A TPP for a new medicine for chemoprotection

The following is an excerpt from "Designing the next generation of medicines for malaria control and eradication". For references, please refer to the full paper.

In any disease eradication agenda, preventing the population from becoming infected is a key activity. In malaria this has been primarily achieved to date with bed nets. Vaccination is another strategy, but apicomplexan parasites have developed sophisticated immuno-evasive strategies. Chemoprotective medicines offer an additional approach to disease control (Table 6). These medicines could be used to protect vulnerable populations, and also in the situation where there was an outbreak of malaria in an area previously shown to be malaria-free. This medicine would contain a combination of two anti-malarial APIs based on TCP-4 since its widespread use would raise significant concerns about resistance emerging if used alone. Since prophylaxis can come from causal or suppressive activity it is ideal if the combinations partners target the same parasite stage. It is preferable for the medicine to be given infrequently. Current chemoprotection regimens in children are given monthly throughout the season. The technical challenge of developing a medicine which can protect for several weeks is enormous, and will require extensive safety studies. Within the chemoprotection concept are also the medicines for intermittent presumptive treatment for pregnancy (IPTp) and its equivalent in infants (termed IPTi) and children, (termed either IPTc) or seasonal malaria chemoprotection. Over the next decade, these therapies are most likely to involve new combinations of existing registered medicines, but in the longer term new classes of medicines will be needed. Cost is an important driver here: as the incidence of malaria falls to a level where elimination is feasible or achieved then the cost-benefit ratio of chemoprotection increases.

Table 6 TPP-2 for a new medicine for chemoprotection

Parameter to be demonstrated for the combination in clinical evaluation	Minimum essential	Ideal SEC
Dosing regimen	Oral, once per week	Oral, once per month
Rate of onset of action	For asexual blood stage action – slow onset (48 h) - before rapid killing	
Clinical efficacy	Prevents primary infection of *Plasmodium* >95%	Prevents *Plasmodium* infection including relapse >95%
Transmission blocking	No	Yes
Bioavailability/ Food Effect	>30% for each molecule, <3-fold	>50% for each molecule, none
Drug-drug interactions	No unmanageable risk in terms of solid state or pharmacokinetic interactions	No risks in terms of solid state or pharmacokinetic interactions
Safety	Few drug related SAEs in phase III	No drug related SAEs; minimal drug-related AEs
Use in patients with G6PD deficiency	Testing not obligatory due to low risk	No enhanced risk
Pregnancy	Not contra-indicated in second and third trimester	Not contra-indicated
Formulations	Co-formulated tablets or equivalent, with taste masking for pediatrics	Co-formulated tablets for adults. Dispersible or equivalent with taste masking for pediatrics
Cost of treatment course	≤ $1.00 for adults, $0.25 for infants under two years	
Shelf life of formulated product (ICH guidelines for Zones III/IV; combination only)	≥ 2 years	≥ 5 yr
Susceptibility to loss of efficacy due to acquired resistance	Very low; no cross resistance with partner	Very low; no cross resistance and orthogonal mechanism from those used in treatment