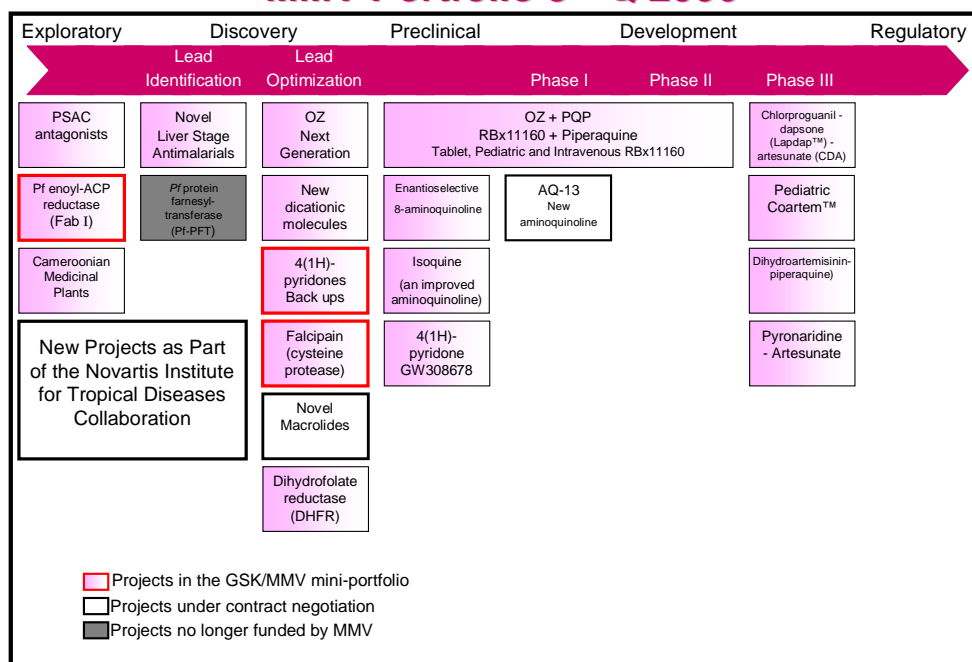




Medicines for Malaria Venture

MMV'S DRUG R&D STRATEGY

MMV Portfolio 3rd Q 2006



When MMV was established late in 1999, the greatest antimalarial unmet medical need was for additional Artemisinin Combination Therapies (ACTs) for the oral treatment of uncomplicated malaria caused by *Plasmodium falciparum*. The particular advantages of artemisinin derivatives over existing antimalarials were already recognised: rapidity of action in patients; activity against existing drug-resistant strains, including multidrug resistant strains; potent gametocidal and hence anti-transmission activity. However, at that time, Novartis' artemether/lumefantrine¹ was the only co-formulated ACT registered with Good Clinical Practice Clinical Studies and made under conditions of Good Manufacturing Practice (GMP).

No paediatric formulation of artemether/lumefantrine had been registered, even though in sub-Saharan Africa, most mortality and morbidity caused by malaria occurred in children. Novartis had however collaborated with WHO in carrying out the necessary clinical trial to register the present tablets if crushed with sweetened condensed milk for infants down to 5 kg body weight. Although effective in treating infants the tablets tasted bitter and infants frequently spit the medication out causing difficulties in correct dosing. MMV's strategy to deal with this unsatisfactory

¹ Coartem™

situation was to support the development of a dispersible paediatric formulation of artemether/lumefantrine which would be easy to use and taste good, insuring better compliance.

Because artemether/lumefantrine was the only GMP co-formulated ACT registered, national malaria control programmes adopting it for first line use faced limited options for second line (rescue) therapy. Furthermore, concerns were already circulating at the time of MMV's establishment that acquired drug resistance to artemether/lumefantrine would rapidly emerge once it was deployed extensively. This meant that there was an urgent need for more ACTs for the oral treatment of uncomplicated malaria caused by *P. falciparum*. The expectation was that resistance would initially be directed towards the long lived component of the combination, lumefantrine, since it continues to circulate in patients long after the artemether component and its metabolites have been eliminated. It was known that 4-aminoquinolines and related heterocycles (henceforth referred to as 4-AQs) such as lumefantrine, piperazine and pyronaridine did not show cross-resistance to each other. The best approach to this issue therefore was considered to be development of new ACTs in which the lumefantrine was replaced by other 4-AQs. This is the basis of MMV's support for the DHA²/piperazine³ and pyronaridine/artesunate⁴ projects. It is expected that such products will retain full activity against artemether/lumefantrine-resistant parasites.

