Colombia Thailand Vietnam	60 planned	Males, females/6 months–15 years	Yes <i>P. vivax</i>

Treatment allocation	Status	Phase	Outcome	Reference
T1) DHA/PQP+TQ 300 mg (single dose)+PQ-placebo (for 14 days) T2) DHA/PQP+PQ 15 mg (for 14 days)+TQ-placebo T3) DHA/PQP+PQ-placebo (for 14 days)+TQ placebo	R	III	Study is ongoing	NCT02802501
<b>T1) CQ + TQ 300 mg (single dose)+PQ-placebo daily for 14 days</b> <b>T2) CQ + TQ placebo+PQ 15 mg daily for 14 days</b>	<b>C</b>	<b>III</b>	<b>Number (%) of recurrence-free participants at 6 months post-treatment:</b> <b>T1) CQ + TQ: 112/166 (76%)</b> <b>T2) CQ + PQ: 60/85 (71%)</b> <b>Overall incidence of clinically relevant hemolysis:</b> <b>T1) CQ + TQ: 2.4%</b> <b>T2) CQ + PQ: 1.2%</b>	<b>NCT02216123 (GATHER), 24</b>
<b>T1) CQ + TQ 300 mg (single dose)+PQ-placebo daily for 14 days</b> <b>T2) CQ + TQ placebo+PQ 15 mg daily for 14 days</b> <b>T3) CQ + TQ placebo+PQ-placebo daily for 14 days</b>	<b>C</b>	<b>III</b>	<b>Number (%) of recurrence-free participants at 6 months post-treatment:</b> <b>T1) CQ + TQ: 155/260 (60%)</b> <b>T2) CQ + PQ: 83/129 (64%)</b> <b>T3) CQ: 35/133 (26%)</b>	<b>NCT01376167 (DETECTIVE, Part 2), 24</b>
T1) TQ loading dose 200 mg/day for 3 days followed by weekly dose of 200 mg TQ for 26 weeks T2) MQ loading dose 250 mg/day for 3 days followed by weekly dose of 250 mg MQ for 26 weeks Upon return to Australia: T1 received placebo twice a day for 14 days T2 received PQ 15 mg twice a day for 14 days	P	III	Malaria prophylaxis: number (%) of <i>P. vivax</i> uninfected participants at 6 months exposure: T1) 492/492 (100%) T2) 162/162 (100%) Post-exposure prophylaxis, number (%) of <i>P. vivax</i> uninfected participants at 3 months post-exposure: T1) 488/492 (99%) T2) 161/162 (99%)	40, 80
All study participants took doxy during their stay of at least 2 months in a malaria endemic region. The study started after their return and participants were randomized to 4 arms: T1) TQ 400 mg 1× daily for 3 days T2) TQ 200 mg 2× daily for 3 days T3) TQ 200 mg 1× daily for 3 days T4) PQ 7.5 mg 3× daily for 14 days+doxy 100 mg for 14 days	P	II/III	Number (%) of <i>P. vivax</i> uninfected participants at 12 months post-exposure: T1): 223/242 (92%) T2): 156/161 (97%) T3): 386/406 (95%) T4): 429/464 (92%) Most common AEs were GID. Most AEs were mild or moderate	19
T1) TQ 200 mg/day for 3 days followed by TQ 200 mg 1× per week for 51 weeks T2) Placebo daily for 3 days followed by placebo 1× per week for 51 weeks	R	II	Study is ongoing	NCT03320174
T1) CQ + TQ single dose (100–300 mg depending on weight)	R	II	Study is ongoing	NCT02563496

(Continued)

