Malaria Policy Advisory Committee Meeting

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Background document for Session 2

The cardiotoxicity of antimalarials

WHO Evidence Review Group Meeting, 13–14 October 2016
Varembé Conference Centre, Geneva, Switzerland

Executive summary

The cardiotoxicity of antimalarial medicines has received renewed interest in recent years following the 'Thorough QT' assessment of the dihydroartemisinin-piperaquine formulation approved by the European Medicines Agency, which showed evidence of QT interval prolongation. Piperaquine is a bisquinoline antimalarial that is structurally related to chloroquine. Many drugs among the quinoline and structurally-related medicines affect myocardial depolarization and repolarization. WHO currently recommends the artemisinin-based combination treatment dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria. This treatment is being considered alongside other antimalarial medicines for preventive therapy and mass drug administration.

To inform WHO recommendations, a group of experts met in October 2016 to review evidence on the cardiotoxicity risk of quinoline antimalarials and structurally-related medicines in people with and without clinical malaria.

The following recommendations were proposed by the WHO Evidence Review Group for consideration by the WHO Malaria Policy Advisory Committee and the WHO Advisory Committee on Safety of Medicinal Products.

WHO/HTM/GMP/MPAC/2017.2

Summary of findings and proposed recommendations

1. Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity.

2. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval.

3. Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether-lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.

4. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-containing medicines are probably similar for healthy volunteers and malaria patients.

5. Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.

1. Introduction

Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects; it is well known that they prolong the QT interval of the surface electrocardiogram (ECG). Of these antimalarials, WHO currently recommends quinine, chloroquine, amodiaquine, mefloquine, lumefantrine and piperaquine for the treatment of clinical malaria in combination with either an artemisinin derivative or another antimalarial medicine. Quinidine, the dextrorotatory diastereoisomer of quinine, has been associated with significant cardiotoxicity; therefore, WHO recommends that quinidine be given with careful clinical and ECG monitoring for the treatment of severe malaria only in cases where no other parenteral antimalarial is available. Halofantrine causes marked QT interval prolongation and has been associated with over 30 reports of sudden cardiac death; it has never been recommended by WHO for the treatment of malaria.

A prolonged corrected QT interval (QTc) is a sensitive but not specific indicator of increased risk of torsade de pointes (TdP), a polymorphic ventricular tachycardia that can degenerate in some cases into ventricular fibrillation and lead to sudden cardiac death. However, the relationship between QTc interval prolongation and TdP is not straightforward. Drugs that cause QTc interval prolongation have been inconsistently associated with life-threatening tachyarrhythmias, and only a small proportion of patients with QTc interval prolongation have developed such conditions.

The risk of cardiotoxicity of antimalarial drugs has received renewed interest following the European Medicines Agency's (EMA) marketing authorization of Eurartesim® (dihydroartemisinin-piperaquine) in 2011. The regulatory review identified a potential risk of arrhythmia based on a 'Thorough QT' (TQT) study in healthy volunteers that showed evidence of QTc interval prolongation. Dihydroartemisinin-piperaquine (DHA-PPQ) has since been used extensively in the treatment of uncomplicated malaria and in large studies of mass treatment in healthy subjects. It is now being considered alongside other antimalarial medicines for preventive therapy and mass drug administration (MDA).

Abbreviations

ACT	artemisinin-based combination therapy
ADR	adverse drug reaction
AL	artemether-lumefantrine
ASAQ	artesunate-amodiaquine
ASMQ	artesunate-mefloquine
C_{max}	peak plasma concentration
DHA-PPQ	dihydroartemisinin-piperaquine
DNDi	Drugs for Neglected Diseases Initiative
DOT	directly observed therapy
ECG	electrocardiogram
EMA	European Medicines Agency
EMP	Essential Medicines and Health Products
ERG	Evidence Review Group
FDA	United States Food and Drug Administration
GMP	Global Malaria Programme
GSK	GlaxoSmithKline
HDSS	health and demographic surveillance system
hERG	human ether-à-go-go related gene
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IDRC	Infectious Diseases Research Collaboration
INESS	INDEPTH Effectiveness and Safety Studies
IPT	intermittent preventive therapy
IPTi	IPT of infants
IPTp	IPT of pregnant women
LSTM	Liverpool School of Tropical Medicine
MDA	mass drug administration
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
MORU	Mahidol-Oxford Tropical Medicine Research Unit
OUCRU	Oxford University Clinical Research Unit
PDP	product development partnership
PK/PD	pharmacokinetic/pharmacodynamic
QTc	corrected QT interval
QTcB	QTc with Bazett's correction
QTcF	QTc with Fridericia's correction
SMC	seasonal malaria chemoprevention
SMQ	Standardised MedDRA Query
SMRU	Shoklo Malaria Research Unit
SP	sulfadoxine-pyrimethamine
TdP	torsade de pointes
TQT	thorough QT
WANECAM	West African Network for Antimalarial Drugs
WWARN	Worldwide Antimalarial Resistance Network

The other antimalarials in current use that have this same qualitative effect – i.e., quinine, chloroquine and amodiaquine – were introduced over 50 years ago, at a time when the potential risk of drug-induced TdP was not appreciated. Despite their extensive use, these drugs have not been subject to the same pre-registration scrutiny as dihydroartemisinin-piperaquine.

To inform the risk assessment of antimalarial drugs, the WHO Global Malaria Programme (GMP) initiated an evidence review of antimalarial cardiotoxicity, in collaboration with the WHO Essential Medicines and Health Products (EMP) Department.

2 Overview

2.1 Objectives

The objectives of the evidence review were to:

1. Inform the risk assessment of antimalarial cardiotoxicity;
2. Evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials;
3. Examine pharmacokinetic/pharmacodynamic (PK/PD) studies of the main artemisinin-based combination therapies (ACTs) to evaluate the dose-response effect and risk factors of QTc interval prolongation;
4. Examine comparative clinical trials of DHA-PPQ and other piperaquine-containing combination antimalarials to evaluate PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients;
5. Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments.

2.2 Process

The Evidence Review Group (ERG) was approved by the WHO Advisory Committee on Safety of Medicinal Products in June 2016 and by the Malaria Policy Advisory Committee in September 2016.

In order to document sudden unexplained death and/or TdP following antimalarial drug exposure, as recommended by the expert cardiologists consulted before the meeting, WHO identified and collated relevant reviews and studies with large individual patient data series based on a literature search and in collaboration with the malaria research community, contract research organizations, and manufacturers of originator pharmaceutical products of interest.

Information was collected about the following quinoline and structurally-related antimalarial medicines, either as monotherapy or as part of a combination treatment:

- Artemether-lumefantrine
- Artesunate-amodiaquine
- Dihydroartemisinin-piperaquine
- Arterolane-piperaquine
- Artefenomel-piperaquine
- Pyronaridine-artesunate
- Quinine
- Chloroquine
- Mefloquine
- Halofantrine
- Ferroquine
- Primaquine

Evidence was drawn from publications/manuscripts, reports, data, and presentations (see Annex A for summary). Publications/manuscripts and suitable reports were shared as meeting pre-reads (see Annex B for list), while data were pooled, analysed and presented at the ERG meeting.

Professor Josep Brugada and Professor Nick White co-chaired the meeting. Dr Xin Hui Chan was the meeting rapporteur and WHO technical resource person for the preparation of the meeting. A list of meeting participants is available in Annex C.

During the meeting, presentations and discussions were organized around five thematic sessions:

1. Introduction and Background
2. Sudden Death Following Antimalarial Therapy
3. Studies on the Effects of Antimalarial Medicines on the ECG
4. PK/PD Analyses on the Effects of Antimalarial Medicines on the ECG
5. Priority Research Gaps and Planned Studies on the Effects of Antimalarials on the ECG

3 Evidence reviewed

3.1 Introduction and background

3.1.1 Drug-induced QT interval prolongation

The assessment of QT/QTc interval prolongation is an important part of the regulatory evaluation of new medicines and has become a common reason for drugs being withdrawn from the market. Both the EMA and United States Food and Drug Administration (FDA) have adopted the International Conference on Harmonisation (ICH) preclinical S7B *(1)* and clinical E14 *(2)* ('Thorough QT') guidelines for evaluating QT/QTc prolongation and the proarrhythmic potential of new medicines.

The electrocardiographic QT interval represents the ventricular action potential, i.e., the interval between ventricular depolarization and repolarization, as determined by the dynamic and fine balance of electrical currents mediated by ion channels on ventricular cardiomyocytes. These action potentials vary from cell layer to cell layer. The QT interval reflects the summation of these potentials (Fig. 1).

By far the most common mechanism by which drugs cause QT interval prolongation is by blocking the human ether-à-go-go related gene (hERG) potassium channel, the voltage-gated ion channel that mediates the rapid component of the delayed rectifier potassium current, I_{Kr}. Blockade of the hERG channel lengthens ventricular repolarization and the duration of ventricular action potential. This is reflected on the surface ECG as a prolonged QT interval; it may also result in the reactivation of inward, mainly calcium, depolarizing currents, thereby generating early afterdepolarizations. Under the right spatial and temporal heterogeneity of refractoriness in ventricular cardiomyocytes, early afterdepolarizations can trigger TdP. In the majority of cases, TdP is self-terminating, but if sustained, it can degenerate into ventricular fibrillation and cause sudden cardiac death *(3)*.

The relationship between QT/QTc interval prolongation and TdP is not straightforward. Drugs that cause QT/QTc interval prolongation lead to life-threatening tachyarrhythmias in only a small proportion of patients. Sudden cardiac death can also occur in individuals whose QT/QTc intervals are within the normal range. Prolongation of the QT/QTc interval is therefore a sensitive but not specific marker of an increased risk of TdP. Although imperfect, QT/QTc interval prolongation remains at present the best available surrogate indicator for TdP risk.

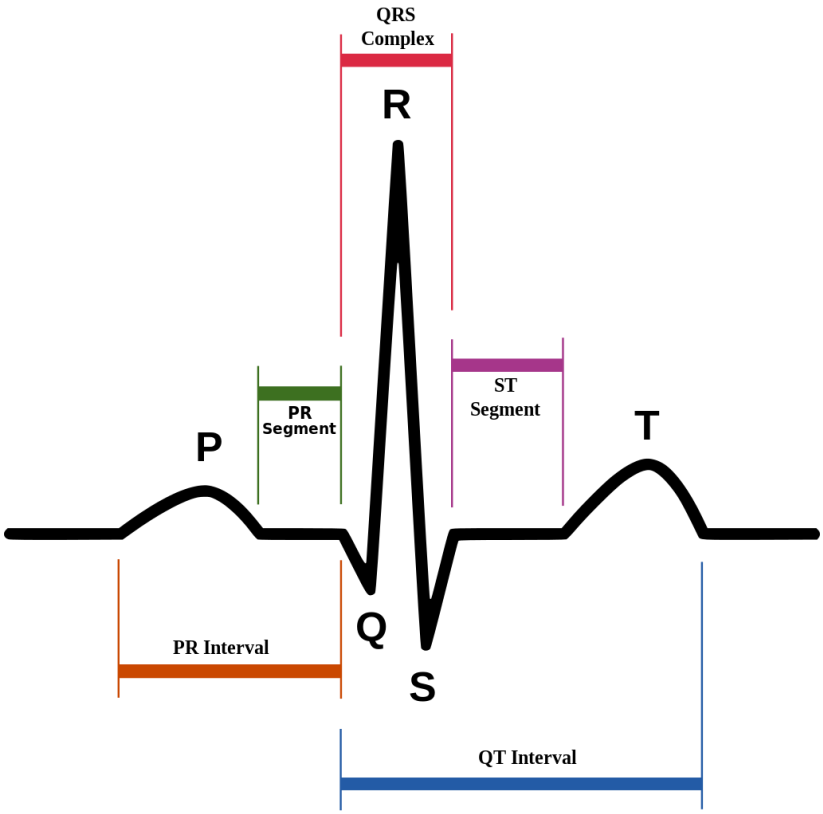


Fig. 1. The surface electrocardiogram in normal sinus rhythm

Experience with both QT/QTc interval-prolonging medicines and congenital long QT syndrome suggests:

- A QT/QTc[i] interval >500ms[ii] is associated with a higher risk of TdP and sudden cardiac death;
- Among drugs with QT/QTc interval-prolonging potential, antiarrhythmics have been associated with TdP in 1–5% of exposed subjects, while non-cardiovascular drugs have been associated with TdP at much lower frequencies, e.g., one in 100 000 exposures for moxifloxacin *(4)*;

[i] The measured QT interval is routinely adjusted for heart rate using one of a range of correction formulae to account for the inverse relationship between QT interval and heart rate. QTc refers to this corrected QT value.