It is known, however, that resistance to 4-AQs develops more rapidly if high resistance to any one of them is already present in the exposed parasite population. This means (a) that the second generation ACTs are likely to be compromised more quickly by acquired drug resistance than artemether/lumefantrine and (b) that such resistance will expose the artemisinin derivative itself to the development of resistance. MMV's strategy to deal with (a) is to develop non-4-AQ-containing ACTs, hence the inclusion of the CDA (chloroquine/dapsone/artesunate) project into the portfolio. Its strategy to deal with (b) is to develop ACTs with a novel endoperoxide component which might not be fully cross-resistant with the artemisinin derivatives, hence the inclusion of RBx11160⁵/piperazine into the portfolio. A bonus of this combination is that since RBx11160 can be synthesised entirely in a chemical reactor, it can readily be produced in whatever quantity is needed, eliminating at a stroke the artemisinin derivative supply bottle neck of ACT production. Furthermore, alternative or additional 4-AQ-containing ACTs could be developed if required by substituting the piperazine component of RBx11160/piperazine with one of two other 4-AQs in the portfolio, AQ-13 or isoquine.

Despite high pharma R&D project attrition rates and the propensity of malaria parasites to develop resistance to new chemotherapies, there is every reason to believe that MMV's strategy should ensure that at least one fully effective GMP co-formulated ACT will be available to national malaria control programmes at any given time over the next 10-15 years. In fact, chances are that more than one will be available, providing control programmes with both the opportunity to select the most appropriate for their particular region or country and the challenge of how best to

² Dihydroartemisinin.

³ Artekin™

⁴ Often referred to affectionately in MMV circles as Panda

⁵ Often referred to affectionately in MMV circles as OZ.

recommend their use into the existing matrix of mostly non-GMP, non-co-formulated ACTs to which they will have access. Availability of multiple GMP co-formulated ACTs will also challenge the malaria research community to determine if any of them could be reserved for Intermittent Preventive Treatment of malaria in infants (IPTi). Some, if not all, of these 4-AQ-containing ACTs will treat malaria caused not only by *P. falciparum*, but also that caused by *Plasmodium vivax*, a feature that will be of particular value in countries, mostly in Asia, where both parasites exist and multiple infections are common. MMV's pyronaridine/artesunate is being fast-tracked to include this indication, patients with *P. vivax* malaria receiving subsequent treatment with primaquine to prevent relapse. A parenteral formulation of RBx11160 is in the portfolio to deal with severe disease caused by *P. falciparum* where patients cannot take drugs by mouth.

Ultimately, however, all the ACTs will be compromised by acquired drug resistance. Furthermore, it is recognised that ACTs have two serious limitations: first, because of embryo-toxicity, they should not be used to treat pregnant women during the first trimester; second, since they do not kill the hypnozoite stage, they will not eliminate the need for primaquine, which is quite toxic and has a patient unfriendly dosing regimen, to prevent *P. vivax* malaria relapse.

Thus a new generation of GMP co-formulated Non-Artemisinin Combination Therapies (NACTs) will ultimately be needed. MMV's strategy here is to begin the necessary R&D now, since such work will be challenging in the extreme. The artemisinin derivatives have so many positive attributes, most particularly the rapidity of their action in patients and their gametocidal activity, that this process is likely to take 10-15 years and will have high rates of project attrition. To maximise the chances of success, more discovery research projects are being sought and the concept of the mini-portfolio, developed initially with GlaxoSmithKline to enable flexibility of resources between projects, is being expanded, with the recent inclusion of a mini-portfolio collaboration with Novartis. Work on New Chemical Entities (NCEs) such as AQ-13, isoquine, an enantiomeric 8-aminoquinoline, 4-pyridones, falcipain inhibitors, novel dications, macrolides and DHFR inhibitors, and many more in the future, is being supported with the expectation that if those that can be developed successfully are appropriately combined, new products will emerge that are not cross-resistant with the ACTs and can therefore be used by national malaria control programmes as replacements. Combination of two such molecules with relatively long half lives may mean that single dose regimens become feasible, a particularly valuable property during malaria epidemics. Absence of an endoperoxide component may mean that these new GMP co-formulated NACTs can be used in pregnant women both for treatment during all trimesters and for Intermittent Preventive Treatment (IPTp). Presence of an 8-aminoquinoline or imidazolidinedione may mean that *P. vivax* patients can have their blood schizonts and liver hypnozoites killed by administration of a course of just one co-formulated NACT.

Such a range of products should ensure that the gains in the control of malaria mortality and morbidity which will surely come during the next decade from the widespread use of ACTs will be continued during the subsequent era of the NACTs.