MEDICINES FOR MALARIA VENTURE (MMV)

Development of combination therapies for the treatment of uncomplicated *Plasmodium falciparum* malaria

5th October 2010, MMV, Geneva, Switzerland

Contents

List of abbreviations

ACPR	adequate clinical and parasitological response	MHRA	Medicines and Healthcare products Regulatory Agency
ACT	artemisinin-based combination therapy	NCE	new chemical entity
ARV	antiretroviral therapy	PCR	polymerase chain reaction
AZT	azidothymidine	PD	pharmacodynamic
CDA	chlorproguanil-dapsone-artesunate	PK	pharmacokinetic
d4T	stavudine	PP	per protocol
EBA	early bacterial activity	PRR	parasite reduction ratio
FDA	US Food and Drug Administration	TB	tuberculosis
FDC	fixed-dose combination	WHO	World Health Organisation
HAART	highly active antiretroviral therapy	WWARN	WorldWide Antimalarial Resistance Network
HCV	hepatitis C virus	o.d.	once daily
HIV	human immunodeficiency virus	b.i.d.	twice daily
ITT	intent to treat	3TC	lamivudine

Objectives

1. To discuss and clarify the strategy of moving from single agent to combination therapy in antimalarial drug development for 2020.

Summary of recommendations

- New approaches for dose finding need to be developed for antimalarial combination therapy.
- The best method for determining the contribution of separate agents to antimalarial combination therapy needs to be examined on a case-by-case basis. Early collaboration with regulatory agencies is recommended.
- For short-course (1-day) therapy, studies need to demonstrate sufficient pharmacokinetics (PK) to maintain efficacy, especially in patients with malabsorption issues.
- Antimalarials should be developed as paediatric formulations, also suitable for adult use.
- New antimalarials should be developed as fixed-dose combinations (FDCs). These are more useful and less prone to misuse than monotherapy used in 'appropriate' loose combinations.
- If possible, an artemisinin monotherapy active control arm should be included in Phase IIa studies assessing proof of concept of new monotherapy using parasite reduction ratio (PRR) as an endpoint.
- Adaptive study designs need to be looked at very carefully as they may take longer than a classical design for antimalarial combination drug development.
- For new chemical entities (NCEs), a precautionary approach would be to conduct a thorough QT study before commencing Phase III, even if there are no preclinical signals.

WHO role to set up recommendation for surveillance:
Adequate clinical and parasitological response (ACPR) at Day 28, corrected for new infection using polymerase chain reaction (PCR) genotyping still appropriate as the primary endpoint.

- Follow-up at Day 42 or 63 is of interest for drugs with half-lives longer than 7 days; PCR-corrected ACPR is also of interest for these endpoints in Phase III studies.
- Obtaining drug blood concentrations should be routine.
- Analysis must include per protocol (PP) and intent to treat (ITT) population analysis. Kaplan–Meier survival analysis, with populations defined as per Appendix 9 of the WHO 2009 protocol is the most relevant analysis for the clinicians and should also be included.

Dose finding and factorial study design:

- Factorial design should be considered for Phase IIb combination therapy dose finding as a pioneering methodology in antimalarial drug development.
- The statistical and practical input to conduct factorial Phase IIb dose-finding studies is considerable and MMV needs to examine how this could be best obtained.
- Regulatory discussion and positive feedback on a factorial design can be helpful and is recommended (though it is not a guarantee that the completed study will be acceptable).

Historical position of combination therapy for malaria and comparison with other infectious diseases

Landscape of combination therapy for malaria

David Ubben

Current models of antimalarial drug development evolved from regulatory requirements and precedent, in particular, the development of artemisinin-based combination therapy (ACT). ACT has been recommended by the World Health Organisation (WHO) since 2003:

- Highly efficacious (cure >95%) and cheap (<$1 per adult treatment).
- Deployed ACTs are combinations of 'old' drugs (mostly discovered/used in China).
- The utility of failing drugs (e.g. mefloquine) was restored by inclusion in ACT.
- Stringent regulatory approval was not sought in most cases.
- Until recently, new combinations were tested in Thailand border areas.
- Dose finding has been empirical; in general, formal dose finding was not conducted and therapies are not necessarily optimised.

Current requirements for new antimalarial therapies:

- Combination therapy.
- Maximum of 3-day dosing (o.d. or b.i.d.).
- Developed as FDCs.

