How the drugs in clinical trials compare to each other based on seven different parameters.

Malaria: The Global Pipeline

Drug Discovery for Tropical Diseases, 2013.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Phase</th>
<th>Name: Company</th>
<th>Composition</th>
<th>Treatment</th>
<th>Prophylaxis</th>
<th>Reapses</th>
<th>Transmission</th>
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<td>Registn.</td>
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<td>✔</td>
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<td>✔</td>
</tr>
<tr>
<td>8</td>
<td>IIb/III</td>
<td>GSK</td>
<td>Tafenoquine</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>9</td>
<td>IIa</td>
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<td>OZ439</td>
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<td>✔</td>
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<td>Immtech</td>
<td>AQ13</td>
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<td>I</td>
<td>Ipca</td>
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INTRODUCTION

The table and notes here below are primarily for purposes internal to Drug Discovery for Tropical Diseases. Although we strive to be accurate, mistakes are possible. In the Table, we analyze the Global Malaria Pipeline, as posted by the Medicines for Malaria Venture (www.mmv.org) for Q2 2013 across seven parameters that a malaria drug should ideally possess [1-3].

THE 7 CRITERIA

1. Have a rate of onset as fast as Artemisinin derivatives. So-far, however, only peroxides can do so. As a compromise, one may expect a rate of onset at least equivalent to the one of chloroquine. [1] The relevant parameter is the Parasite Reduction Rate, i.e. the fold reduction in parasitemia over 48 hrs (= one life cycle). The log PRR, is:[4]

- Artemisinin > 8
- Pyronaridine : 4.8
- Lumefantrine: 4.8
- Piperaquine 4.6
- Chloroquine : 4.5
- Mefloquine : 3.7

2. Not be prone to drug resistance. This means that the new drug should be active against known drug-resistant strains. It also means that mutations should not arise against the new drug (or only extremely slowly). Verifying this experimentally involves lengthy drug-pressure experiments that last months, often undertaken to decipher the mode of action. Success at obtaining drug-resistant strains casts a doubt on how durable the drug will be once exposed to wild type parasites. The usual argument is that the drugs will be used as combination, and resistance will hardly appear. This may be, to some extent, wishful thinking. For synthetic ozonides (OZ277, OZ439) and for Albitiazolium (T3/SAR97276), drug-resistant mutants could not be produced in the laboratory, which is promising, and therefore assigned a green mark (✔). However, the same goes true for artemisinin derivatives, against which resistance nevertheless is slowly emerging, and are therefore assigned a ± sign.

3. Have the potential to cure humans in a single dose. For drugs in Phase II or III, human data is available. For other drugs, single dose activity in the mouse, although imperfect, is arguably the best predictor.

4. To be slowly eliminated, with t 1/2 > 1 week, rather than daily usage. This is to enable chemoprevention with a weekly, rather than daily dosage.

5. To be active against the liver stage of the parasite. The liver is the first organ that parasites invade once inoculated into a human, and activity against the liver stage prevents the disease from taking a foot hold; Such drugs can therefore to be used as chemoprotection.
6. To be active against hypnozoites. Hypnozoites are a form of the parasite that can remain dormant in the liver years, and induces relapses. P. vivax, but not P. falciparum, can form such hypnozoites. Drugs active against hypnozoites are desirable to prevent relapses, and provide what is known as a radical cure.

7. To be active against gametocytes. Gametocytes are the form of the parasite that are ingurgitated by the mosquito, and fuse in the mosquito midgut to provide new parasites ready to infect the next human being. Drugs that prevent the formation of gametocytes, or that kill them, can block the disease from being transmitted to others. This is a useful property for an elimination/eradication of the disease.

NOTES FOR EACH COMPOUND

Entry 1: Dihydroartemisinin/piperaquine (Eurartesim)
Piperaquine has the potential to eliminate all liver forms over 14 days, but not when used as a partner drug with dihydroartemisinin for a 3-day treatment. The combination is approved in adults for uncomplicated malaria, not chemoprevention. Yet, some chemoprotection after treatment was shown in clinical trials.[5]

Entry 2: Artesunate/pyronaridine (Pyramax)
Fever resolution was significantly more rapid with the combination of pyronaridine + DHA (35.7 ± 24.7 h) than with DHA alone (52.6 ± 38.9 h, P < 0.01). Time to parasite clearance was significantly faster with the combination (23.8 ± 10.1 h) than with pyronaridine alone (49.4 ± 20.3 h, P < 0.01). Gametocyte carriage was 20.0% for the combination, 16.7% for DHA alone and 60.9% for pyronaridine alone, which was significantly higher than for the combination (P < 0.01).[6] No activity against liver stages. [6] Resistance has been documented, and is emerging slowly. [6] However, this combination is also the best one against artemisinin resistant strains. [7]

Entry 3: Artesunate/Mefloquine
A high failure rate of mefloquine/artesunate in some areas due to resistance,[8] and some activity again gametocytes.[9-11]

Entry 4: Arterolane (OZ277)/piperaquine
Gametocytocidal activity of arterolane (OZ277) + PQP is comparable to that of Coartem. [12]

Entry 5: Artemisinin/Naphthoquine (ARCO)
Naphthoquine easily generates resistance if given as a single-dose.[13] High rate of post-treatment gametocytes.[14] No data found on liver stages.