[ii] There is a no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from baseline. While lower limits increase the false-positive rate, high limits increase the risk of failing to detect a signal for concern. In clinical trials, a QTc prolongation >500ms during therapy has been a threshold of particular concern. Conducting multiple analyses using different limits is a reasonable way to approach this uncertainty, including:

- Absolute QTc interval prolongation:
  - QTc interval >450ms
  - QTc interval >480ms
  - QTc interval >500ms
- Change from baseline in QTc interval:
  - QTc interval increases from baseline >30ms
  - QTc interval increases from baseline >60ms

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf

- TdP degenerates into ventricular fibrillation in ~10% of cases.
- The incidence of drug-induced TdP and life-threatening ventricular arrhythmias has been reported as 3.2–13 per million person years in active surveillance studies conducted in Europe *(5–7)*; very little evidence has emerged from tropical areas.

Apart from hERG blockade, several risk factors decrease the repolarization reserve *(8)* and facilitate the development of arrhythmias in individual patients. These include:

- PK/PD effects, e.g., CYP450 inhibition from drug interactions leading to higher drug levels;
- Female gender, which is associated with a risk that is approximately two-fold greater after puberty *(9)*;
- Structural heart disease, e.g., ischaemic cardiomyopathy, left ventricular hypertrophy;
- Genetic defects of cardiac ion channels, including subtle genetic polymorphisms;
- Electrolyte disturbances, e.g., hypokalaemia, hypomagnesaemia, hypocalcaemia;
- Bradycardia, e.g., from increased vagal tone;
- Hepatic impairment, e.g., from alcoholic cirrhosis;
- Concomitant use of medicines that prolong the QT/QTc interval, see http://crediblemeds.org.

As there are no simple screening tests to identify people who may develop TdP and fatal ventricular tachyarrhythmias, it is important to study outliers in drug safety studies (i.e., those with abnormal electrocardiographic intervals) in order to identify the factors that increase the risk of individuals developing life-threatening arrhythmias associated with drug-induced QT/QTc interval prolongation.

To identify better predictors of drug-induced TdP, the FDA has invested in a research programme that includes a Comprehensive *in vitro* Proarrhythmia Assay *(10)*, which assesses the effects of drugs on multiple ion channels; the use of detailed ECG collection in early clinical studies with exposure-response analysis *(11)*; and the use of ECG biomarkers to distinguish between patterns of drug blockade of multiple ion channels *(12)*. This programme is expected to be completed over the next 2 years.

Key conclusions

- Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk.
- Drug-induced QT/QTc interval prolongation is a sensitive but not specific surrogate indicator for drug-induced TdP risk; despite its limited specificity, it is the best marker available.
- A QT/QTc interval >500ms is associated with a higher risk of TdP and sudden cardiac death:
    - Among drugs that prolong the QT/QTc interval, antiarrhythmics have been associated with TdP in 1–5% of exposed individuals, while non-cardiovascular drugs have been associated with a much lower risk of TdP. Around one in 10 cases of TdP degenerate into life-threatening tachyarrhythmias.
- Risk factors for drug-induced QT/QTc interval prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels.

3.1.2 Malaria, antimalarial medicines and cardiotoxicity

Antimalarial medicines are a vital tool for reducing malaria-related morbidity and mortality in individual patients, as well as for controlling and eliminating malaria. These medicines are deployed on a vast scale, with over 400 million treatments now distributed annually, and 2.2 billion courses of ACTs delivered between 2005 and 2015.

In malaria-endemic regions, antimalarial medicines are used for the treatment of clinical malaria, for preventive therapy in high-risk populations, and in the form of MDA for malaria control and elimination. The objectives of treatment with oral antimalarial medicines are as follows:

1. Case management

   ACTs have been the mainstay of recommended treatments for uncomplicated malaria. A complete therapeutic course is taken over 3 days. The clinical objectives of treating uncomplicated malaria are to achieve cure and to prevent progression to severe disease or chronic infection by ensuring as rapid and as complete elimination of the parasite from the blood as possible. The public health objectives of treatment are to reduce onward transmission of malaria and to prevent the emergence and spread of resistance to antimalarial drugs.

2. Preventive Treatment

   Administration of full therapeutic courses of an antimalarial either alone or in combination to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk. Preventive treatment includes chemoprophylaxis, intermittent preventive therapy of pregnant women (IPTp), intermittent preventive therapy of infants (IPTi), and seasonal malaria chemoprevention (SMC) of children aged 3–59 months.

3. Mass drug administration

   MDA is the administration of antimalarial treatment to every member of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated

intervals. Mass drug administration is usually performed in order to reduce the parasite reservoir of infection radically and thus reduce transmission in a population. WHO now recommends that MDA of antimalarial medicines be considered for the elimination of malaria in areas approaching interruption of transmission, where there is good access to treatment, effective implementation of vector control and surveillance, and minimal risk of infection being reintroduced, as well as for epidemics and complex emergences . Use of time-limited MDA is also recommended to reduce malaria morbidity and mortality rapidly for epidemic control as part of the initial response, along with the urgent introduction of other interventions, as well as in complex emergencies during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects. These include *(13)*:

1. Exacerbation of malaria-related orthostatic hypotension, e.g., quinine, chloroquine, mefloquine;
2. Acute hypotension with rapid parenteral injection, e.g., chloroquine, quinine, quinidine;
3. Sinus bradycardia, e.g., mefloquine;
4. QRS complex widening, e.g., quinidine, quinine, chloroquine;
5. QT interval prolongation, e.g., halofantrine, quinidine, quinine, chloroquine, amodiaquine, piperaquine.

Chloroquine hypotension from peripheral vasodilation and negative inotropy was the probable cause of sudden death reported following the rapid parenteral administration of chloroquine for the treatment of malaria in children. PK/PD assessments found that toxicity resulted from transiently very high plasma concentrations following parenteral administration. This effect was circumvented by using a slow, continuous, rate-controlled infusion or smaller, more frequent intramuscular or subcutaneous doses to administer the drug *(14)*.

Quinidine, the diastereoisomer of the cinchona alkaloid quinine, is the prototype for drugs causing QT interval prolongation; it is a well-known cause of syncope and, rarely, sudden death. In the 1920s, the Dutch cardiologist Wenckebach began to use quinidine as an antiarrhythmic *(15)*. In the 1960s, it became the first drug to be associated with marked QT interval prolongation and symptomatic TdP *(16)*, such that iatrogenic QT interval prolongation was termed the 'quinidine effect'. WHO now recommends that quinidine be given with careful clinical and ECG monitoring for the treatment of severe malaria only in cases where no other parenteral antimalarial is available. Halofantrine is a lipophilic phenanthrene methanol compound that was discovered by the Walter Reed Army Institute of Research. Since the initial case reports from the Thai-Burmese border *(17)*, halofantrine has been associated with TdP *(18)* and more than 30 reports of sudden cardiac death *(19)*. WHO has never recommended halofantrine for the treatment of malaria. In April 2016, GlaxoSmithKline (GSK) discontinued production of proprietary halofantrine (Halfan®).

Hundreds of metric tonnes of chloroquine have been dispensed annually since the 1950s, making chloroquine one of the most widely used drugs in humans. Despite this extensive use, the lethality of the 4-aminoquinoline chloroquine in overdose has caused concern over the use of chloroquine for the treatment of malaria. More recently, there has been uncertainty over the potential risk of QT interval prolongation associated with bisquinoline piperaquine; in fixed-dose combination with dihydroartemisinin, bisquinoline piperaquine is the latest addition to the ACTs recommended by WHO for the treatment of malaria. Piperaquine has also been used on a large scale; 140 million piperaquine treatments were consumed in China between 1978 and 1992, until piperaquine resistance prompted a change in treatment policy. As both chloroquine and piperaquine have

terminal elimination half-lives of approximately 1 month, there has been considerable exposure to both drugs without apparent or reported cardiovascular concerns.

In assessing the iatrogenic effects of antimalarial drugs on the heart, it is important to also consider the underlying disease effects of malaria on the cardiovascular system.

Uncomplicated malaria is a febrile illness associated with nausea, vomiting and orthostatic hypotension. Severe falciparum malaria is characterized by multiple vital organ dysfunction caused mainly by the extensive sequestration of parasitized red blood cells in the microvasculature, including the myocardial capillaries. Despite this, there is no evidence of myocarditis or a negative inotropic effect, and myocardial dysfunction is unusual in acute malaria. Patients with severe malaria tend to have a low systemic vascular resistance with a high cardiac index. They are usually not hypovolaemic, hypokalaemic, hypomagnesaemic or markedly hypocalcaemic, although metabolic acidosis, hypoglycaemia and acute kidney injury are common.

For a disease with an extensive range of systemic complications and multiple vital organ dysfunction, it is notable that arrhythmias have only very rarely been reported in malaria patients, even in severe cases.

Acute malaria illness has significant effects on the QT interval. Before treatment, patients are usually febrile, anxious, upright, tachycardic and often anorexic. The sympathetic nervous system is activated and the QT interval is shortened. As the patient recovers, often lying in bed, the fever settles, appetite returns, the heart rate declines and the QT interval lengthens. The difference between the shortened QT interval before treatment and the day-3 normalized QT interval (which often coincides with peak antimalarial drug levels) may be misattributed to a drug effect. If there is a drug effect, it may be compounded by this systemic physiological response to recovery *(13)*. In addition, usual QT correction formulae designed to normalize the QT interval tend to "overcorrect" (i.e., the QTc interval appears longer) at fast heart rates and "undercorrect" (i.e., the QTc interval appears shorter) at normal or slow heart rates. These factors should be taken into account when interpreting results from ECG safety studies in malaria patients.

Central to the selection of appropriate drugs for emerging and current indications for antimalarial medicines is the risk–benefit assessment of their intended use in the target population. This risk–benefit assessment differs when antimalarials are to be used for case management, preventive therapy or MDA. Malaria causes significant morbidity, can progress to severe illness and death in vulnerable groups, and is endemic in settings with limited access to health care services. Among people with malaria – whether symptomatic or asymptomatic – or otherwise healthy subjects, it is not possible to predict who may develop TdP and fatal tachyarrhythmia as a result of drug-induced QT interval prolongation. Making ECG recording and interpretation a requirement, even with the presence of mobile technologies, would be operationally impossible in the field and severely limit the use of any drug. Screening for family history is limited, as it is difficult to ascertain whether arrhythmia was the cause of sudden unexplained death. Further work is required to develop appropriate tools with which to identify and monitor people at higher risk of life-threatening arrhythmias, e.g., those with congenital long QT syndrome, in malaria-endemic regions, as well as in the context of antimalarial therapy with QT interval-prolonging drugs.

Key conclusions

- Antimalarial drugs are vital for malaria treatment, prevention, control and elimination.
- Drugs structurally related to quinine may affect cardiac myocyte depolarization and repolarization.
- Quinidine and halofantrine have been associated with significant cardiotoxicity. WHO has never recommended halofantrine for the treatment of malaria.
- Apart from halofantrine, the oral antimalarial drugs, particularly chloroquine and piperaquine, have been used extensively with very few reports of cardiotoxicity.
- Rapid parenteral administration of chloroquine, quinine or quinidine may cause life-threatening hypotension.

3.2 Sudden death following antimalarial therapy

Understanding the frequency of drug-related sudden death is key to assessing the risk of antimalarial cardiotoxicity, particularly in malaria-endemic regions with very limited access to ECG monitoring for arrhythmia detection.

3.2.1 Overall

DHA-PPQ was the only antimalarial drug for which high-quality adverse event data from research studies were available for all indications of antimalarial therapy in malaria-endemic areas, i.e., MDA, preventive therapy and case management. This information is summarized in Table 1, and further analysis by treatment indication is presented in sections 3.2.2 to 3.2.4.

Table 1. Sudden unexplained deaths following antimalarial therapy with DHA-PPQ

Study type	Subjects	Courses	Doses	Sudden unexplained deaths	Source(s)
MDA	154 762	~428 929	1 179 523	1*	Table 2
IPT & non-MDA repeated courses	14 014	~28 376	~85 128	0	Systematic review *(20)* & START-IPT (unpublished)
Case management	25 198	~25 198	~75 594	0	Table 4 & INESS *(21)*
Total	**193 974**	**482 503**	**1 340 245**	**1***	

*In all of these reviews, one sudden unexplained death following MDA was considered to be possibly drug-related.
~Derived from another denominator.

This analysis suggests that the risk of sudden unexplained death following DHA-PPQ is one in 193 974 individuals treated in studies with confirmed active follow-up over 3 days from initiation of drug treatment. Of note:

- Follow-up over 3 days from drug administration captures adverse events during the period when the risk of drug-induced QT/QTc interval prolongation is highest, as piperaquine levels are at their peak;
- The choice of number of subjects as the main denominator for exposure reflects expert advice that individuals' repolarization reserve is unlikely to change considerably during the period of repeated dosing in MDA and IPT;
- Sudden unexplained death may be caused by TdP degenerating into life-threatening ventricular tachyarrhythmias, but other causes cannot be excluded with certainty.