Experience of drug combination therapy in TB

Ann Ginsberg

Resistance develops very readily in tuberculosis (TB). Combination therapy is the only option; monotherapy for more than 2 weeks is not ethical. Even with combination therapy, persistent bacterial populations necessitate long treatment regimens; compliance is a major issue. Poor compliance drives resistance. Drug resistance testing is uncommon. New quick resistance testing kits need to be developed concurrently with new drugs.

Indication	Current situation	Therapy objectives
Drug-susceptible TB	At least 6-month dosing with four drugs.	Shorter, simplified.
Drug-resistant TB	Few therapy options; injectable drugs, regimens with significant toxicities, at least 18 months' therapy.	Oral, more effective, safer, affordable, scalable.
HIV/TB co-infection	Complicated by drug–drug interactions.	Elimination/minimisation of drug–drug interactions.
Latent TB infection	6–9-month isoniazid monotherapy.	Short, safe.

Combination therapy development strategy

TB drug development is undergoing a paradigm shift from the serial substitution of each component of existing combination therapy (timescale 6 years per substitution, 24 years to replace all components) to the investigation of a completely novel combination therapy (timescale 6 years total). This is necessary because all components of current therapy have

limitations (efficacy, safety, PK) and is possible because there is a wealth of alternative components available for investigation.

Development plan

Animal model(s): Used to examine the activity of individual agents and identify promising combinations in mouse models of acute infection (bactericidal effect) and stable cure; can be used to demonstrate the requirement for at least three drugs in combination.

Single component evaluation: Full preclinical, Phase I and Phase IIa evaluations of individual components. Early bacterial activity (EBA) studies of 14-day monotherapy allow proof of concept and dose ranging. The chosen dose is likely to be lower than the maximum tolerated dose for safety reasons.

- For current agents, there is good agreement between mouse models and EBA studies. However, this is not confirmed for new drug classes and will have to be looked at retrospectively after Phase III is completed.

Combination therapy evaluation: Explore drug–drug interactions and, as appropriate, preclinical toxicology of the combination; progress to Phase I. Population PK data are routinely collected throughout clinical development.

- Phase IIa: Dose finding for the combination is a key decision point. Only combinations that are as active as current therapy are progressed to Phase IIb. There is no quantitative statistical analysis of endpoints; equivalence is evaluated qualitatively based on the clinically relevant difference between new agents current therapy. Doses are based on the monotherapy evaluation; there is no formal dose-finding in Phase II for combination therapy because of the long endpoints.
- Phase IIb: 2-month study using the sputum conversion rate; a predictive marker of eventual efficacy across a population (not in individual patients). Serial sputum colony counts are conducted to generate time to sputum negative. Can be powered with as few as 50 patients per arm.
- Phase III:
  - Current treatments have >95% efficacy against drug susceptible pathogens, requiring non-inferiority studies, but ≤75% efficacy against drug-resistant pathogens, allowing superiority trials.
  - There are no validated surrogate markers and clinical trials are lengthy; 6-month treatment period plus 1–2 years of follow-up. At least 800 patients per arm are needed for 90% power. Endpoint is treatment failure at end of therapy combined with relapse at follow up (up to 24 months).

Experience of drug combination development in HIV and HCV

John Pottage

In just over 20 years, HIV antiretroviral therapy (ARV) has progressed from azidothymidine (AZT) monotherapy to highly active antiretroviral therapy (HAART) combination therapy. This has transformed the infection from a fatal to a chronically managed disease. However, even with prolonged undetectable virus, patients still have reduced life spans. Treatment strategies must consider drug sequencing and combination throughout the patient's life to extend effective therapy for as long as possible.

Rationale for combination therapy

Although 'wild-type' virus is prominent, all patients will have viral sub-populations resistant to all ARVs. Viral replication is rapid, so these resistant populations emerge quickly under monotherapy. Combination therapy aims to increase the genetic barrier to resistance emergence by requiring a greater number of viral mutations to escape drug suppression.

- Combination therapy is also required as not all ARVs are effective against both HIV-1 and HIV-2; patients may have mixed infections.
- Reservoirs of (drug-resistant) virus (e.g. CNS) may re-infect other compartments.

Combination strategies may be complex:

- Multiple attacks on the virus (convergent therapy): Lamivudine (3TC) is used to induce the M184V mutation which has a high fitness cost for the virus making it more susceptible to other ARVs in combination.
- PK boosting: Ritonavir is too toxic to use at therapeutic doses, however, sub-therapeutic doses can boost protease inhibitor drug levels through cytochrome P450-3A4 (CYP3A4) inhibition.