**Table 2** List of clinical studies focusing on TQ efficacy

	Study drugs	Study type/endpoint(s)	Study period	RC/Pro	Location	No. of participants	Sex/age	Infected on inclusion
8	TQ CQ <sup>a</sup> PQ	Randomized, double-blind, dose-ranging Optimal TQ dose, safety and tolerability, efficacy of TQ + CQ for <i>P. vivax</i> radical cure compared to CQ at 6 months after treatment	2011 – 2013	RC	Brazil Peru India Thailand	329 included	Males, females/≥16 years	<i>P. vivax</i>
9	TQ CQ PQ	Randomized, placebo-controlled, double-blind Efficacy and safety of TQ for treatment of <i>P. vivax</i>	2003 – 2005	Treatment and RC	Thailand	70 included	Males, females/20–60 years	Yes <i>P. vivax</i>
10	TQ MQ	Randomized, placebo-controlled, double-blind Prophylactic efficacy of <i>Plasmodium falciparum</i> infection of TQ compared to MQ within 6 months	2000 – 2003	Pro	Kenya	306 included	Males, females/18–55 years	No
11	TQ MQ	Randomized, placebo-controlled, double-blind Prophylactic efficacy against <i>P. falciparum</i> infection of TQ compared to MQ during 17 weeks	1998 – 2003	Pro	Ghana	521 included	Males/18–60 years and Females/50–60 years	No
12	TQ	Randomized, double-blind Prophylactic efficacy against <i>P. falciparum</i> infection and safety of different doses of TQ	1999	Pro	Gabon	417 included	Males, females/12–20 years	<i>P. falciparum</i>



Treatment allocation	Status	Phase	Outcome	Reference
<b>Single dose of each:</b> T1) CQ + TQ 50 mg T2) CQ + TQ 100 mg T3) CQ + TQ 300 mg T4) CQ + TQ 600 mg T5) CQ + PQ 15 mg over 14 days T6) CQ only	P	II	<b>Number (%) of recurrence-free participants at 6 months post-treatment:</b> T1) 29/55 (53%) T2) 29/57 (51%) T3) 48/57 (84%) T4) 43/56 (77%) T5) 34/50 (68%) T6) 21/54 (39%) <b>QT prolongation was the most common SAE:</b> 2% in TQ group 8% in PQ group 4% in CQ alone <b>AEs:</b> <b>Headache (28%), pyrexia (24%) and chills (23%), high incidence of diarrhea in T4</b>	15 <b>Part I of DETECTIVE</b>
T1) TQ 400 mg/day for 3 days+CQ placebo for 3 days, then PQ placebo from day 4 to day 18 T2) CQ 1,000 mg on day 1 and day 2 and CQ 500 mg on day 3, then +TQ placebo on day 1 to day 3, then PQ 15 mg/day from day 4 to day 18	P	II	Number (%) of participants cured at day 28 after T1) TQ: 40/43 (93%) T2) CQ + PQ: 22/22 (100%) Number (%) of recurrence-free participants at 4 months after treatment start: T1) TQ: 35/35 (100%) T2) CQ + PQ: 19/20 (95%) Safety: 5 SAE in TQ group as increased MHB (related to drug)	22
T1) TQ 200 mg/day for 3 days, then TQ 200 mg weekly for 24 weeks T2) MQ 250 mg/day for 3 days, then MQ 250 mg weekly for 24 weeks T3) Placebo for 3 days, then placebo weekly for 24 weeks	C	II	Number (%) of <i>P. falciparum</i> uninfected participants within 6 months after treatment start: T1) TQ: 12/102 (12%) T2) MQ: 7/99 (7%) T3) Placebo: 6/99 (6%)	NCT02488980
T1) Placebo/day for 3 days, then placebo weekly for 13 weeks T2) TQ 25 mg/day for 3 days, then TQ 25 mg weekly for 13 weeks T3) TQ 50 mg/day for 3 days, then TQ 50 mg weekly for 13 weeks T4) TQ 100 mg/day for 3 days, then TQ 100 mg weekly for 13 weeks T5) TQ 200 mg/day for 3 days, then TQ 200 mg weekly for 13 weeks T6) MQ 250 mg/day for 3 days, then MQ 250 mg for 13 weeks	P	II	Number (%) of <i>P. falciparum</i> uninfected participants within 17 weeks after treatment start: T1) Placebo: 9/94 (10%) T2) TQ 25 mg: 35/93 (38%) T3) TQ 50 mg: 78/91 (86%) T4) TQ 100 mg: 83/94 (88%) T5) TQ 200 mg: 79/91 (87%) T6) MQ: 40/46 (87%) Safety and tolerability: musculoskeletal, GID and respiratory systems collectively accounted for 52%–70% of the total AEs in each group	50
T1) TQ 250 mg/day for 3 days T2) TQ 125 mg/day for 3 days T3) TQ 62.5 mg/day for 3 days T4) TQ 31.25 mg/day for 3 days T5) Placebo/day for 3 days	P	II	Number (%) of <i>P. falciparum</i> uninfected participants at week 11 after treatment start: T1) TQ 250 mg: 84/84 (100%) T2) TQ 125 mg: 78/79 (99%) T3) TQ 62.5 mg: 83/86 (97%) T4) TQ 31.2 mg: 63/79 (80%) T5) Placebo: 68/82 (83%) Abdominal was the most AE reported mainly in the TQ 250 mg group	17