3.2.2 Mass drug administration

High-quality pharmacovigilance data from populations exposed to MDA are essential for defining the cardiotoxicity risk of antimalarials used for this indication. Compared to healthy volunteer study populations examined in the pre-approval clinical development phase, populations exposed to MDA with antimalarial medicines differ in terms of age (6 months to >80 years versus 18–50 years), ethnic composition *(22)*, presence of comorbidities, exposure to concomitant medications, and possible low-level parasitaemia. Target populations for antimalarial IPT and SMC also differ (i.e., pregnant women and young children, respectively). Furthermore, there are different risk–benefit ratios associated with exposure to antimalarials in MDA or preventive therapy compared to the use of the same medicines for the treatment of uncomplicated malaria. In particular, the evaluation of medicines for case management is based on clinical trials in populations with a confirmed diagnosis of acute malaria, which often specifically exclude patients with risk factors for QT/QTc interval prolongation.

In addition, given the rarity of drug-induced TdP and life-threatening tachyarrhythmias, as indicated by available evidence (presented in section 3.1.1), the number of patients exposed to antimalarial drugs in pre-approval clinical trials alone is not sufficiently large to detect these very rare events *(23)*.

Present experience and recent studies on malaria MDA

Because of its high efficacy, good tolerability and long post-treatment prophylaxis resulting from the 20- to 30-day terminal elimination half-life of piperaquine, DHA-PPQ is currently being evaluated for its potential role in MDA as part of malaria elimination efforts. Four studies in Asia and Africa yielded information on MDA with DHA-PPQ; these data are summarized in Table 2.

Table 2. Malaria elimination studies incorporating antimalarial MDA with DHA-PPQ

Study	Location(s)	No. of participants	No. of courses	No. of doses	No. of deaths within 30 days of drug* unexplained / total	Adverse event surveillance in addition to passive spontaneous reporting
MACEPA *(24)*	Zambia	103 963ˆ	336 821 in four rounds	903 600ˇ	0 / 1	DOT – first and third doses of each course, line listing surveillance/adherence visit with or after third dose
CISM	Mozambique	36 820	~57 913 in two rounds	173 738ˇ	1 / 1	DOT – first dose of each course, HDSS record linkage
TME	Thailand, Myanmar, Cambodia, Viet Nam, Lao PDR	10 042	22 384 in three rounds	67 152	0 / 17	DOT – all three doses of each course, line listing/census follow-up at health facility or home at 3, 6, 9 and 12 months
BMEP	Myanmar	3937	11 811 in three rounds	35 433	0 / 0	DOT – all three doses of each course, line listing follow-up following MDA rounds only
Total		**154 762**	**~428 929**	**1 179 523**	**1 / 19**	

MACEPA = Malaria Control and Elimination Partnership in Africa. CISM = Centro de Investigação en Saúde Manhiça. TME = Targeted Malaria Elimination. BMEP = Border Malaria Elimination Programme. DOT = directly observed therapy. HDSS = Health and Demographic Surveillance System. ˆThis is probably an underestimation by approximately 30–50 000 participants, as it assumes that MDA was received by the same individuals in all rounds of treatment; this is unlikely to be the case, however, as the focal MDA component of this programme targeted only malaria rapid diagnostic test-positive households, which would have varied from one round to another. ˇThese figures take into account subsample adherence figures provided by each programme. ˜Number of courses was derived from number of doses. *As detected by the adverse event surveillance system of each programme described in the final column of the table.

In all four MDA studies, participants were given multiple rounds of a 3-day treatment course of DHA-PPQ tablets. Participants were divided into age- or weight-based treatment groups in order to achieve daily therapeutic dose ranges of dihydroartemisinin (2–10 mg/kg body weight) and piperaquine (16–26 mg/kg body weight). Each round was conducted at least 1 month from the next. In the studies conducted in Asia, primaquine (0.25 mg base/kg body weight) was also administered with the first dose of each treatment course. All participants were exposed to at least one course of DHA-PPQ. All studies had a lower age limit of ~6 months (range = 3 to 12 months), and excluded individuals who were pregnant, had contraindications to study drugs, or had acute illness at the time of drug administration.

There was one sudden unexplained death following DHA-PPQ administration in this MDA group. An otherwise healthy 16-year-old female in Mozambique collapsed and died on the way to hospital after complaining of palpitations. This occurred several hours after the second dose of her first course of DHA-PPQ. She had no history of previous hospital admissions or any other medical conditions, and no past or concomitant intake of any other medication. According to her stepmother, the girl had self-administered her second dose of 40/320mg DHA-PPQ about 20 minutes after a meal of rice, cooked salad, and bread. Both the malaria rapid diagnostic test and pregnancy test performed at her enrolment the day before were negative. No autopsy or ECG was performed. Cardiology experts at the ERG reviewed this case and deemed her death to be consistent with sudden cardiac death, possibly causally related to drug exposure.

The remaining 18 deaths recorded in these studies had alternative explanations (see Table 3): accidents and infections accounted for seven deaths each, reflecting the risks inherent in the resource-limited rural and peri-urban settings of these MDA studies; three were due to complications of gastrointestinal conditions; and the final death was attributed to vascular disease in a patient with known predisposing factors.

Table 3. Causes of death in malaria elimination studies following MDA with DHA-PPQ

Cause of death	No. of deaths	Autopsy?	Study	Further information
Traffic accident	4	No	TME	
Tuberculosis	3	No	TME	
Septic abortion	2	No	TME	
Melioidosis	1	No	TME	
Diphtheria	1	No	TME	
Diarrhoea	1	No	TME	
Haematemesis	1	No	TME	12-year-old female who died 2 weeks after completing second course of DHA-PPQ
Abdominal pain	1	No	TME	30-year-old male who died 8 days after completing third course of DHA-PPQ
Drowning	1	No	TME	Three other drownings over 18 months of study in control group or in MDA group >30 days after drug administration

Cause of death	No. of deaths	Autopsy?	Study	Further information
Homicide	1	No	TME	35-year-old male found dead with gunshot wound in forest 16 days after completing second course of DHA-PPQ
Choking	1	Yes	MACEPA	2-year-old male seen to choke on pill, and upper tracheal obstruction by white powder with oedema of both lungs confirmed on autopsy
Vascular disease	1	No	TME	56-year-old male with chronic heart disease and hypertension on enalapril suddenly collapsed and died while chopping a tree after climbing a hill more than 24 hours after completing his second course of DHA-PPQ
Total	**18**			

TME = Targeted Malaria Elimination. MACEPA = Malaria Control and Elimination Partnership in Africa.

A conservative approach was adopted for this analysis, in that exposure figures from individual programmes were retained only if there was a system in place for following individual patients over time. All studies had confirmed active follow-up of individual subjects over at least 3 days from the initiation of the drug treatment, i.e., during the period of maximum risk. However, as with other spontaneous reporting systems, deaths could have been underreported in programmes with only passive surveillance of subjects between 3 and 30 days post-treatment. At the same time, sudden deaths are notable events in communities where MDA is conducted; therefore, if they did occur, they would have the potential to undermine confidence in the MDA programme. In light of this, it is noteworthy that there was no evidence of such concerns about deaths or other adverse events in any of the four programmes contributing data to this review.

Historical studies on malaria MDA

Two key published reviews *(25,26)* on past MDA with antimalarial medicines were also analysed for reports of sudden unexplained deaths. The systematic review *(25)* included 32 published studies between 1931 and 2013, while the second review *(26)* also included unpublished work and grey literature. Overall, the safety data were of low quality, reflecting passive reporting from routine pharmacovigilance systems. Few studies reported mortality, only 10 studies reported adverse events, and only four studies included some form of active surveillance. From these studies, the only two deaths reported were from haemoglobinuria following intramuscular mepacrine (quinacrine, Atabrine) and plasmochin (plasmoquine, pamaquine).

3.2.3 Preventive treatment and other indications requiring repeated dosing

Literature review

DHA-PPQ has been studied as a potential alternative for IPT. In order to assess the efficacy and safety of repeated exposure to 3-day treatment courses of DHA-PPQ, a systematic review and random effects meta-analysis *(20)* of previously published studies was performed, comparing DHA-PPQ with other antimalarials and placebo. A total of 11 recent studies were included.

Of the nine IPT studies:

- five were in children aged <5 years (*n* = 5481) *(27–31)*
- one was in schoolchildren (*n* = 740) *(32)*
- one was in adult men at occupational risk of malaria (*n* = 961) *(33)*
- two were in pregnant women (*n* = 1846) *(34,35)*

Of the two case management studies:

- one was a randomized controlled trial in children aged <5 years (*n* = 312) *(36)*
- one was a cohort study in pregnant women (*n* = 5288) *(37)*

The 4511 participants exposed to DHA-PPQ received a total of 18 873 courses, with 18 297 courses taken by the 3935 participants who received ≥2 courses; 9131 participants were exposed to placebo or comparator therapies. Comparator interventions were placebo, artemether-lumefantrine (AL), sulfadoxine-pyrimethamine (SP), SP + amodiaquine, SP + piperaquine, SP + chloroquine, and co-trimoxazole + piperaquine. Treatments were administered at 1-, 2- and 3-month intervals, or as three courses during the second and third trimesters of pregnancy. Antimalarials were administered as directly observed therapy (DOT) for at least the first dose of each course (10 studies), or intake was recorded by the subjects' parents (one trial).

None of the 11 studies reported sudden or unexplained deaths, or serious adverse events consistent with sudden cardiac death. Risk of death was similar between DHA-PPQ and comparator arms. DHA-PPQ was also not associated with increased loss to follow-up compared to comparator drugs, but was associated with a higher loss to follow-up compared to placebo; however, this finding was driven primarily by the high loss to follow-up in a single study *(33)* and probably unrelated to the drug.

IPT studies in progress

Data were also presented from three recently completed preventive therapy studies that used DHA-PPQ at standard weight-based doses to achieve daily therapeutic dose ranges of dihydroartemisinin (2–10 mg/kg body weight) and piperaquine (16–26 mg/kg body weight).

There were two deaths reported among the 10 079 participants of the START-IPT cluster randomized trial of monthly SMC in schoolchildren in Jinja, Uganda. These deaths were due to a road traffic accident and tetanus, respectively, and were considered unrelated to DHA-PPQ (Duocotexin®). Participants received up to six rounds of SMC, and all three doses of each treatment course were administered as DOT.

There were no deaths or cardiac events among 2279 pregnant women in the STOPMIP study in Papua, Indonesia, approximately 700 of whom received monthly IPTp with DHA-PPQ (Eurartesim®) during antenatal care visits in their second and third trimesters of pregnancy. The first and third doses of each course were administered as DOT. All women were followed up until 6–8 weeks after delivery.

There were no deaths or cardiac events among 100 HIV-infected pregnant women exposed to DHA-PPQ (Duocotexin®) in the PROMOTE BC2 IPTp study in Tororo, Uganda. Participants received DHA-PPQ every 4 weeks during antenatal care visits in their second and third trimesters of pregnancy, with the first dose of each course administered as DOT. A total of 468 courses of DHA-PPQ were administered, and all 100 women were followed up until delivery.

There were no cases of TdP or ventricular tachyarrhythmia in the START-IPT, STOMIP and PROMOTE BC2 nested ECG substudies (discussed in further detail in section 3.4.2); these included 155 schoolchildren, 33 women and 13 women, respectively.

3.2.4 Case management

Literature review

A systematic review of all published antimalarial clinical efficacy trials was undertaken using the WWARN publication library to identify deaths following antimalarial therapy with quinoline and structurally-related antimalarials. SP was included as a comparator. The review yielded publications on 810 clinical trials that tested in at least one arm a quinoline compound or SP for the treatment of uncomplicated falciparum malaria. A total of 210 156 participants were enrolled in these trials, with 194 845 patients treated with a quinoline drug or SP. Participants received up to one course of each antimalarial. The vast majority of efficacy trials had a follow-up period of ≥14 days. Further information was obtained by contacting the corresponding authors or interrogating the WWARN data repository. The 2005 WHO-Uppsala Monitoring Centre system *(38)* was used for standardized case causality assessment.

The data showed 80 deaths following treatment with the antimalarial medicines of interest (listed in section 2.2), details of which are summarized in Table 4. Mortality in the treatment of uncomplicated falciparum malaria generally ranges from 0.1% to 1%. Exposures and deaths following quinine were not included in Table 4, as severe rather than uncomplicated malaria was the primary indication for the use of this antimalarial.