NB: The first combination therapy investigated was AZT/stavudine (d4T). This was less effective than monotherapy because of antagonism. Despite this, studies were progressed in the belief that the *right* combination would be more effective than monotherapy.

Development issues

- The aim of the drug development programme is to determine the contribution of the investigational drug to combination therapy. HIV RNA is used as a surrogate endpoint to measure drug effect.
- In the past, clinical studies were conducted as a monotherapy added on to failing antiviral therapy. However, patients who fail therapy are becoming more difficult to find as drug treatments become more effective. If patients do fail it is likely because of non-compliance and so these are not the ideal patients to include in clinical trials.
- ARVs are generally developed as single agents for use in appropriate combination therapy. There are two main strategies for combination therapy:
  - Intensification, adding drugs to existing regimens.

  - Induction-maintenance; reducing the number of drugs once viral suppression is achieved.
- **The role of FDCs is limited.** FDCs are used for treatment-naïve patients, but for treatment-experienced patients drug combinations need to be more flexible.
  - Although FDCs may improve compliance and may be more convenient to the patient, there is no evidence for a beneficial effect on outcomes. The availability of generic components makes co-administered regimens more cost effective than FDCs.
  - FDCs are not seen as the endpoint of drug development in HIV. Development is limited by pill size, drug–drug interactions, the need for matching PK and toxicity. Only 100 patients are needed to show that an FDC of drugs used in loose combination has acceptable safety.

Development plan

Preclinical: *In vitro* activity and resistance profiles are generated. New drugs need to require multiple viral mutations for resistance development.

Phase IIa: Monotherapy for 7 days in treatment-naïve patients is used to evaluate potency. Minimum effectiveness is a change in HIV RNA from baseline of 0.5 log, though changes of at least 1.5 log are now usual for new ARVs.

Phase IIb:
- Treatment-naïve patients: New drugs are combined with a nucleoside backbone and evaluated against standard care in a 24–48-week trial. Virus should be fully suppressed in >90% of patients by 24 weeks.
- Treatment-experienced patients, with resistance to the same class of ARV: monotherapy for 7 days then optimise therapy with two or more other active drugs.

Phase III: Similar to Phase IIb, but with more patients. Non-superiority trials are conducted in treatment-naïve patients and superiority trials in treatment-experienced patients.

Future trends

- Future combination therapies in HIV may include:
  - Drugs that support immunity; this is impaired even when virus is undetectable.
  - Anti-TB drugs if CYP450 issues can be overcome for use in the HIV/TB epidemic.
- The population living with HIV/AIDS is aging, making drug toxicity a greater issue.
- Given the greater activity of new ARVs, it may be possible to move to induction-maintenance therapy whereby initial combination therapy is stepped down to protease inhibitor monotherapy after achieving stable viral suppression. This is being investigated, but has not yet been proven effective. The advantage would be decreased toxicity and increased simplicity, important goals for lifelong therapy.

Discussion and recommendations for malaria drug development

Regulatory guidelines: There are no regulatory guidelines available that are specific to the development of antimalarial combination therapy although there are several guidance documents available that are of considerable relevance, including general guidance on the development of FDCs. Regulatory guidelines specific to antimalarial agents would be useful for both regulators and development groups. However, as these drugs are quite 'rare' in the overall workload of agencies, developing specific guidelines may not be viewed as a priority.

- Safety and efficacy are major issues in evaluating new antimalarial therapies. Preliminary evidence regarding the potential for resistance development may be available before initial approval. Post-approval evaluations are likely to be expected.
- Increasingly, regulatory agencies interact with each other to try to provide developers with broadly consistent advice though the final advice from each agency is, and will likely remain, separate.

Dose finding: Dose selection up to the present has often been rather empirical. Estimating PK in malaria patients is problematic because of drug sequestration in erythrocytes and penetration into tissues; drug plasma values are misleading. The lack of a good basis for PK/PD evaluation for antimalarials makes formal dose-finding studies very difficult. These issues can make it difficult to provide regulatory authorities with a robust rationale for the dose regimen(s) evaluated in confirmatory studies.
Recommendation: New approaches for dose finding need to be developed for antimalarial combination therapy.