(Continued)

**Table 2** List of clinical studies focusing on TQ efficacy

	Study drugs	Study type/endpoint(s)	Study period	RC/Pro	Location	No. of participants	Sex/age	Infected on inclusion
13	TQ	Randomized, placebo-controlled, double-blind Prophylactic efficacy against <i>P. falciparum</i> infection of TQ compared to placebo within 17 weeks	1997 – 1998	Pro	Kenya	235 included	Males, females/18–55 years	No
14	TQ CQ*	Randomized, open-label, dose escalation, Safety, tolerability, and efficacy of TQ for <i>P. vivax</i> radical cure compared to CQ at 6 months after treatment	1996 – 1997	RC	Thailand	44 included	Males, females/18–60 years	<i>P. vivax</i>
15	TQ	Randomized, placebo-controlled, double-blind Safety and prophylactic efficacy of TQ against <i>P. vivax</i> and drug-resistant <i>P. falciparum</i> infection	1998	Pro	Thailand	205 included	Males/18–55 years	No
16	TQ PQ CQ <sup>a</sup>	Randomized, open-label Safety, tolerability, and efficacy of TQ for <i>P. vivax</i> radical cure	1998 – 1999	RC	Thailand	80 included	Males, females/18–55 years	<i>P. vivax</i>
17	TQ CQ	Open-label Efficacy of TQ for <i>P. vivax</i> radical cure	n.i.	RC	Australia	27 included	Males, females/mean age: 25 years	<i>P. vivax</i>