Table 4. Deaths following antimalarial therapy in historical case management efficacy trials

	Subjects/ courses	Sudden unexplained	Severe malaria	Infections other than malaria	Trauma/ accidents	Poisoning	>28 days after drug	Other	Unknown aged 6–59 months	Total
Halofantrine	2027	2								2
AL	34 576		9	6	3	1	5			24
ASAQ	18 815		4	4		1	1	1	1	12
Amodiaquine	5981		1	1	1		1			4
ASMQ	18 815		2		1		2	1		6
Mefloquine	6606							1		1
Pyronaridine-artesunate	4422				1					1
DHA-PPQ	14 273		3	3	1		3	3		13^
Chloroquine	23 773		2	3		1	1	1	2	10
SP	17 568		5						2	7
Quinolines	*129 288*	*2*	*21*	*17*	*7*	*3*	*13*	*7*	*3*	*73*
Grand Total	**146 856**	**2**	**26**	**17**	**7**	**3**	**13**	**7**	**5**	**80**

AL = artemether-lumefantrine. ASAQ = artesunate-amodiaquine. ASMQ = artesunate-mefloquine. DHA-PPQ = dihydroartemisinin-piperaquine. SP = sulfadoxine-pyrimethamine. ^These 13 deaths were from nine clinical trials also reviewed either as part of a Cochrane review of the efficacy and safety of DHA-PPQ *(39)* or the Sigma Tau meta-analysis on the clinical use of piperaquine; eight of the nine studies were reviewed in both.

Only two cases were assessed as probably drug-associated: two sudden unexplained deaths following halofantrine treatment. One death occurred in a 37-year-old woman with a lifelong history of syncope and palpitations; after having been treated with mefloquine 21 days before, she had a cardiac arrest just before receiving the final dose of a 3-day course of high-dose halofantrine *(17)*. Another death of a 22-year-old man occurred during the recovery phase after receiving micronized halofantrine *(40)*. Two other deaths were assessed as possibly drug-related: One was of an 11-month-old girl *(41)* with severe malaria who died 3 days after artesunate-amodiaquine (ASAQ) with uncontrolled administration of traditional medicine of an unknown nature; the other was of an 18-month-old girl *(42)* who died from severe malaria 7 hours after a single dose of AL, but investigators could not exclude other aetiologies, including sepsis and hypoglycaemia.

Of the 80 cases of death listed in Table 4, 53 had age documentation: 4% (3/53) of the deaths occurred in infants aged <6 months, and 60% (32/53) in children aged 6–59 months. In keeping with the life-threatening nature of acute malaria, 32.5% (26/80) of the deaths were consistent with the progression to severe malaria, while 21% (17/80) were associated with other infections, including HIV/AIDS, pneumonia and diarrhoea, which reflect the main causes of mortality in children under 5 in low- and middle-income countries where malaria is endemic. Deaths from trauma, 9% (7/80), were due to gunshots (2), landmines (2) and other injuries. Given the elimination half-lives of the antimalarial drugs in question, the 16% (13/80) of deaths that occurred >28 days after treatment were thought very unlikely to be drug-related.

There were five deaths of children aged 6–59 months for which a cause had not been determined, but further assessment of these cases was not possible with the limited information available. However, considering the more common causes of death for children of that age group in malaria-endemic regions, it was thought unlikely that sudden cardiac death would be the most probable explanation for these deaths.

Plasmodium falciparum infections are much more likely to progress to severe malaria than *P. vivax* infections. In the case of chloroquine, 10 deaths out of 23 773 participants were reported following chloroquine treatment in falciparum malaria, while no deaths were reported among 11 848 participants receiving chloroquine for vivax malaria ($P < 0.01$). Given that the pharmacokinetic properties of chloroquine are similar in these two malarias, it is more likely that the difference was caused by the disease rather than the drug.

This review was limited by the quality of information available about causes of death and the subjectivity of causality assessment, as well as by the heterogeneity of adverse event monitoring and rates of loss to follow-up in individual trials.

Cochrane review on DHA-PPQ

A 2014 Cochrane review *(39)* evaluated the effectiveness and safety of DHA-PPQ compared to other WHO-recommended ACTs for the treatment of uncomplicated falciparum malaria. The review included 27 randomized controlled trials conducted between 2002 and 2010 enrolling 16 382 participants. The risks of serious adverse events including death were similar when comparing DHA-PPQ with AL and also with artesunate-mefloquine (ASMQ). No cardiac arrhythmias were reported.

Phase 4 safety monitoring assessment of DHA-PPQ

Between 2013 and 2014, the INDEPTH Effectiveness and Safety Studies platform (INESS) conducted a phase 4 prospective observational study on DHA-PPQ (Eurartesim®) at eight Health and Demographic Surveillance System (HDSS) sites of the INDEPTH network in Tanzania, Burkina Faso, Mozambique and Ghana, as part of the EMA risk management plan for the drug. This study

is significant for being the largest and most rigorously conducted post-marketing safety monitoring assessment of any antimalarial medicine in real-life conditions in sub-Saharan Africa. A total of 10 925 patients with uncomplicated malaria aged >6 months were treated with at least one dose of DHA-PPQ. Of these, 10 591 patients received a full course of DHA-PPQ and completed follow-up visits on day 5 ± 2 days and day 28. Out of all the 10 925 patients who received DHA-PPQ, six deaths were reported, of which three were assessed as being unrelated to DHA-PPQ. It was assessed that the remaining three deaths were unlikely to be related to DHA-PPQ: One was of a 17-month-old boy who presented 14 days after DHA-PPQ with severe diarrhoea secondary to acute gastroenteritis and died within 24 hours of admission; one was of a 4-year-old girl who presented within 24 hours of recruitment with severe anaemia and died on the way to a higher referral facility for blood transfusion; and the last was of a 3-year-old girl who died at home from severe malaria 3 days after recruitment, as suggested by verbal autopsy. Among the 1002 patients in the nested cardiac safety cohort who underwent ECG monitoring at baseline before and after the third dose and on day 7, there was no documented report of clinically relevant cardiotoxicity, TdP or ventricular fibrillation *(21)*.

3.2.5 Case safety report databases

Spontaneous reports to pharmacovigilance centres and drug manufacturers are another important source of information that can be used to detect rare adverse events. The goal of such spontaneous reporting systems is to highlight possible signals of adverse drug reactions (ADRs) and not to make estimates of their incidence. These systems provide information throughout the lifetime of a drug. However, there is significant and widespread underreporting of ADRs (including serious or severe ADRs) to spontaneous reporting systems *(43)*. Reports also vary in quality and completeness. The subjectivity and use of different methods to perform causality assessment are further limitations *(44)*.

WHO global database of individual case safety reports

VigiBase® is the WHO Global Database of Individual Case Safety Reports, i.e., spontaneous reports of ADRs, received from national pharmacovigilance centres that are members of the WHO Programme for International Drug Monitoring. Three summary reports were generated on:

1. Sudden death and TdP/QT interval prolongation with any antimalarial
2. Suspected ADRs and TdP/QT interval prolongation with halofantrine
3. Suspected ADRs and TdP/QT interval prolongation with DHA-PPQ

A total of 40 cases of sudden death and/or death as an outcome of TdP/QT interval prolongation following any antimalarial were reported, all of which originated in Europe and North America. In 22 cases, the antimalarial was used for an indication other than malaria, with drug dosages and durations varying accordingly. In 16 cases, concomitant use of another medicine that could potentially increase the risk of QT/QTc interval prolongation was reported. Quinidine was the suspected antimalarial in 16 cases; in 12 of these cases, there was evidence of a cardiac-related indication and/or concomitant medications, suggesting quinidine was used as an antiarrhythmic. Exposure to chloroquine and hydroxychloroquine was reported in six and five cases of sudden death, respectively. In four of these cases, overdose was listed as the indication. Hydroxychloroquine was used to treat rheumatoid arthritis, systemic lupus erythematosus and small cell lung carcinoma in one case each. Long-term use of chloroquine or hydroxychloroquine may cause myopathy, which may involve cardiac muscle. Collagen vascular diseases are also associated independently with cardiomyopathy and conduction defects. Exposure to mefloquine was reported in six cases of sudden death; in one of these cases, mefloquine was administered concomitantly with halofantrine. Halofantrine, quinine (as treatment for restless legs syndrome in one case, and as an intentional overdose in another), and pyrimethamine (as treatment for

toxoplasmosis in two cases) were the antimalarials in the remaining cases identified. Only four reports were of good quality, i.e., had a completeness score ≥0.8.

Halofantrine was associated with 30 reports of TdP/QT interval prolongation based on a search using broad Standardised MedDRA Queries (SMQ)[iii]. These included two reports of TdP, three of ventricular fibrillation, and four that resulted in death. In three of these deaths, concomitant medications included chloroquine in two cases and mefloquine in one case (also reported as a death after mefloquine). Of the 30 reports, 18 were from France, where the drug was used more extensively than in other countries. A further four deaths were identified among reports of sudden death and general cardiac-related ADRs.

For DHA-PPQ, four reports were identified through the broad SMQ for TdP/QT interval prolongation. There was one report of QT interval prolongation that was transient and resolved; this was also the only report that was identified using a narrow SMQ term specific to the condition of interest, i.e., QT interval prolongation. The remaining three reports were found using broad SMQ terms of syncope and loss of consciousness, which are symptoms that can be presentations of TdP/QT interval prolongation, along with a range of other conditions, including orthostatic hypotension and vasovagal episodes. In two of these cases, tamsulosin, which is known to cause orthostatic hypotension, was a concomitant medication. Another medication potentially causing QT/QTc interval prolongation, ciprofloxacin, was a concomitant medication in the final case. All patients had malaria, which itself is associated with orthostatic hypotension, listed as the indication.

Pharmaceutical company safety databases

The sales figures and number of sudden unexplained deaths following exposure to halofantrine, artemether-lumefantrina and dihydroartemisinin-piperaquine based on the safety database of the respective manufacturers are presented in Table 5.

Table 5. Sudden unexplained deaths from pharmaceutical company safety database searches

	Halofantrine (Halfan®)	AL (Coartem®/Riamet®)	DHA-PPQ (Eurartesim®)
Period	1988–October 2016	1998–October 2016	2011–October 2016
Sales figures[†] (doses)	23.2 million^	>840 million	2.8 million
Sudden unexplained or cardiac deaths	36	0	1

[†]Pharmaceutical company sales figures represent a proportion of the total sales of these antimalarials, which are mostly sold as generics (with the exception of halofantrine). ^Halfan® sales figures were available only up until 2012, while global safety database information was available to October 2016; the product was discontinued in April 2016, so it is unlikely that up-to-date sales figures would be much higher than those reported here.

Fatal cardiotoxicity related to halofantrine was reviewed *(19)* based on a systematic literature search and access to the GSK global safety database. Cases added to the GSK database after this first review's March 2005 cut-off were assessed for the ERG using the same methodology. Thirty-six cases were identified, the majority of which – 58% (21/36) – had received concomitant drugs that could also induce QT/QTc interval prolongation. There were 32 cases for which the time from the first dose to death was available: All occurred within 3 days of the first dose, and 84% (27/32) of these died within 24 hours. While reporting bias cannot be ruled out, the reported time of

[iii] SMQ are validated, standardized sets of search terms used to facilitate retrieval of MedDRA-coded data.

occurrence of these deaths is consistent with the timing of peak drug concentrations following halofantrine administration in uncomplicated malaria, when drug-induced cardiotoxicity risk is at its highest *(45)*. All cases identified in VigiBase® had corresponding records with identical demographic details and case descriptions in the GSK global safety database; these records were all included in the halofantrine cardiotoxicity review *(19)*. Both sudden unexplained deaths identified in the case management literature review (presented in section 3.2.4) were also included in the GSK database and halofantrine cardiotoxicity review *(19)*.

Of the six cases with fatal outcomes following AL reported by Novartis, the investigators reported no drug-related causality: One death was from severe malaria, three were neonatal deaths from other causes, one occurred 151 days after dosing, and one had insufficient detail for assessment.

The Sigma Tau safety database yielded two cases of possible serious cardiovascular events following DHA-PPQ. The first was the sudden death of a 16-year-old female following MDA (as presented in section 3.2.2). The other was of a 36-year-old healthy male volunteer in a clinical trial *(46)* who reported feeling lightheaded in the evening, about 10 hours after having taken the third dose of DHA-PPQ with breakfast. At the time of the adverse event, ECG monitoring showed that he had an irregular bradycardic rhythm. He then became unresponsive and apnoeic with a similar irregular bradycardia followed by asystole for 43 seconds. After at least 10 seconds of cardiopulmonary resuscitation, he reverted to normal sinus rhythm at a rate of 66 beats per minute and a blood pressure of 118/62mmHg. The subject stated retrospectively that he had had bloating and diarrhoea on the day of the event. After review of the case report, the ERG considered it consistent with vasovagal syncope rather than TdP. Two other cases of sudden unexplained death following DHA-PPQ were also presented. The first death was of a 28-month-old boy who had been frequently unwell from birth. He had presented with fever and abdominal pain to the health centre, where he underwent a malaria rapid diagnostic test, which was negative. He was then treated with a 3-day course of mebendazole for an intestinal parasitic infection. The day after his last dose of mebendazole, he died 5–15 minutes after his first dose of DHA-PPQ, which was given as SMC. The investigators considered his death to be potentially related to a drug interaction between DHA-PPQ and mebendazole. However, in light of the very brief interval between DHA-PPQ intake and death, the pharmacokinetics of piperaquine, as well as the short terminal elimination half-life of mebendazole of 3–6 hours after oral dosing, the ERG considered it unlikely that the death had been drug-related. The second case was of a 5-year-old boy who died the day after receiving the third dose of DHA-PPQ in an observational malaria treatment study. The verbal autopsy indicated that the child had died after a tonic-clonic seizure following repeated vomiting that had started on the first day of treatment. The ERG concluded that the repeated vomiting would have probably interfered with drug absorption, making it unlikely that the drug had caused the child's death.