Monotherapy studies: Demonstrating the contribution of each agent to the combination requires monotherapy studies. There may be ethical issues in exposing *P. falciparum* malaria patients to monotherapy to evaluate new drugs. Different agencies may place different weight on such data. For example, in the review of artemether-lumefantrine, the FDA emphasised the importance of studies comparing monotherapy for each agent versus the combination. The MHRA took into account the differences in PK and antimalarial modes of action of the two components when considering the scientific justification for the FDC and considered that the efficacy and safety of the combination should be the primary focus of the assessment.
Recommendation: The best method for determining the contribution of separate agents to antimalarial combination therapy needs to be examined on a case-by-case basis. Early collaboration with regulatory agencies is recommended.

Dose duration: A maximum of 3-day dosing is required to achieve high levels of adherence. Short-course (1-day) dosing may be possible with some of the new combinations.
Recommendation: For short-course (1-day) therapy, studies need to demonstrate sufficient PK to maintain efficacy, especially in patients with malabsorption issues or who cannot take the formulation under conditions that optimise systemic bioavailability (e.g. with fatty foods) due to anorexia, nausea or vomiting associated with acute malaria.

Special populations: In malaria, paediatric formulations have sometimes been developed only after initial studies have been completed with tablet formulations. The heightened regulatory requirements to drive early development of paediatric formulations may present an additional barrier to rapid antimalarial development.

Recommendation: Antimalarials should be, from the start, developed in suitable paediatric formulations that would also be applicable for adult use.

Registration target: The HIV model is to register individual NCEs for use in combination therapy. This may be possible in malaria, though it is not clear how the prescribing information could be worded. Also, there is limited experimentation with different antimalarial combinations by investigators. There is concern that regardless of the prescribing info, if an NCE is not presented as part of a FDC or as a co-packaged combo then there is a high risk that combination therapy would actually not be accomplished and/or that a NCE would be used in regimens not shown to be acceptably safe and effective.

Recommendation: New antimalarials should be developed as FDCs. These are more useful and less prone to misuse than monotherapy used in 'appropriate' loose combinations.

Summary of key comparisons: TB, HIV and malaria

Comparison	TB	HIV	Malaria
Object of combination therapy	Prevent emergence of resistance in drug-susceptible strains. Overcome resistance in drug-resistant strains.	Improve efficacy to achieve viral suppression. Present high genetic barrier for selection of resistant virus. Reduce toxicities of individual drugs.	Benefit from rapid parasiticidal activity of artemisinins at short (3-day) dosing while preventing recrudescence and possible emergence of resistance.
Resistance development during monotherapy	Rapid	Rapid	Depends on agent. Fast for target specific agents, slow for non-specific agents
PK considerations	Half-lives are short for all agents.	Matched PK to prevent essential 'monotherapy' and increased risk of resistance emergence.	Mismatched in ACT. Artemisinin is rapidly parasiticidal, reducing parasite load. Long half-live partner is needed to prevent recrudescence. Resistance emergence is unlikely if fast-acting agent reduces biomass sufficiently.
Dosing duration	Short-course = 6 months Aim is to achieve 2-month therapy.	Lifelong therapy, possibility of induction–maintenance strategies with new highly potent agents (yet to be proven).	Maximum = 3 days. Aim is to achieve short-course therapy = 1 day.
Use of animal efficacy models	Establish bactericidal effect and potential for stable cure with single and combination agents. Dose finding as monotherapy and in combination.	Not important. Efficacy evaluated *in vitro*.	Highly varied and poorly validated for *P. falciparum* and *P. vivax*. In *P. vivax* models, the ability to perform liver biopsy can be useful.
Surrogate endpoints	Not available for Phase III. EBA and time to sputum clearance in Phase II.	Reduction in viral load (HIV RNA) is used at all stages of clinical development.	Not available for Phase III. For rapidly parasiticidal agents, PRR can be used in Phase II for proof of concept and dose finding.
Development model	Collaborative, focusing on many possibilities at early stages but with limited options in late-stage development because of cost/duration of studies. Aim to replace all components of current therapy with new combination.	Pre-registration industry-led; collaboration limited to joint ventures and co-development agreements. Registration is for monotherapy for use in combination therapy. Numerous post-registration investigator-led studies on different combinations.	Collaborative. Older agents registered as monotherapy. ACTs usually registered as FDCs, though may initially be co-presented. Post-registration investigator studies mainly on established combinations and often limited to surveillance.
Resistance testing	Testing not generally available.	Routinely determined and used to optimise individual patient treatment regimens.	Monitored clinically as decreased efficacy. Some genetic testing, but not routine/widespread.