Treatment allocation	Status	Phase	Outcome	Reference
T1) TQ 400 mg/day for 3 days, then placebo weekly for 13 weeks T2) TQ 200 mg/day for 3 days, then TQ 200 mg weekly for 13 weeks T3) TQ 400 mg/day for 3 days, then TQ 400 mg weekly for 13 weeks T4) Placebo for 3 days, then placebo once weekly for 13 weeks	P	II	Number (%) of <i>P. falciparum</i> uninfected participants within 17 weeks after treatment start: T1) 38/54 (70%) T2) 46/53 (87%) T3) 51/57 (89%) T4) 5/59 (8%) Safety: AEs similar number of volunteers in the 4 treatment groups, GID more common in TQ 400 mg dose, 2 hemolytic events occurred in TQ recipients (G6PD status not been correctly checked)	42
T1) CQ + TQ 300 mg/day for 7 days T2) CQ + TQ 500 mg/day for 3 days, then 1 week later TQ 500 mg/day for 3 days T3) CQ + TQ 500 mg once T4) CQ only	P	II	Number (%) of recurrence-free participants at 6 months post-treatment: T1) 15/15 (100%) T2) 10/11 (90%) T3) 8/9 (89%) T4) 5/9 (56%) Safety/tolerability: Except of MHB elevations, no clinically important laboratory value abnormalities GID were slightly more frequent in the TQ groups than among the CQ group only	21
T1) TQ 400 mg/day for 3 days, then 400 mg/month for 5 months T2) Placebo: same dosing schedule	P	II	Number (%) of <i>P. falciparum</i> and <i>P. vivax</i> uninfected participants at 6 months after TQ start treatment start: <i>P. vivax</i> : T1) 103/104 (99%) (1 vivax) T2) 71/101 (70%) (21 vivax, 8 falci, 1, mixed) Safety: GID more common among TQ recipients than among placebo recipients Most TQ recipients had transient, asymptomatic elevations of MHB	23
T1) CQ + TQ 300 mg/day for 7 days T2) CQ + TQ 600 mg/day for 3 days T3) CQ + TQ 600 mg single dose T4) CQ only T5) CQ + PQ 15 mg/day for 14 days	P	II	Number (%) of recurrence-free participants at 6 months post-TQ treatment start: 26/27 (96%) T1) 18/18 (100%) T2) 19/19 (100%) T3) 17/18 (94%) T4) 5/13 (38%) T5) 9/12 (75%) Safety/tolerability: Transient elevations in the MHB, AEs among the treatment groups were mild and transient, higher proportion of GID among TQ recipients, no SAE	20
CQ: 600 mg+300 mg on day 1, 300 mg on day 2 and 300 mg on day 3 to treat acute infections Volunteers who already had $\geq 1$ episode of <i>P. vivax</i> malaria relapse received TQ: TQ: TQ 200 mg/day for 3 days, then TQ 200 mg once/week for 8 weeks	P	II	Number (%) of recurrence-free participants at 6 months post-TQ treatment start: 26/27 (96%) No SAE, TQ was well-tolerated	57

(Continued)

**Table 2** List of clinical studies focusing on TQ efficacy

	Study drugs	Study type/endpoint(s)	Study period	RC/Pro	Location	No. of participants	Sex/age	Infected on inclusion
18	TQ	Randomized, placebo-controlled, double-blind, CHMI trial Prophylactic efficacy of TQ against <i>P. falciparum</i> infection by CHMI (blood stage)	2017	Pro	Australia	16 included	Males, females/ 20–42 years	No
19	TQ	Randomized, placebo-controlled, double-blind, CHMI trial Prophylactic efficacy of TQ against <i>P. falciparum</i> infection by CHMI (blood stage)	n.i.	Pro	USA	6 included	Males, females/ median age 25±5 years	No

**Notes:** Bold: key studies. Study intervention: TQ, MQ, DHA/PQP, AL, Doxy. Outcome: AEs, SAEs. †If not otherwise indicated, in these studies CQ was given as an oral dose of 600 mg on day 1, 600 mg on day 2, and 300 mg on day 3. ‡Clinical relevant hemolysis was defined as a decrease in Hb of ≥30% or 3 g/dL from baseline or an overall drop in Hb below 6 g/dL.

**Abbreviations:** AL, artemether+lumefantrine; C, complete; CHMI: controlled human malaria infection with *P. falciparum*; CQ, chloroquine; DHA/PQP, dihydroartemisinin+piperazine; Doxy, doxycyclin; FDA, Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; GID, gastrointestinal disturbances; Mhb, methemoglobinemia; MQ, mefloquine; NA, not applicable; n.i., not indicated; NR, not yet recruiting; P, peer-review published; PQ, primaquine; R, recruiting; RC/Pro, TQ efficacy investigated for *P. vivax* radical cure (RC) or for malaria prophylaxis (Pro) (all *Plasmodium* species); TQ, tafenoquine.

## Key studies

The following three key studies established 300 mg of TQ as an effective single dose treatment for radical cure of *P. vivax* malaria combined to CQ standard treatment.