The 2011 Sigma Tau meta-analysis on the clinical use of piperaquine reported no excess risk of death between DHA-PPQ and comparator arms in both IPT and case management studies. In total, 19 446 patients treated with DHA-PPQ were considered in 55 trials: 9015 in 34 controlled and 561 in seven uncontrolled studies for the treatment of uncomplicated malaria; 192 in nine PK studies; and 9678 in five IPT studies. Comparators in case management studies included AL, ASAQ and ASMQ. Comparators in IPT studies included SP, SP + amodiaquine, and placebo. The Cochrane systematic reviews of case management with DHA-PPQ *(39)* (see section 3.2.4) and repeated doses of DHA-PPQ *(20)* (see section 3.2.3) included 22 out of 34 of the controlled trials and two out of five of the IPT studies, respectively. Both reviews had similar findings to this meta-analysis. None of the 10 deaths identified following DHA-PPQ was thought to be consistent with sudden cardiac death. Eight of the nine deaths identified from case management studies were also assessed independently in the case management literature review (presented in section 3.2.4), while the one death in IPT was also included in the repeated doses of DHA-PPQ review *(20)* (discussed in section 3.2.3).

No ventricular tachyarrhythmias or TdP have been documented following exposure to AL or DHA-PPQ.

Liverpool School of Tropical Medicine (LSTM) Centralised Antimalarial Safety Database

This database of adverse events following antimalarial administration includes safety data collected from studies conducted by the ACT Consortium and Malaria in Pregnancy Consortium. There were no reports of serious adverse events of sudden death, TdP/QT interval prolongation or cardiac arrhythmias within 14 days of follow-up after antimalarial therapy. In a mix of healthy volunteer, IPT and case management studies, 4694 subjects received AL, 2316 received DHA-PPQ, 843 received ASAQ, 849 received ASMQ, 4111 received SP, 1365 received chloroquine + SP, and 1370 received azithromycin + SP. One of the published IPTp studies was also included in the systematic review on repeated doses of DHA-PPQ *(20)* (section 3.2.3). It was not clear if the unpublished studies were also included in other evidence considered.

Key conclusions

- DHA-PPQ treatment has been associated with one possible sudden cardiac death post-MDA out of 193 974 trial subjects with close follow-up in malaria MDA, IPT and case management studies, the majority of whom were exposed to repeated courses in MDA and IPT studies.
- IPT studies and therapeutic clinical trials did not show a different risk of death between DHA-PPQ and other antimalarials recommended by WHO for the treatment of uncomplicated malaria.
- Neither DHA-PPQ nor AL has been associated with documented life-threatening arrhythmias.
- AL treatment has not been associated with any sudden unexplained deaths.
- Reported deaths following chloroquine and hydroxychloroquine have been associated with use in overdose or for chronic indications other than the treatment of malaria.
- Concomitant use of QT/QTc interval-prolonging drugs has been found to increase the risk of antimalarial cardiotoxicity.

3.3 Studies of the effects of antimalarial medicines on the ECG

3.3.1 Halofantrine

The FDA approved halofantrine as Halfan® in 1992 under SmithKline Beecham (now GSK).

The absorption of halofantrine is highly variable and enhanced substantially by fatty foods and bile salts. The drug is highly bound to plasma lipoproteins and has a large apparent volume of distribution with a moderately long distribution phase. Halofantrine is metabolized to desbutylhalofantrine by CYP3A4 and inhibits CYP2D6. It undergoes enterohepatic recycling with faecal elimination of both parent drug and metabolite.

Halofantrine blocks hERG channels and has been associated with a dose- and concentration-related prolongation of the QTc interval in preclinical models *(47)*, healthy volunteers *(48,49)* and patients with uncomplicated malaria *(17)*. QTc interval prolongation with halofantrine has been associated with TdP, syncope and >30 cases of sudden death (section 3.2.5). Prior exposure to mefloquine is a risk factor that increases QTc interval prolongation with halofantrine *(17)*. Food-

mediated lymphatic absorption and consequent high thoracic duct drug concentrations may also increase risk *(50)*.

3.3.2 Artemether-lumefantrine

Artemether-lumefantrine was first registered as Coartem® in Gabon in 1998 and as Riamet® in Switzerland in 1999. It is currently registered in around 86 countries worldwide, including the European Union and the United States.

In the *in vitro* whole cell patch clamp study, lumefantrine and its metabolite desbutyl-lumefantrine showed a concentration-dependent inhibition of the hERG current, but at a much higher 50% inhibitory concentration (IC_{50}) than mefloquine, chloroquine and halofantrine; only halofantrine had an IC_{50} lower than its free therapeutic plasma maximum concentration (C_{max}) *(51)*. No QTc interval prolongation was seen *in vivo* in dogs with AL administered orally, except at extremely high total doses of 600mg/kg/day.

Following the experience with halofantrine, ECG evaluations have been included in most studies of AL treatment. In a randomized, double-blind, double-dummy, two-period crossover, single-dose study conducted in 13 fed, healthy, male volunteers, halofantrine had a mean maximum increase in QTcB of 28ms, but no QTcB interval prolongation was observed with AL *(52)*. In a randomized, double-blind, parallel group, 4-week trial to compare the safety and efficacy of AL with halofantrine in adult male and female travellers returning to Europe with acute falciparum malaria, 26.9% (14 subjects) had a QTc interval increase of >15% from baseline with halofantrine as compared to 7.8% (four subjects) with AL *(53)*.

The TQT study performed in healthy adult volunteers showed that, relative to placebo, AL was associated with a mean maximum increase in QTcF of 7.45ms at the 68-hour time point. The period of QTcF prolongation over zero effect, as defined in the ICH E14 guideline, was 3.5–4 days after the last dose of the standard six-dose regimen. Post-hoc analysis showed an association between the maximum observed values of QTcF change from baseline adjusted from placebo and concentrations of lumefantrine. At typical clinical concentrations of lumefantrine, an increase of >10ms was excluded. In clinical trials conducted with the six-dose AL regimen, a post-baseline QTcF interval >500ms was reported in 0.2% of adult patients, while no paediatric patient aged <12 years had a post-baseline QTcF interval >500ms.

The small increase in QTc interval associated with AL does not appear to be associated with a significant risk of arrhythmia. The small number of adverse events affecting the cardiovascular system were almost all of mild intensity and resolved without intervention.

3.3.3 Dihydroartemisinin-piperaquine

Dihydroartemisinin-piperaquine (Eurartesim®) received EMA marketing authorization in 2011.

Preclinical *in vitro* studies were performed comparing the effects of DHA-PPQ with those of other antimalarials *(54)*. In the whole cell patch clamp study, only halofantrine had an IC_{50} lower than its free therapeutic C_{max}, while chloroquine, mefloquine, lumefantrine, piperaquine, dihydroartemisinin, and the positive control dofetilide blocked hERG with IC_{50}s ranging from 3- to 30-fold their C_{max} values. Neither DHA-PPQ nor AL induced potential torsadogenic effects in the rabbit ventricular wedge preparation, affected hERG trafficking, or inhibited the sodium or slow potassium currents. Chloroquine facilitated hERG trafficking at 30-fold its C_{max}, showed a medium risk of torsadogenic effects in the rabbit ventricular wedge preparation, and blocked the sodium current at about 30-fold its C_{max}.

The TQT study performed in healthy adult volunteers showed that DHA-PPQ administered in the fasting state was associated with a mean maximum time-matched increase in QTcF relative to

placebo of 21.0ms compared with 9.9ms for AL. Time to C_{max} was reported as 4–6 hours post-dose for piperaquine. QTcF interval prolongation was transient for both DHA-PPQ and AL.

The results of a phase 2 PK/PD and safety study comparing a new paediatric DHA-PPQ dispersible formulation with crushed film-coated DHA-PPQ tablets in 300 infants aged 6–12 months with uncomplicated malaria were also presented. Both formulations had similar piperaquine pharmacokinetic and adverse effect profiles. There was a ~15–20% reduction in mean heart rate between day 0 and 4 hours post-dose on day 2 consistent with fever resolution, accompanied by an increase in mean QTcF of ~20ms in both groups. Mean QTcF returned to day 0 levels by day 7. There were no cardiovascular adverse events.

Two accidental cases of overdose with DHA-PPQ have been reported in paediatric patients with fever treated with DHA-PPQ for microscopy-confirmed malaria. The first was of a 9-year-old African girl who received nine tablets instead of three of DHA-PPQ at 17:45 on 2 April 2016. Her QTcF interval at 06:30 on 3 April was 464ms compared to 413ms at admission on 1 April. The second was of a 5-year-old African boy who received three tablets instead of one of DHA-PPQ at 17:30 on 7 September 2016. At 09:30 the next day, he had a QTcF interval of 381ms compared to 346ms at admission. Neither child had clinical signs of arrhythmia.

3.3.4 Pyronaridine-artesunate

In 2012, pyronaridine-artesunate (Pyramax®) became the first ACT to be granted a positive scientific opinion under the EMA Article 58 procedure. Pyronaridine tetraphosphate was first synthesized in the 1970s.

In *in vitro* hERG studies, pyronaridine inhibited the hERG current at an IC_{50} of 0.65µM, ~28 times the free therapeutic C_{max} in humans and ~8 times the maximum concentration of pyronaridine achieved in clinical trials. Up to 300µM artesunate, ~1000 times the C_{max} in humans, had no effect on the hERG current. No QTc interval prolongation was seen in the *in vivo* QT assay in dogs, except at doses several times greater than the human equivalent dose of pyronaridine-artesunate used in phase 3 trials.

In phase 1 studies, QTc data were available for 222 healthy subjects who received pyronaridine-artesunate either as a single dose or for 3 days. The maximum mean change of QTcB from baseline was 7ms to 13ms and that of QTcF was -1ms to 1ms. The maximum QTcB interval measured in any individual was 470ms, while the maximum QTcF interval – in a different subject – was 469ms.

In phase 2 and 3 studies in patients with uncomplicated malaria, QTc data were available for 2817 patients who received pyronaridine-artesunate. The maximum QTcB interval measured in any individual was 475ms, while the maximum QTcF individual – in a different subject – was 473ms. There were no cardiovascular adverse events following pyronaridine-artesunate that were potentially attributable to QTc interval prolongation.

In the phase 3b West African Network for Antimalarial Drugs (WANECAM) repeat dosing study, pyronaridine-artesunate had the least potential to prolong the QTc interval compared to AL, ASAQ and DHA-PPQ. There were no cases of QTcB or QTcF interval >500ms among patients who received pyronaridine-artesunate. In addition, repeat dosing did not have an appreciable effect on QTc parameters.

In granting the positive Article 58 opinion, the EMA agreed that a TQT study was not mandatory for Pyramax®.

3.3.5 Artefenomel-piperaquine

Artefenomel (OZ439) is a novel aromatic trioxolane that is being trialled in combination with piperaquine for the treatment of uncomplicated malaria.

In the *in vitro* hERG assay, OZ439 inhibited the hERG current at an IC_{50} of ~22µM, while the IC_{50} concentrations of two of its main metabolites were >10µM. Considering that the average free therapeutic plasma C_{max} after a single OZ439 dose of 800mg is 0.12µM, taking into account 96% protein binding, this suggests a 180-fold safety margin. There was no effect on QTc in the *in vivo* assay in conscious dogs with OZ439 exposures equivalent to the C_{max} of free therapeutic plasma *(55)*.

Exposure-response analysis was performed on data from a placebo-controlled, single-dose, phase 1 study with OZ439 and piperaquine. In the study, 59 healthy subjects aged 18 to 55 years received OZ439 alone or placebo in the first period, followed by OZ439 + piperaquine or matching placebos in the second period. OZ439 and piperaquine doses ranged from 100mg to 800mg and 160mg to 1440mg, respectively. Pre- and post-dosing, 12-lead ECG tracings and PK samples were collected serially. A significant relationship between plasma concentrations and placebo-corrected change from baseline QTcF was demonstrated for piperaquine, but not for OZ439, with a mean slope of 0.047ms/ng/ml (90% confidence interval: 0.038–0.057). This result suggests that piperaquine, but not OZ439, prolongs the QTcF interval in a concentration-dependent way. A linear mixed effects model accounting for the plasma concentrations of both piperaquine and OZ439 predicted a largest mean QTcF effect of 14ms (90% confidence interval: 10–18ms) and 18ms (14–22ms) at expected plasma concentrations following administration in the fasted state of a single dose of OZ439 800mg combined with piperaquine 960mg (188ng/ml) and 1440mg (281ng/ml), respectively *(55)*.