Designing appropriate studies for optimising combination therapy in malaria

Study designs in moving from Phase I to Phase II with single agents

Jörg Möhrle

Key points

- There is no accepted template for antimalarial early clinical development; a variety of studies and approaches have been taken.
- Although previous ACTs were developed including studies with monotherapy, it may no longer be ethical to conduct such studies. Versus standard of care:
  - Patients treated with monotherapy with rapidly-eliminated agents are exposed to an increased risk of relapse.
  - Patients treated with monotherapy with a low-acting agent have slower parasite and fever clearance and longer symptom duration.
- Alternatives for early Phase II (proof of concept) studies include:
  - Parasite clearance time over 36-hours after monotherapy can be measured and then the partner drug added as sequential combination therapy.
  - Conducting dose-ranging studies in *P. vivax* first as there is a lower risk to patients than with *P. falciparum*.
  - Testing in semi-immune patients, though useful dose-ranging information cannot be obtained because the contribution of immunity is difficult to quantify.
- Phase II studies in *P. vivax* and *P. falciparum* can be conducted concurrently to gain early efficacy data in both species. However, development timelines may become 'decoupled' because of differences in the timing of patient recruitment.

Discussion

PRR as an endpoint: PRR is not prospectively validated. However, it appears to be relevant for rapidly parasiticidal drugs and artemisinins can be used as the benchmark.

- There is a higher development risk when using different endpoints for Phase II (PRR) than for Phase III (PCR-corrected Day-28 ACPR).
- Detecting the difference in PRR between treatments with statistical robustness cannot be accomplished in small numbers of patients; it would have to be based on what is a clinically relevant difference
- Comparing the difference in PRR for new agents with historical PRR data for artemisinins is a high-risk option, even though data are recent and from the same study site.

Recommendation: *If possible,* an artemisinin monotherapy active control arm should be included in Phase IIa studies assessing proof of concept of new monotherapy using PRR as an endpoint. This is because it has been agreed that a minimum number of patients could be exposed to monotherapy, especially those likely to have parasites already resistant to some agents

Monitoring antimalarial drug efficacy and implications for drug development

Pascal Ringwald

Key points

- The original 1996 protocol for antimalarial drug surveillance was designed to provide quick answers regarding the presence and extent of chloroquine resistance. However, it was interpreted in some cases as a template for drug development which led to the development of inappropriate protocols.
- Single-arm studies are sufficient for surveillance purposes.
- Endpoints beyond Day 28 are generally difficult for surveillance studies, but not impossible.
- The Day 28 endpoint is the most relevant in daily practice. Patients with failure before Day 28 are considered to have a recrudescence of the initial infection and are treated with a rescue therapy, whereas patients with failure after Day 28 are considered to have a new infection and are re-treated with first-line therapy. Currently it is day 14 but this threshold will be rediscussed during the next Treatment Guidelines committee.
- Endpoints after Day 28 may not detect many more PCR-corrected failures, increase the cost, increase the risk of patients being lost to follow-up, increase errors related to PCR limits, and bias results towards combinations including partner drugs with longer half-lives.
- The focus of therapy remains radical cure. Currently, post-treatment prophylaxis is not consider as an outcome in the WHO standard protocol.
- Obtaining drug blood concentrations at day 7 is now recommended even in routine monitoring for some medicines.
- Analysis must include at least ACPR in PP population and Kaplan–Meier survival analysis, with population defined as per Appendix 9 of the WHO 2009 protocol.
    - The outcomes between PP and Kaplan–Meier analysis are often correlated but with higher efficacy rates for PP. The difference will increase as more patients are lost to follow up.

Suggestions for Phase III clinical trials

The 2009 protocol highlights that it has not been designed for drug development. However, clinical trials for new antimalarials should be ‘inspired’ by this protocol.

- ACPR at Day 28, corrected for new infection using PCR genotyping must still be used as the primary endpoint.
    - This endpoint is well understood and allows health authorities to interpret new information within their current recommendations.
    - In the WHO 2009 protocol ACPR and parasitological cure rate are equivalent.
    - Follow-up at Day 42 or 63 is of interest for drugs with half-lives longer than 7 days; PCR-corrected ACPR is also of interest for these endpoints in Phase III studies.