DETECTIVE, Part 1 (NCT01376167), was a phase IIb/III dose finding study conducted in four different countries (Brazil, Peru, India, and Thailand).<sup>15</sup> Single doses of 50, 100, 300, or 600 mg TQ (combined to a standard regimen of 3 days CQ) were compared to 14 days PQ (15 mg/day) + CQ and CQ only. Of 329 participants enrolled, 225 received CQ + TQ. Recurrence-free efficacy 6 months after treatment with CQ + TQ 300 mg was 89% (95% CI = 77–95) compared to 38% (95% CI = 23–52) receiving CQ only and 77% (95% CI = 63–87) in the CQ + PQ group, corresponding to 48/57, 21/54, and 34/50 participants without a recurrence at 6 months, respectively. Recurrence-free efficacy at 6 months for the other doses was for CQ + TQ 50 mg 58% (95% CI = 43–70), and for CQ + TQ 100 mg 54% (95% CI = 40–66), and for CQ + TQ 600 mg 92% (95% CI = 80–97). Based on the safety and efficacy data from this study, TQ 300 mg was selected as the lowest efficacious dose for further evaluations in part 2 of DETECTIVE study.<sup>15</sup>

DETECTIVE, Part 2 (NCT01376167), was a phase III study which confirmed efficacy of the selected TQ 300 mg single dose, and the study was conducted in Brazil, Peru, Colombia, Thailand, Philippines, and Ethiopia.<sup>24</sup> Among the 522 included *P. vivax* malaria patients, recurrence-free

efficacy at 6 months was for CQ + TQ 62% (95% CI = 55–69; n=155/260), for CQ + PQ 70% (95% CI = 60–77; n=83/129 and 28% (95% CI = 20–36; n=35/133) for CQ.<sup>24</sup>

GATHER (NCT02216123) was a phase III study conducted in Brazil, Colombia, Ethiopia, Peru, Thailand, and Vietnam to assess the effect of the single dose of 300 mg CQ + TQ and 14-day course of CQ + PQ on clinically relevant hemolysis defined as an Hb decrease of ≥30% or >30 g/L from baseline or an overall drop in Hb below 60 g/L. In total, 251 participants were enrolled and, of those, 166 received a single dose of TQ 300 mg compared to PQ. Occurrence of clinically relevant hemolysis was similar between both groups: 2.4% for CQ + TQ vs 1.28% for CQ + PQ. The 6 months recurrence-free efficacy was similar between both regimens: 73% (95% CI = 65–79; n=112/166) for CQ + TQ and 75% for CQ + PQ (95% CI = 64–83; n=60/85).<sup>24</sup>

These three studies showed an acceptable safety profile of the TQ 300 mg dose, when given together with CQ during a 6 month follow-up period and similar efficacy against recurrence for CQ + TQ compared to CQ + PQ.

## Supporting studies

Several additional trials have been conducted evaluating TQ efficacy against hypnozoites at different TQ doses and regimens (1-, 3-, and 7-day treatment). The findings of studies published until 2015 were summarized by a Cochrane review.<sup>58</sup> A trial conducted in Thailand compared a high

Treatment allocation	Status	Phase	Outcome	Reference
T1) TQ 200 mg/day for 3 days, then TQ 200 mg on day 10. T2) placebo CHMI with 2,800 viable <i>P. falciparum</i> schizonts on day 13	P	I	Number (%) of <i>P. falciparum</i> uninfected participants until day 32 after treatment start: T1) TQ: 12/12 (100%) T2) Placebo: 0/4 (0%)	63
T1) TQ 600 mg single, oral dose on day 1 T2) placebo on day 1 CHMI with <i>P. falciparum</i> by bites of 5 infected mosquitoes on day 2	P	I	Number (%) of <i>P. falciparum</i> uninfected participants until day 65 after treatment start: T1) TQ: 12/12 (100%) T2) Placebo: 0/2 (0%)	12