3.3.6 Ferroquine

Ferroquine is a 4-aminoquinoline analogue with a structural homology to chloroquine that is currently in pre-approval clinical trials.

In the *in vitro* hERG assay, ferroquine inhibited the hERG current at an IC_{50} of 2.0µM, and its more slowly-eliminated active metabolite SSR97213 had an IC_{50} of 0.183µM – respectively ~200–500 times and ~40–80 times the free therapeutic C_{max} in human subjects. In the conscious dog *in vivo* QT assay, ferroquine had no effect on QTc at 3, 10 and 30mg/kg doses.

In phase 1 studies in healthy subjects, 117 subjects received up to 1600mg of ferroquine, either alone or in combination with artesunate; 55 subjects received ferroquine up to a dose of 1200mg in combination with OZ439. Preclinical and clinical studies have shown that artesunate *(56)* (section 3.3.4) and OZ439 *(55)* (section 3.3.5) are not associated with QTc interval prolongation. Of these 172 subjects, only one had a QTcF interval >450ms and none had a QTcF interval >500ms. ECG analysis from pooled phase 1 studies showed an estimated mean increase in QTcF compared to placebo of 3.1ms (95% confidence interval: 1.4–4.8), 3.3ms (0.8–5.8), and 5.9ms (3.9–7.8) at the higher single doses of 800, 900, and 1200mg, respectively. In the 3-day repeated ferroquine monotherapy ascending-dose study, morphological changes were observed at the 800mg dose of ferroquine on day 1, with four out of six subjects developing T wave flattening, and one out of six patients developing an inverted U wave. Due to the T wave changes observed at the 800mg dose level, enrolment was discontinued for the 1000mg dose level.

3.3.7 Other antimalarial drugs

Amodiaquine and primaquine both affect cardiac electrophysiology and both are used widely; however, very few studies have recorded ECGs. The limited data available suggest that artesunate-amodiaquine is associated with QTc interval prolongation similar to that following

chloroquine *(57)*, and that primaquine does not cause significant QTc interval prolongation *(58–60)*. However, more information is needed. It is notable that with the extensive global usage of quinine in the first half of the 20th century and the enormous use of chloroquine (and to a lesser extent amodiaquine) in the second half, there have been no reports of sudden unexplained death suggestive of cardiac arrhythmia at the doses used for malaria treatment.

Key conclusions

- Halofantrine treatment has been associated with substantial dose- and concentration-dependent QTc interval prolongation at therapeutic doses in healthy volunteers and malaria patients; it has also been associated with conduction abnormalities, TdP, syncope and sudden death.
- Artemether-lumefantrine treatment has been associated with slight concentration-dependent QTc interval prolongation at therapeutic doses, but this transient QTc interval prolongation has not been associated with cardiovascular adverse events.
- DHA-PPQ treatment has been associated with greater QTc interval prolongation than AL at therapeutic doses, but this QTc interval prolongation is transient and has not been associated with cardiovascular adverse events.
- Studies have shown pyronaridine-artesunate treatment to have the lowest potential to prolong the QTc interval compared to AL, ASAQ and DHA-PPQ, even after repeat dosing.
- Artefenomel (OZ439) has not been associated with concentration-dependent QTc interval prolongation.
- More information is needed on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine.

3.4 PK/PD analyses on the effects of antimalarial medicines on the ECG

3.4.1 Pooled analyses

Preliminary analyses from individual subject data shared with the ERG (see Annex A for list) were pooled, analysed and presented. A subset of studies with central ECG readings performed by Cardiabase were also analysed and presented separately. In addition, results from nonlinear mixed effects PK/PD modelling of individual subject measurements from selected studies of chloroquine and DHA-PPQ were presented.

QTc measurement methodologies

A number of QTc measurement methodologies were used in a variety of combinations, including:

- ECGs with automated machine readouts versus semi-automated central digital readings versus manual measurements on paper; in some studies, only a subset of ECGs, such as those with prolonged QTc intervals as determined by other methods, were sent for central reading;
- Superimposed median beat measurements versus averaged measurements of multiple complexes from a particular ECG lead, usually lead II but occasionally others;
- Threshold versus tangent method for determining the end of the T wave;
- 50mm/second versus 25mm/second paper speed.

ECGs were recorded at a variety of time points, although all studies measured ECGs at baseline and at least one other point in time following drug dosing (usually at the expected time of peak drug concentration). The possibility of a detection effect in studies with more frequent ECG

measurements was discussed. Members of the ERG also noted the widely observed inter-observer variability in QTc measurements.

Despite the heterogeneity in ECG measurement methodologies, there was remarkable agreement among individual studies in terms of the findings related to QTc parameters (see sections 3.3 and 3.4.2), as well as between the Cardiabase pooled statistical analyses of studies utilizing relatively standardized ECG measurement procedures and the ERG pooled statistical analysis, which included data from studies using a diverse range of ECG measurement methods.

Correction factor sensitivity analysis

The Bazett ($QT \times RR^{-0.5}$) and Fridericia ($QT \times RR^{-0.333}$) corrections are the two most commonly used in clinical practice to adjust the measured QT interval for heart rate, with the RR interval representing the duration between QRS complexes. In addition, the Fridericia correction has been the subject of increased interest following an April 2012 recommendation from the ICH E14 TQT Implementation Working Group that its use is adequate for the majority of TQT studies.

In both pooled statistical analyses, QTcB was found to be the better correction factor at baseline for patients with malaria, while QTcF was more appropriate for healthy subjects in general. In the Cardiabase analysis, study-specific corrections were close to Bazett's correction for malaria patients and non-Caucasian healthy subjects, while study-specific corrections approximated Fridericia's correction for healthy volunteers from predominantly Caucasian populations. Study-specific sensitivity analyses conducted in the STOPMIP IPTp and ADJusT case management studies with DHA-PPQ confirmed that Bazett's correction offered better heart rate correction, whereas the large START-IPT SMC study in schoolchildren favoured Fridericia's correction.

In the preliminary pooled PK/PD analysis of DHA-PPQ data, the overall population correction in malaria patients was close to Bazett's correction. The daily population correction exponent gradually decreased in absolute value over several days to approach Fridericia's correction as patients recovered from malaria.

Degree of QTc interval prolongation

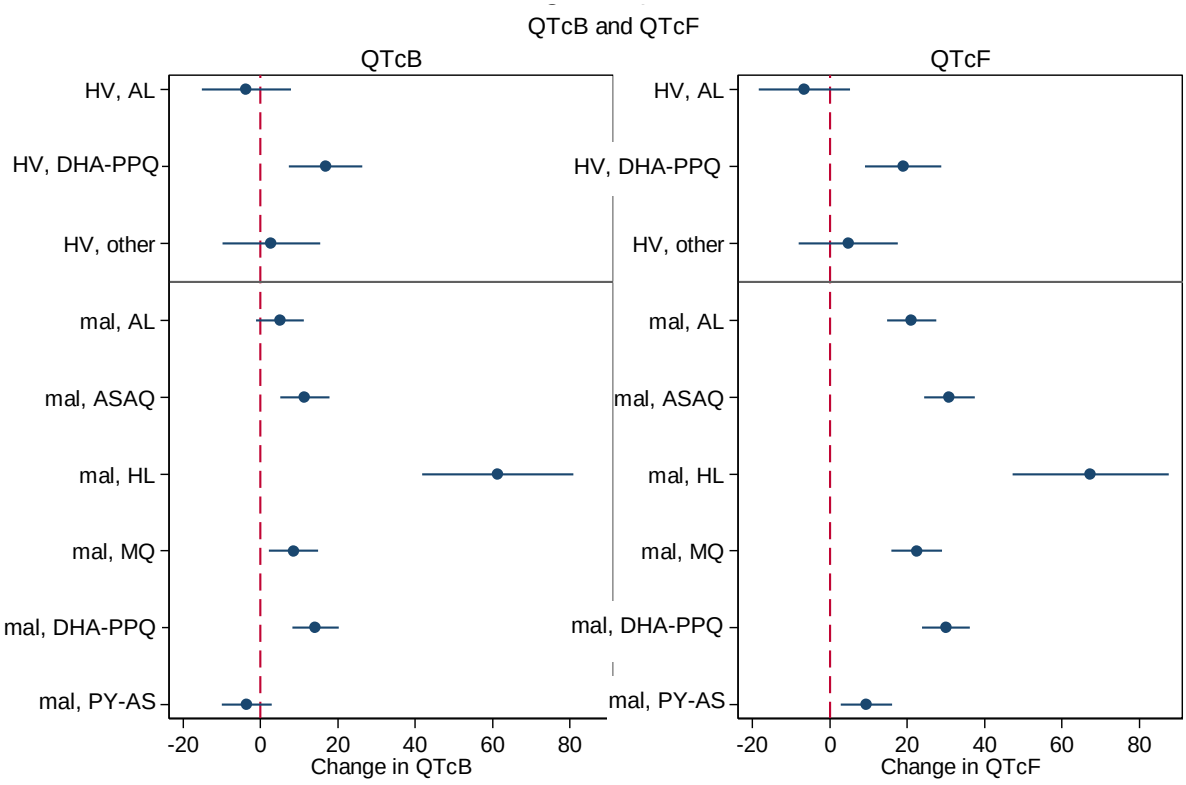
Nonlinear mixed effects PK/PD modelling of measurements from two randomized 3-period crossover studies in healthy Thai volunteers *(58,60)* found chloroquine to be associated with QTc interval prolongation greater than that of DHA-PPQ. The approximate mean concentration–QTcF effect of chloroquine was a 10.2ms increase in QTcF per 100ng/mL increase in plasma chloroquine concentration compared to a 3.12ms increase in QTcF per 100ng/mL increase in plasma piperaquine concentration. In these healthy volunteer studies, patients received single oral doses of each antimalarial drug at standard therapeutic doses. ECGs were recorded pre-dose and over 24 hours post-dose, while pharmacokinetic sampling was performed pre-dose and over 36 days following administration of chloroquine or DHA-PPQ. Pharmacokinetic assessment was performed using both model-independent and nonlinear mixed effects PK/PD modelling approaches.

The preliminary pooled PK/PD modelling analysis of DHA-PPQ found similar slopes for the mean concentration–QTcF effect of piperaquine in healthy volunteers and in malaria patients, with a mean concentration–QTcF effect of 3.3ms of QTcF prolongation per 100ng/mL increase in piperaquine concentration. Healthy volunteer data were included from the crossover study in healthy Thai volunteers *(58)* and the DHA-PPQ (Eurartesim®) TQT study, while uncomplicated malaria patient data were drawn from the 1002 subjects included in the nested ECG and PK substudy of the INESS *(21)* phase 4 safety monitoring assessment of DHA-PPQ (also discussed in section 3.2.4). Three INESS patients had a QTcF interval >500ms at C_{max}, but there were no episodes of TdP, ventricular fibrillation or adverse clinical sequelae *(21)*. Both TQT and INESS patients received full 3-day treatment courses of DHA-PPQ. In the TQT study, subjects who

received DHA-PPQ were in three arms, each with different food conditions: fasting, high-fat/low-calorie, and high-fat/high-calorie.

Individual patient data provided to the ERG to evaluate the effect of full therapeutic courses of antimalarials on QTc measurements were pooled and analysed. Quinine was not included in this analysis, as the data shared were related to its use in the treatment of severe malaria. A preliminary analysis was undertaken to determine the mean change in QTc associated with each antimalarial medicine in patients with uncomplicated malaria and in healthy subjects (where data were available). Change in QTc was defined as the difference in QTc measured at baseline and at a follow-up ECG selected to be either 2–8 hours after the last dose of the treatment course (where time of dose was available) or approximately 52 hours after the baseline ECG (where time of dose was not available). Preliminary results of this ERG pooled analysis using Bazett's and Fridericia's corrections are shown in Fig. 2 and summarized in the paragraph below.