Entry 6: Azithromycin/chloroquine
Meant for IPT (intermittent preventative treatment). The two drugs are additive or synergistic. Azithromycin has a human T1/2 of 60 hrs, [15] and clears parasites very slowly [Fig. 7 of ref [4]]. It does not clear gametocytes and has no hypnozoite activity.[15] Plasmodium strains resistant to azithromycin have been obtained for mechanistic studies.[16] Azithromycin is widely used as antibiotic, and resistance is known for other parasites. While we don’t have data on the effect of azithromycin on liver stages, the prophylactic efficacy of azithromycin against P. vivax has been known for over 15 years.[17]
Although chloroquine has a $T_{1/2} = 1–2$ months, it is not given as a single dose, but twice on day 1, and then once a day over the next two days. However, for prophylaxis, it is given once weekly (see here). Chloroquine actually increases gametocytes count.[18]

**Entry 7: co-trimoxazole (Bactrim)**
Co-trimoxazole is a 1:5 ratio trimethoprim (a DHFR inhibitor and sulfonamide potentiator) and sulfamethoxazole.[19] It is as fast-acting as chloroquine.[19] The half-half-lives are 9 h for trimethoprim and around 8.5 h for sulfamethoxazole.[20] Administered once a day for 3 consecutive days, each week for 12 weeks.[21]

**Entry 8: Tafenoquine**
Meant for prophylaxis and radical cure. The transmission blocking potential of tafenoquine can act as a radical cure,[22] and as a chemoprophylactic,[23] and to block transmission.[24] Tafenoquine has a much longer elimination half-life compared with primaquine (14 days versus 6 h).[25] Remember, however, that the activity is due to one ore more metabolites.

**Entry 9: OZ439**

**Entry 10: KAE609 (NITD-609)**
KAE609 is fast acting, but not as fast as artemether: In mouse, KAE609 achieves 90% parasitemia reduction after 24 hours, vs. 6 hours for artemether [see also fig. S1 in ref [29]]. Orally administered KAE609 displayed a long half-life in mouse and rat ($T_{1/2} = 10$ and 27.7 hours) and excellent bioavailability ($F =100\%$) in rodents [29]. It also potently inhibits transmission.[30] However, no prophylactic activity in mouse, contrary to GNF179.[31] In mouse, single dose activity is seen only at very high doses 100 mg/kg, casting doubt about the real possibility of single dose in human. human Phase II study, it is given over 3 days, although a single-dose study is planned.

**Entry 11: KAF156 (GNF-156)**
GNF156 is active against transmission and liver stages, but not hypnozoites.[32] In Phase 2, it is given as a 3-day dosing. Its cousin GNF179 exhibits a low clearance ($CL = 22$ml/min per kg, ~25% of hepatic blood flow in mice), a large volume of distribution (steady-state volume of distribution, $V_{ss} = 11.8$ l/kg), a mean residence time (MRT = 9 hours), and suitable terminal half-life ($t_{1/2} = 8.9$ hours).

**Entry 12: Fosmidomycin/piperaquine**
Fosmidomycin is fast acting in adults but not children.[32] It is given every eight hours.[33] Additional references: [34-36]

**Entry 13: Artemisone**
Artemisone it 4–10 times more potent than artemisinin.[37, 38] [39] Concentrates in infected erythrocytes [40], is active against murine cerebral malaria.[41] A combination of artemisone (10 mg/kg) and mefloquine (5 mg/kg)
cures monkeys in a single-dose. \cite{42} Toxicity on embryos \cite{43} suggests that it is safer than artemisinin for pregnant women \cite{44}. Human T1/2 = 2.8 hrs \cite{45}.

**Entry 14: Methylene blue**

Already approved for other indications. Potent against all stages of gametocyte development \cite{46}. In a Phase II trial, substantially decreases gametocytes. \cite{47} Induces haemolysis when G6PD deficiency, but effect is limited \cite{48}. Human oral T1/2 = 12-27 hours, with 139± 52 oral bioavailability. \cite{49}

**Entry 15: Albitiazolium**

A bis-cation \cite{50} with high potency, curative as a single dose in mouse at 7 mg/kg \cite{51}. Its high polarity makes it highly water soluble, but not orally available. Resistance not observed.

**Entry 16: Ferroquine**

Activity is independent of level of chloroquine resistance \cite{52} due to an additional mode of action \cite{53} \cite{54}

**Entry 17: DSM265**

A DHODH inhibitor T1/2 = 12–28 hours in mouse, and 100% bioavailability in rat \cite{55}.

**Entry 18: AQ13**

No data

**Entry 19: CDRI 97-78**

Some PK data \cite{56}

**Entry 20: N-tert-butyl isoquine**

N-tert-butyl isoquine (GSK369796) was designed to avoid the formation of quinone imines, and entered Phase I studies. It is potent \textit{in vitro}, including in the chloroquine-resistant strain K1 (EC$_{50}$ = 13 nM) and is active \textit{in vivo} with an ED$_{50}$ = 3.8 mg/kg/day, thus being comparable to amodiaquine. \cite{57-59} In spite of the excellent exposures and near quantitative oral bioavailabilities in animal models, its development was discontinued due to exposures insufficient to demonstrate drug safety superior to chloroquine. \cite{60} For additional chemistry data, see \cite{57-59}

**Entry 21: Actelion antimalarial**

No data

**Entry 22: DF02**

Heparin analog; no data.