single dose (600 mg) of TQ vs a 3-day regimen of daily 600 mg TQ or 7 days 300 mg TQ.<sup>20</sup> Another study in Thailand tested a slightly lower single dose (500 mg) of TQ vs 3 days 500 mg TQ followed by the same dose (3 times 500 mg) 1 week later<sup>21</sup> or vs 300 mg TQ given daily for 7 days. In both studies, TQ was compared to CQ alone and in the first study additionally to CQ + PQ. Data from these studies suggested that a single day treatment is sufficient to prevent *P. vivax* relapses. The rate of protection in the first study of the different TQ doses combined was 93% (95% CI = 7–99.9) and 91% in the second study (95% CI = 39–99). A third study performed in Thailand compared TQ 400 mg monotherapy (without CQ) for 3 days to CQ + PQ.<sup>22</sup> This study revealed that monotherapy of TQ is efficacious, but parasite and fever clearance is slower compared to treatment with CQ, so that combination therapy should be given. Apart from one study where doxycycline was given with TQ,<sup>19</sup> all participants were treated with a standard full course of CQ regimen (1,500 mg for 3 days) to treat the *P. vivax* infections. Pregnant/lactating women, children, individuals with G6PD-deficiency, or a mixed infection with malaria parasites other than *P. vivax* were not included in these studies.

In all these studies, activity against recurrences was evaluated without differentiating between relapse and new infection. Only samples of Detective Part 1 (NCT01376167) were additionally analyzed by a genotyping approach using three discriminatory markers.<sup>59</sup> Recurrent infections that differed by at least one marker from pre-treatment infections were defined as heterologous. The authors suggested that analysis of the frequency of homologous and heterologous recurrences could be used for estimation of TQ's anti-hypnozoite

efficacy against *P. vivax*, as they saw a dose response effect, ie, a reduction in homologous recurrences (probably relapses) at high doses of TQ, but not in heterologous recurrences (probably new infections). A separate analysis investigated, by mathematic modelling, the exposure response effect in time-to-recurrence of the infection. This revealed that a 300 mg dose led to a systemic exposure of TQ greater than AUC 56 µg/h/mL in 90% of individuals, an exposure that would lead to a significant lower 6 months recurrence rate.<sup>56</sup>

Two studies assessing anti-recurrence efficacy are still ongoing: NCT02802501, a phase III study in Indonesia, testing the superiority of DHA + PPQ + TQ against DHA + PPQ alone and DHA + PPQ + PQ for the prevention of *P. vivax* malaria recurrence at 6 months in 150 healthy adult volunteers; and NCT02563496, a phase II, prospective, open-label, multicenter, non-comparative, single arm study of children with *P. vivax* malaria in Colombia, Thailand, and Vietnam to assess safety and efficacy of CQ + TQ single dose in a total of 60 pediatric individuals aged 6 months to <16 years.

## Prophylactic efficacy of TQ

In August 2018, the FDA also approved TQ, under the name ARAKODA, and shortly later Australia TGA, under the name KODATEF, for prophylaxis against all species of *Plasmodium* in patients aged 18 years and older for up to 6 months continuous dosing.<sup>1</sup> For this indication, TQ was co-developed by the US Army and 60 Degrees Pharmaceuticals. The proposed prophylactic regimen is a loading dose of 200 mg once daily for 3 days before travel to a malaria endemic region, followed by a weekly 200 mg maintenance

dose during the stay and one final 200 mg dose in the week following exit from the malaria area.<sup>38</sup>

Several studies have been undertaken since the first trial done in 1998 showed a protection in three out of four individuals (75%) exposed to experimental infection with *P. falciparum* by mosquito bite after intake of a 600 mg single dose TQ.<sup>12</sup> Since then, different doses and regimens have been evaluated that are nicely summarized in previous reviews.<sup>60–62</sup> Five pivotal/key studies provided evidence for safety and prophylactic efficacy that led to drug approval: three phase II conducted in Africa (two in Kenya, one in Ghana), endemic for *P. falciparum* malaria<sup>42,50</sup> (NCT02488980), and one phase III prophylactic efficacy study in non-immune Australian soldiers deployed in East Timor.<sup>40</sup>