Of the antimalarial drugs studied, halofantrine was associated with the most substantial QTc interval prolongation in patients with uncomplicated malaria. DHA-PPQ and ASAQ had comparable QTc interval prolongation in patients with uncomplicated malaria followed by AL; this was also the case in the Cardiabase pooled analysis. AL was associated with a lesser degree of QTc interval prolongation than DHA-PPQ in healthy subjects. DHA-PPQ was associated with similar QTc interval prolongation both in healthy subjects and in uncomplicated malaria patients with both Bazett's and Fridericia's corrections. AL was associated with similar QTcB interval prolongation in healthy volunteers and uncomplicated malaria patients, but there appeared to be greater QTcF interval prolongation associated with AL in malaria patients than in healthy volunteers. Mefloquine (as monotherapy or in combination with either artesunate or artemether) was associated with a QTc interval prolongation similar to that of AL. Pyronaridine-artesunate was associated with the smallest QTc interval prolongation in both statistical analyses. In the Cardiabase analysis, OZ439 was associated with a QTc interval prolongation comparable to that of pyronaridine-artesunate.



HV = healthy volunteers, mal = patients with uncomplicated malaria.
AL = artemether-lumefantrine, DHA-PPQ = dihydroartemisinin-piperaquine, other = trimethoprim-sulfamethoxazole, ASAQ = artesunate-amodiaquine, HL = halofantrine, MQ = mefloquine / artesunate-mefloquine / artemether-mefloquine, PY-AS = pyronaridine-artesunate.

Fig. 2. Predicted change in QTc in milliseconds with 95% confidence intervals

Disease and non-drug factors affecting QTc interval prolongation

In addition to heart rate, temperature was a significant covariate, accounting for a 16% increase in the slope of the mean concentration–QTcF effect of piperaquine among malaria patients in the PK/PD modelling analysis. As would be expected with recovery from malaria, the median heart rate and temperature of patients with malaria decreased between baseline and time of follow-up ECG in pooled studies. There was no significant change in heart rate between baseline and time of follow-up ECG for healthy subjects.

QTcB interval >500ms following antimalarial therapy

The ERG chose Bazett's correction for this analysis, as the vast majority of subjects in the analysis set had clinical malaria. Of the 4025 individuals who received DHA-PPQ, 24 or 0.6% had a QTcB interval >500ms. Of the 1202 individuals who received AL, four or 0.3% had a QTcB interval >500ms; this figure is similar to the 0.2% with a QTcF interval >500ms drawn from the Novartis database (see section 3.3.2). The median and mean time of QTcB interval >500ms was 2 days from baseline, i.e., on day 3 of antimalarial therapy, when the C_{max} values of piperaquine and lumefantrine are expected to occur.

3.4.2 Special risk groups

Preventive therapy in pregnant women, infants and schoolchildren

PK and ECG substudies were conducted as part of the DHA-PPQ preventive therapy studies of the Uganda Infectious Diseases Research Collaboration (IDRC). Four populations were evaluated in the PROMOTE birth cohort IPTp and IPTi studies, and one population in the START-IPT SMC study:

- BC1 mothers *(35)*: HIV-uninfected women enrolled at 12–20 weeks gestation, randomized to 8-weekly SP, 8-weekly DHA-PPQ, or 4-weekly DHA-PPQ from 20 weeks gestation to delivery;
- BC2 mothers: HIV-infected women on efavirenz-based antiretroviral therapy enrolled at 12–28 weeks gestation, randomized to daily trimethoprim-sulfamethoxazole or daily trimethoprim-sulfamethoxazole + 4-weekly DHA-PPQ until delivery (discussed also in section 3.2.3);
- BC1 women: a subset of BC1 mothers enrolled at 34–54 weeks postpartum as controls for BC1 mothers who received a single 3-day course of DHA-PPQ;
- BC1 children: birth cohort of children born to BC1 mothers, randomized to 12-weekly or 4-weekly DHA-PPQ between 8 and 104 weeks of age;

and

- START-IPT: cluster randomized trial evaluating the impact of monthly SMC of asymptomatic schoolchildren with DHA-PPQ for up to six rounds on community-level malaria indicators (discussed also in section 3.2.3).

ECGs were recorded during each course of DHA-PPQ prior to the first dose and 3–4 hours after the third dose. In the PROMOTE birth cohort populations, venous and capillary blood samples

were collected at different time points post-dose; the venous and capillary blood samples collected simultaneously at 24 hours were used to establish correlations between capillary and venous plasma piperaquine concentration results. In the START-IPT population, only capillary samples were collected. A previous study demonstrated that capillary blood piperaquine concentrations are approximately 3-fold higher than venous plasma concentrations *(61)*.

PROMOTE birth cohort groups receiving DHA-PPQ had a mean 15–20ms increase in QTcF or 12–21ms increase in QTcB from baseline, while groups receiving SP or trimethoprim-sulfamethoxazole only had no significant change in QTc. The QTc increases were similar with both Bazett's and Fridericia's corrections in all study populations receiving DHA-PPQ. The number of prior courses of DHA-PPQ was not related to the degree of QTc interval prolongation. There were no cases of QTcB or QTcF intervals >500ms in the 98 patients who received DHA-PPQ in the ECG substudies. No significant correlation was found between change in QTc and piperaquine exposure or concentrations. This may be related to pregnancy, HIV-positivity with efavirenz treatment, or infancy – each being associated with significantly lower piperaquine exposure and C_{max}.

In START-IPT, treatment was associated with a mean increase in QTcF of 16.6ms (95% confidence interval: 15.1–18.1). Of the 155 participants, 18 in the ECG substudy experienced 22 episodes of QTcF interval prolongation, none of which were clinically significant and all of which were resolved. The risk of QTcF interval prolongation did not appear to increase with repeated rounds of DHA-PPQ. There were three cases of QTcF interval >480ms, of which one was >500ms; all three patients were excluded from further rounds of DHA-PPQ and remained clinically well. Peak piperaquine concentrations were associated with change in QTcF from baseline. Final multivariate analyses are in progress.

In the STOPMIP IPTp study using DHA-PPQ in Papua, Indonesia (also discussed in section 3.2.3), a nested PK and ECG substudy of 33 women was performed. ECGs were performed at baseline and 4–6 hours after the third dose of DHA-PPQ for each course. DHA-PPQ was associated with a mean increase in QTcF of 20ms and in QTcB of 15ms. This prolongation was not affected by the number of previous courses of DHA-PPQ taken. Mean QTc and increase in QTc from baseline decreased with each successive course of DHA-PPQ, regardless of whether Bazett's or Fridericia's correction was used. Two women had a post-baseline QTcF interval >480ms (and a QTcB interval >500ms) and did not receive further courses of DHA-PPQ. Piperaquine drug concentrations are expected to be available in early 2017.

There were no clinically significant cardiovascular adverse events or arrhythmias observed in these substudies or their main trials.

Case management in children in the 5–24.9kg weight band

In the ADJusT dose optimization study to evaluate the cardiac safety of DHA-PPQ in the treatment of uncomplicated falciparum malaria in children weighing 5–24.9kg in Malawi, 96 children received a full 3-day course of DHA-PPQ at daily doses of 1.7–3.8mg/kg body weight of DHA and 13.6–30.0mg/kg body weight of PPQ[iv]. QTc was measured 4–6 hours after the third dose of DHA-PPQ and compared to baseline and day 28 readings. There were no arrhythmias, or QTcF or QTcB intervals >500ms. A linear exposure-response model was fitted to describe the relationship between the change in QTcB from baseline adjusted for the baseline value and the whole blood concentration of piperaquine. An increase of 440ng/mL in the whole blood concentration of piperaquine was associated with an increase of 30ms from baseline in QTcB (95% confidence interval: 402–486ng/mL).

[iv] The current WHO-recommended daily therapeutic dose range of DHA-PPQ for children weighing <25kg is 2.5–10mg/kg body weight dihydroartemisinin and 20–32 mg/kg body weight piperaquine.

Key conclusions

- Halofantrine was associated with the greatest QTc interval prolongation of the antimalarial drugs studied.
- Chloroquine has been associated with a larger QTc interval prolongation than DHA-PPQ in healthy volunteers.
- DHA-PPQ and ASAQ have been associated with comparable degrees of QTc interval prolongation in malaria patients, although more data on amodiaquine are needed.
- QTc interval prolongation associated with DHA-PPQ has been found to be similar in both malaria patients and healthy subjects.
- AL has been associated with smaller QTc interval prolongation than DHA-PPQ in malaria patients and in healthy subjects.
- Pyronaridine-artesunate was associated with the smallest QTc interval prolongation of the antimalarials studied.

3.5 Priority research gaps and planned studies on the effects of antimalarials on the ECG

It was agreed that the preliminary analyses initiated on the data gathered for the ERG should be continued and completed. The following evidence gaps and priorities for further research were identified at the meeting:

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
  - Age-based dosing in children
  - Weekly drug administration in MDA
- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity, through:
  - Further investigation of individual outliers in antimalarial drug safety studies
  - Further investigation of special risk groups such as malnourished children
  - Pooling data from potential trial participants with a QTc interval >450ms at screening
- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
  - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
  - Further nested PK/PD studies, especially in populations exposed to MDA
  - Preclinical *in vitro* and *in vivo* assays conducted by independent laboratories

In particular, more evidence is needed with respect to chloroquine, amodiaquine and primaquine.

- Centralization and standardization of the format of reporting adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:

    - Spontaneous reports to international and national pharmacovigilance centres
    - Serious adverse event and loss to follow-up reporting from clinical trials
    - Active pharmacovigilance strategies in populations exposed to MDA
- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.

The plans of the WWARN piperaquine safety study group to further build on the reviews presented at this meeting, including the pooled PK/PD modelling analysis of piperaquine-containing medicines, were introduced.

4 Conclusions and recommendations

The ERG panel addressed the following key questions and made the following recommendations for consideration:

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines?

Halofantrine has been associated with >30 sudden deaths attributed to cardiotoxicity. This is the only antimalarial considered to have an unacceptable risk.

Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. There have been no sudden deaths attributed to cardiotoxicity following artemether-lumefantrine. One possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported among ~200 000 individuals with close follow-up treated in clinical studies of malaria treatment, prevention, control and elimination. This is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc interval-prolonging medicines in current use (see section 3.1.1).

Despite hundreds of millions of doses administered in the treatment of malaria, there have been no reports of sudden unexplained death associated with quinine, chloroquine or amodiaquine, although each drug causes QT/QTc interval prolongation. Unfortunately, there are relatively few prospective studies of the electrocardiographic effects of these drugs.

Intravenous chloroquine, quinine and quinidine may cause lethal hypotension if administered too rapidly. Large doses (>3.5mg base/kg) of intramuscular or subcutaneous chloroquine may also cause hypotension.

2. What is the frequency of life-threatening ventricular tachyarrhythmias and TdP following treatment with antimalarials that prolong the QT interval?

No episodes of TdP or life-threatening ventricular tachyarrhythmias have been documented following dihydroartemisinin-piperaquine or artemether-lumefantrine.

Although drug-induced QT/QTc interval prolongation is an imperfect surrogate indicator for drug-induced cardiotoxicity risk, it is the best currently available. A QT/QTc interval >500ms has been associated with increased risk of TdP and sudden cardiac death. Among drugs that prolong the QT/QTc interval, antiarrhythmics have been associated with TdP in 1–5% of exposed individuals, while non-cardiovascular drugs have a much lower risk of TdP. Approximately one in 10 cases of TdP will degenerate into life-threatening tachyarrhythmias.

Dihydroartemisinin-piperaquine has been associated with a QTc interval >500ms in 0.6% of individuals exposed, while artemether-lumefantrine has been associated with a QTc interval >500ms in 0.2–0.3% of individuals exposed. No data are available for such QTc analyses to predict the risk of drug-induced TdP and life-threatening tachyarrhythmias in the general population, to estimate the differential risks in specific population subgroups, or to quantify these risks for individual antimalarial medicines.

Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity. Out of ~200 000 people treated with close follow-up, the one reported case of sudden death considered to be possibly causally related to treatment with dihydroartemisinin-piperaquine suggests that, while cardiotoxicity may occur as a very rare *(62)* event, safety monitoring should continue in clinical studies of malaria treatment, prevention, control and elimination. This cardiotoxicity risk is likely to be similar to that following treatment

with chloroquine or artesunate-amodiaquine, and higher than that following treatment with artemether-lumefantrine or pyronaridine-artesunate. These findings are consistent with the risk of TdP and life-threatening ventricular tachyarrhythmias associated with other QT/QTc interval-prolonging medicines in current use.

3. What factors increase the frequency of life-threatening ventricular tachyarrhythmias following exposure to antimalarial medicines that induce QT interval prolongation?

The general risk factors for TdP should also be considered risk factors for antimalarial medicines that prolong the QT/QTc interval. Concomitant medications that can induce QT/QTc interval prolongation or potentiate the effects of QT/QTc interval-prolonging drugs, structural heart disease, genetic defects of cardiac ion channels, electrolyte abnormalities such as hypokalaemia, bradycardia and hepatic impairment increase the risk of life-threatening ventricular tachyarrhythmias following exposure to QT/QTc interval-prolonging drugs, including antimalarial medicines.