More than 1,250 adults, semi-immune and naïve, aged 18–55 years were included in the TQ prophylactic efficacy studies. The first time the now licensed prophylactic regimen (3 days 200 mg/day followed by weekly 200 mg) was given was in a study in Kenya comparing this regimen to 1) 3 days 400 mg/day followed by weekly placebo, 2) 3 days 400 mg/day followed by 400 mg weekly, and 3) placebo.<sup>42</sup> After 13 weeks of prophylaxis in the placebo group, 54/94 had malaria, in group 1, only receiving a loading dose, 16/54 had malaria (68% protective efficacy), and similar efficacy was found between the 200 mg and 400 mg prophylactic regimen, with 7/53 and 6/57 acquiring malaria, and a protective efficacy of 86% and 89%, respectively. As the 200 mg regimen was better tolerated, it was taken forward to the following studies, and the 200 mg regimen (n=492 individuals) was compared in a phase III trial to a standard regimen of mefloquine (162 individuals) in Australian soldiers going to East-Timor.<sup>40</sup> No case of malaria occurred in both groups during the 6 months deployment. Another study in semi-immune adults from Ghana evaluated a 3-day loading dose with a following maintenance dose of TQ: 1) 25 mg, 2) 50 mg, 3) 100 mg, 4) 200 mg, vs 5) mefloquine 250 mg, or 6) placebo for 13 weeks. Results showed that 86/94 individuals were infected with malaria in the placebo group, for the regimen: 1) protective efficacy was 32% and 58/93 individuals got infected, 2) 84%, 13/91, 3) 87%, 11/94, 4) 86%, 12/91, and 5): 86, 6/46. These results showed that all weekly TQ doses starting from 50 mg were similarly effective compared to mefloquine for prophylaxis.

Investigations revealed that TQ plasma concentrations of 40 ng/mL were not able to suppress asexual parasites where both *P. falciparum* and *P. vivax* are endemic. TQ plasma concentrations of 80 ng/mL should be achieved to prevent

malaria, a concentration that is usually reached with the now prescribed 200 mg regimen in 95% of individuals.<sup>38</sup>

Schizonticidal activity of TQ chemoprophylaxis against *P. falciparum* has been confirmed by a phase Ib double-blinded, placebo-controlled study in Australia. Two cohorts of eight healthy non-immune participants were assigned to either TQ 200 mg loading doses from day 1 to day 3 followed by another 200 mg on day 10 or placebo. Both groups were inoculated with ~2,800 viable *P. falciparum* parasites on day 13. None of the TQ recipients, but all placebo recipients, developed parasitemia, confirming TQ's schizonticidal activity.<sup>63</sup>

## Discussion

Since 1950, PQ has been the drug of choice for treatment of the hypnozoites of *P. vivax* and *P. ovale*. Major shortcomings are PQ's short half-life, implying a 14 day administration leading to poor compliance and a much lower effectiveness if applied in real life conditions. PQ is not safe in G6PD-deficient individuals, and has to be metabolized by cytochrome 2D6 to be active, a feature that is less pronounced in TQ.

TQ is a long-awaited alternative drug to prevent *P. vivax* relapse that has been licensed after a long clinical development. The activity of TQ was superior to PQ against blood- and liver-stage parasites in vitro. The major advantage of TQ compared to PQ is its long half-life (2–3 weeks), allowing for a single dose regimen to clear hypnozoites. It is generally safe and well tolerated and clinical evidence shows that it is similarly efficacious as PQ against relapses of *P. vivax*. No effectiveness study has been conducted evaluating TQ and PQ in a real-life setting head to head. However, it is obvious that a single dose regimen will be superior, closing the efficacy–effectiveness gap.

Hemolysis in G6PD-deficient individuals and formation of MHB remain the biggest restriction to the future usefulness of TQ. Especially in Asia, where *P. vivax* is most prevalent, a gene variant conferring severe G6PD-deficiency is frequent.<sup>64</sup> TQ should be only given to individuals with a G6PD enzyme activity >70%, whereas for PQ the threshold is >30%, therefore more individuals (usually females) will not be eligible to receive TQ treatment. A model was created by Watson et al<sup>48</sup> estimating the number of individuals that will not be covered by PQ or TQ treatment due to their underlying genetic deficiency. Most available methods to test for the G6PD-deficiency status need trained staff and significant laboratory infrastructure, lacking at many field sites. The most frequently used method includes the fluorescent spot test, a semi-quantitate method based on UV spectrophotometry that can discriminate between normal (>70%) and the deficient

status (<30%), but does not reliably determine the intermediate enzyme activities of heterozygous females.<sup>65,66</sup> Reference testing for this includes flow cytometry to determine the fraction of G6PD-deficient erythrocytes in heterozygous females.<sup>67</sup> The need of easy to use quantitative point-of-care tests has been realized, and several organizations (eg, PATH) support the development.<sup>68,69</sup> A number of new point-of-care tests are in development and will likely facilitate accurate testing in the future.<sup>70</sup>

Overall, the safety data of TQ are good, and higher doses than for PQ can be administered to most individuals, as TQ has a greater therapeutic window. However, here the longer half-life shows its disadvantage: G6PD-deficient individuals are at a potential greater risk of hemolysis, as active concentrations of TQ will remain in the body for several weeks, whereas the PQ course can be stopped if hemolysis aggravates. In addition, TQ shares the shortcoming of PQ that it cannot be given to pregnant or lactating women. Even though clinical infection with *P. vivax* is associated with maternal anemia and may be deleterious for the infant's health,<sup>71</sup> application is contraindicated in this group because of the danger of causing acute hemolytic anemia in the fetus. PQ can be given to children in a weight-adjusted dose. So far, the safety of TQ in children has not been established, but a pediatric trial is ongoing (NCT02563496), so that the indication will hopefully be expanded in future. Combination of TQ with other antimalarial drugs showed no major interactions, an important feature as combination therapy will be the choice for any future drug regimen, for acceleration of parasite clearance, but also for preventing the development of resistances.<sup>55</sup>

Currently no other drug for hypnozoite treatment is in the drug development pipeline. The activity of antimalarial drugs against hypnozoite stages is only poorly understood and candidate drugs are scarce. This might be because, on the one hand, this stage is difficult to target as it is less metabolically active, and on the other hand because none of the *Plasmodium* parasite species that form hypnozoites can be kept in long-term continuous *in vitro* culture. In addition, *in vivo* and *in vitro* hypnozoite assays have only become available recently and are not yet implemented in a large scale in the malaria research community.<sup>72–76</sup> Availability, simplification, and standardization of these assays might lead to new drug candidates for this indication that do not belong to the 8-aminochinolines.

In addition to the application as a drug for radical cure against *P. vivax* hypnozoites, TQ also gained approval for chemical prophylaxis against infections of all *Plasmodium* species. Its long half-life allows for a once weekly regimen for this indication, whereas most other currently recommended

prophylactic drugs need daily administration (doxycycline, atovaquone-proguanil) leading to poor compliance. Mefloquine can be given with a weekly dosing for malaria prophylaxis, but neurologic and psychiatric side effects have been associated with its use for prophylaxis, so that TQ might be a good alternative. Currently, TQ is licensed to be given for the duration of 6 months for prophylaxis. However, a current study is ongoing to evaluate the long-term safety of TQ when it is given as prophylactic regimen for 1 year (NCT03320174), specially focusing on the ophthalmic safety.

## Conclusion

WHO recognized in its recent agenda that more attention has to be paid to *P. vivax* infections to move forward in the elimination efforts. Even though TQ does not overcome all shortcomings of PQ, the TQ single dose anti-relapse treatment for hypnozoites of *P. vivax* as well as of *P. ovale* advances the treatment regimens for these malaria species profoundly. The changes in the WHO agenda might have given the final impulse to keep TQ in the development pipeline and finally bring it to the market.<sup>19</sup>

Currently no other drugs are in the pipeline with potential for anti-relapse therapy.<sup>72,77</sup> Considering that development from the early clinical phase to market approval takes ~10 years, shows that no alternative to 8-AQ for anti-relapse therapy will be available in the near future. The present data suggest that TQ will replace current treatment regimens with PQ and play a major role in the treatment agenda for control and elimination of *P. vivax* malaria.

## Disclosure

The authors report no conflicts of interest in this work.

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