4. What strategies for malaria treatment or chemoprevention can reduce the risk of life-threatening ventricular tachyarrhythmias following exposure to antimalarial medicines that induce QT interval prolongation?

In individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmia, or who are already taking medicines that can prolong the QT/QTc interval, antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution. If possible, closer monitoring is advised when giving quinine, chloroquine, artesunate-amodiaquine or dihydroartemisinin-piperaquine to such individuals.

5. Is the risk of cardiotoxicity of piperaquine-containing medicines higher than that of chloroquine?

No. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, provides no evidence of a significant difference in the risk of cardiotoxicity following exposure to the currently recommended doses of piperaquine, chloroquine or amodiaquine.

6. Is the risk of cardiotoxicity of piperaquine-containing medicines higher in healthy volunteers than in malaria patients?

No. Review of pharmacovigilance and clinical data, along with preliminary results from PK/PD modelling, provides no evidence of a difference in the risk of cardiotoxicity of piperaquine-containing medicines in healthy volunteers compared to malaria patients.

7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity?

The following evidence gaps and priorities for further research were identified at the ERG meeting:

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
    - Age-based dosing in children
    - Weekly drug administration in MDA

- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity through:
    - Further investigation of individual outliers in antimalarial drug safety studies
    - Further investigation of special risk groups such as malnourished children
    - Pooling data from potential trial participants with a QTc interval >450ms at screening
- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
    - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
    - Further nested PK/PD studies, especially in populations exposed to MDA
    - Preclinical *in vitro* and *in vivo* assays conducted by independent laboratories

In particular, more evidence is needed with respect to chloroquine, amodiaquine and primaquine

- Centralization and standardization of the format of reporting of adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:
    - Spontaneous reports to international and national pharmacovigilance centres
    - Serious adverse event and loss to follow-up reporting from clinical trials
    - Active pharmacovigilance strategies in populations exposed to MDA
- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.

Annex A: Summary of evidence

Evidence	Summary
WHO VigiBase® global individual case safety report database analyses	1. Sudden unexplained death or TdP/QT interval prolongation following **any antimalarial** 2. Adverse drug reactions associated with **halofantrine** 3. Adverse drug reactions associated with **DHA-piperaquine**
LSTM antimalarial drug safety database report	Sudden death, TdP/QT interval prolongation or cardiac arrhythmia adverse events following **antimalarial drug** therapy in ACT Consortium and Malaria in Pregnancy Consortium studies
Literature reviews	1. Cardiotoxicity of **antimalarial drugs** x2 2. Effectiveness and safety of **DHA-piperaquine** treatment in uncomplicated malaria
Pooled analyses and meta-analyses	1. Analysis of sudden deaths following mass drug administration of **antimalarial drugs** 2. Systematic review and meta-analysis of safety, tolerability and efficacy of repeated doses of **DHA-piperaquine** with focus on IPT 3. Analysis of deaths following **antimalarial drug** treatment in uncomplicated malaria 4. Pooled analysis of QT effect of **antimalarial drugs** in contributed clinical studies 5. Pooled analysis of QT effect of **antimalarial drugs** in Cardiabase-supported studies
Pooled PK/PD modelling	Analyses of drug exposure–QT relationship and effects of covariates in selected contributed clinical studies on **chloroquine** and **DHA-piperaquine**
IPT collaboration clinical trial data and study reports	1. STOPMIP IPT with **DHA-piperaquine** in pregnant women in Indonesia 2. PROMOTE IPT with **DHA-piperaquine** in infants as well as pregnant and postpartum women with and without HIV in Uganda 3. START-IPT SMC with **DHA-piperaquine** in schoolchildren in Uganda
Research network clinical trial data	1. MORU, SMRU and OUCRU studies on **quinine, chloroquine, halofantrine, mefloquine, artesunate-mefloquine, artemether-lumefantrine and DHA-piperaquine** 2. INESS phase 4 prospective observational study to evaluate safety of **DHA-piperaquine** in public health facilities in East, West and Southern Africa 3. WANECAM phase 3b/4 randomized trial on **pyronaridine-artesunate** versus **DHA-piperaquine** versus **artesunate-amodiaquine** versus **artemether-lumefantrine** for treatment of repeated episodes of uncomplicated malaria in West Africa

Evidence	Summary
PDP and regulator clinical trial data and study reports	1. MMV phase 1 and phase 2b studies on **OZ439-piperaquine** 2. DNDi phase 2b studies on **artesunate-mefloquine** and **artesunate-amodiaquine** 3. FDA phase 1 study on **halofantrine**
Pharmaceutical company proprietary data and reports	• Proprietary safety database case reports of sudden deaths following **halofantrine** [GSK] • Safety overview report of **artemether-lumefantrine** based on information from preclinical studies, clinical trials and proprietary safety database case reports [Novartis] • Clinical study reports and data from phase 1 food and phase 4 clinical trials on **artesunate-amodiaquine** [Sanofi] • Results from preclinical studies on **ferroquine** as well as phase 1 clinical trials on **ferroquine-artesunate** and **ferroquine-OZ439** [Sanofi] • Electrocardiology safety assessment report of **pyronaridine-artesunate** based on results from preclinical to phase 3b studies [Shin Poong] • Meta-analysis on clinical use of **piperaquine** [Sigma Tau] • Safety overview of **DHA-piperaquine** based on information from sponsored clinical trials and proprietary safety database case reports [Sigma Tau] • Preclinical study results on TdP risk of **piperaquine** and **DHA-piperaquine** [Sigma Tau] • Clinical study reports and data from phase 1 food, phase 2 and phase 3 clinical trials of **DHA-piperaquine** [Sigma Tau]
Piperaquine safety study group analysis plan	Proposal to assess the relationship between piperaquine exposure and cardiac safety, adjusting for the effects of confounders using pooled PK/PD data from healthy volunteers, those given preventive treatment, and uncomplicated malaria patients

Annex B: List of pre-reads

Introduction and background

i. Drug-induced QT interval prolongation

I. Expert summary on preclinical and clinical basis for drug-induced QT prolongation [M Drici]

ii. Review of antimalarial cardiotoxicity

II. Published review on the cardiotoxicity of antimalarial drugs [White, 2007] *(13)*
III. WWARN systematic review manuscript on the cardiotoxicity of antimalarial drugs [N White]

Session 1: Sudden death in antimalarial therapy

i. General

1. WHO VigiBase® reports of sudden death, TdP and QT prolongation with antimalarials [N Iessa]
2. ERG analysis of sudden deaths after antimalarial mass drug administration [X Chan]
3. WWARN review of deaths after antimalarial treatment in uncomplicated malaria [P Guerin]
4. LSTM Centralised Antimalarial Drug Safety Database report [C Pace, D Lalloo & F ter Kuile]

ii. Halofantrine

5. WHO VigiBase® reports of suspected adverse drug reactions with halofantrine [N Iessa]
6. Published review on cardiac deaths from literature and GSK safety database [Bouchaud *et al.*, 2009] *(19)*

iii. Dihydroartemisinin-piperaquine/DHA-PPQ

7. WHO VigiBase® reports of suspected adverse drug reactions with DHA-PPQ [N Iessa]
8. Published review and meta-analysis on the efficacy and safety of repeated DHA-PPQ [Gutman *et al.,* 2016] *(20)*

Session 2: Studies on antimalarial effects on the ECG

i. General

9. Published preclinical studies on TdP risk of antimalarial drugs [Borsini *et al.*, 2012] *(54)*

ii. Dihydroartemisinin-piperaquine/DHA-PPQ

10. Sigma Tau meta-analysis on the clinical use of piperaquine [G Valentini]
11. Cochrane review on DHA-PPQ for the treatment of uncomplicated malaria [Zani *et al.*, 2014] *(39)*
12. STOPMIP IPTp study cardiac monitoring report [F ter Kuile & R Ahmed]

iii. Artemether-lumefantrine

13. Novartis Coartem® safety overview [C Winnips]

iv. Pyronaridine-artesunate

14. Shin Poong Pyramax® electrocardiology assessment report [R Miller & J Shin]

v. Artefenomel-piperaquine/OZ439-PPQ

15. Published article on the evaluation of the QT effect of OZ439-PPQ in healthy subjects [Darpo *et al*., 2015] *(55)*

Session 3: PK/PD analyses of antimalarial effects on the ECG

i. Dihydroartemisinin-piperaquine/DHA-PPQ

16. IDRC Uganda IPT study summaries [P Jagannathan, S Staedke & G Dorsey]
17. Published article on the efficacy and safety of DHA-PPQ for IPTp [Kakuru *et al.,* 2016] *(35)*
18. PROMOTE IPTp study manuscript on the results of intensive PK-PD sampling [P Jagannathan] *(63)*

Annex C: List of participants

Panel Members

Professor Karen I BARNES
Division of Clinical Pharmacology
Department of Medicine
University of Cape Town
South Africa

Professor Josep BRUGADA (Co-chairperson)
Cardiovascular Institute
Hospital Clinic Paediatric Arrhythmia Unit
Hospital Joan de Déu University of Barcelona
Spain

Dr Xin Hui Supanee CHAN (Rapporteur)
Mahidol-Oxford Tropical Medicine Research Unit
Bangkok
Thailand

Professor Albertino DAMASCENO
Eduardo Mondlane University
Maputo
Mozambique

Professor Milou-Daniel DRICI
Hôpital Pasteur de Nice
Centre Hospitalier Universitaire de Nice
France

Professor Nilima KSHIRSAGAR
Indian Council of Medical Research
Delhi
India

Professor Peter KREMSNER
Institute of Tropical Medicine
Department of Human Parasitology
University of Tübingen
Germany

Professor Eugène van PUIJENBROEK
Pharmacovigilance Centre Lareb
The Netherlands

Professor Nicholas WHITE (Co-chairperson)
Mahidol Oxford Tropical Medicine Research Unit
Bangkok
Thailand

Participants

Dr Rita BAIDEN
Clinical Trialist
INDEPTH Network Secretariat
Accra
Ghana

Dr Eva Maria HODEL
Malawi-Liverpool-Wellcome Trust Clinical Research Programme
Liverpool School of Tropical Medicine
Liverpool
United Kingdom

Dr Prasanna JAGANNATHAN
School of Medicine – Infectious Diseases
University of California
San Francisco
USA

Mrs Yasmin KHAN
Banook Group/Cardiabase
Nancy
France

Professor Feiko ter KUILE
Kenya Medical Research Institute
Nairobi
Kenya

Mr Clement NARH
Assistant Research Fellow
University of Health and Allied Sciences
Ho
Ghana

Dr Issaka SAGARA
WANECAM Network Coordinator
Bamako
Mali

Professor Joel TARNING
Head of Clinical Pharmacology
Mahidol-Oxford Tropical Medicine Research Unit
Bangkok
Thailand

Dr Anja TERLOUW
Malaria Group Lead
Malawi-Liverpool-Wellcome Trust Clinical Research Programme
Liverpool School of Tropical Medicine
Blantyre
Malawi

Dr Pascal VOIRIOT
Banook Group/Cardiabase
Nancy
France

Dr David WESCHE
Global Health Program
Integrated Development
Bill & Melinda Gates Foundation,
Vice-President Clinical Pharmacology
Great Lakes Drug Development/Certara
Ann Arbor
USA

Observers

Dr Victoria BODEA
EU-QP Pharmacovigilance
Sun Pharmaceutical Industries Ltd.
Cluj-Napoca
Romania

Dr Marie-José CABANIS
Sanofi
Montpellier
France

Dr Marco CORSI
Tropical Medicine Consultant
Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Rome
Italy

Dr Stephan DUPARC
Medicines for Malaria Venture
Geneva
Switzerland

Dr Philippe GUERIN
WorldWide Antimalarial Resistance Network
University of Oxford
United Kingdom

Dr Rita MERINO
Sanofi
Bridgewater, New Jersey
USA

Dr Robert M MILLER
Artemida Pharma Ltd.
Hertfordshire
United Kingdom

Mr Jangsik SHIN
Shin Poong Pharmaceutical Co. Ltd
Seoul
Korea

Dr Giovanni VALENTINI
Head of Clinical Development
Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Rome
Italy

Dr Cornelis WINNIPS
Novartis Pharma AG
Basel
Switzerland

WHO Secretariat

Dr Pedro ALONSO
Director, Global Malaria Programme

Dr Andrea BOSMAN
Coordinator, Prevention, Diagnostics and Treatment, Global Malaria Programme

Dr Peter OLUMESE
Medical Officer, Prevention, Diagnostics and Treatment, Global Malaria Programme

Dr Noha IESSA
Technical Officer, Medicines Safety
Essential Medicines and Health Products

Dr Shanthi PAL
Group Lead, Medicines Safety
Essential Medicines and Health Products

Dr Marian WARSAME
Medical Officer, Prevention, Diagnostics and Treatment, Global Malaria Programme

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