Discussion

- Intent-to-treat (ITT) is the most conservative analysis, followed by Kaplan–Meier analysis then PP analysis. ITT is only relevant for comparative studies.
- The definition of the study population used for the Kaplan-Meier analysis should be consistent across studies. A definition has been co-developed by WWARN and MMV and included in the 2009 WHO protocol. This was discussed first with Stephan Duparc and then sent out to WWARN for comments. (Appendix 9).
- ACTs are based on the principle that the artemisinin rapidly reduces the biomass and the partner drug kills the remaining parasites. Early endpoints such as PRR are interesting especially when at least one of the actives in a combination regimen has a rapid parasiticidal action. In the future there may be combinations of antimalarial agents developed where both components make a major contribution to both parasite clearance at Day 3 and PCR-corrected Day-28 ACPR

Phase IIb and Phase III study designs for the combination, setting the dose and dose ranging

Stephan Duparc

Key points

- Different options are available for comparing dose combinations in Phase IIb trials.
  - Classical: Comparison of several possible (e.g. 3x3) combinations.
  - Adaptive: Start with all potential arms and drop some after an interim analysis.
  - Baysian: Study information can be assessed at any time and the design modified accordingly. It is most valuable when predicting long-term outcomes based on short-term surrogate endpoints.
- The question of correct dosing for 3-day or 1-day dosing will have to be examined in separate trials. One-day treatment with OZ439 partnered with either naphthoquine or ferroquine will be examined initially and if this is not feasible, development will be switched to 3-day dosing with piperaquine.

Discussion

Adaptive design: A truly adaptive design may be advantageous in antimalarial development. This is because the Day-28 ACPR endpoint is required for the slow-acting partner, and in practice, enrolment can be completed before the Day-28 analyses are available.

- Even if there is some precedent for dosing of the 'slow-acting' partner drug from use in other combinations, then it will still need to be tested in the new combination as it may behave differently.

Recommendation: Adaptive study designs need to be looked at very carefully as they may take longer than a classical design for antimalarial combination drug development.

Thorough QT studies

- The need for thorough QT studies should be discussed case-by-case, not conducted systematically.

- If an agent to be used in a combination regimen has already been evaluated for effects on QTc, further QT studies may not be required unless the dose to be used differs from that previously studied and/or plasma exposures are higher when it is administered in a combination due to a DDI effect.
- Whether or not a thorough QTc study is performed close monitoring of ECGs in patients is still advisable.
- If no effect on QTc is expected based on non-clinical studies it may be sufficient to perform this assessment in a subset of the study population.
- For NCEs, not conducting thorough QT studies is a high risk option.
- If considered necessary, QT studies need to be performed before Phase III, so that if there is an issue, intensive monitoring can be included in the Phase III programme.
- In HIV, QT studies are performed on the individual agents, not the combination, but it may be different for malaria and it would depend on the combination.

Recommendation: For NCEs, a precautionary approach would be to perform thorough QT studies before Phase III, even if there are no preclinical signals.

Phase IIb dose-ranging designs for combination therapies

Lynda Kellam

Key points

- Designs for monotherapy dose ranging include conventional phase IIb, combined (seamless) phase IIb/III and adaptive studies.
- For combination therapy dose ranging, factorial study designs can be used. These designs are used extensively for animal models, but their application to clinical dose finding studies has been limited mainly to hypertension.
- Factorial study designs use a model to enable interpolation of dose–response information. This provides a dose–response surface that can be sued to suggest the 'ideal' dose even if that dose was not actually tested.
- Various models are available; model choice is a key consideration. The model includes a number of assumptions. A quadratic model has most frequently been used in phase 2b factorial trials.
- Because data are not compared pair-wise by cells but across the whole matrix, sample sizes for each cell can be quite low and may need to be increased to provide more safety data. Note that the highest and lowest dose combinations have the highest sample sizes if a quadratic model is used.
- There is a significant amount of up-front design work e.g. sensitivity analysis, simulations.
- Statistical input from someone experienced in designing factorial trials is needed. Also, advice on how the trial can actually be conducted on a practical level is required.

Discussion

Seamless Phase IIb/III: This is advantageous when protocol approval takes a long time as the protocols for the Phase IIb and III trials can be approved simultaneously. There is a stop

and interim analysis at the end of Phase IIb when the Phase III dose is chosen. If protocol approvals are generally quick, there is no advantage.

Factorial design
Although ACTs were developed from existing antimalarials, in many cases doses were still sub-optimal. The availability of new antimalarials provides an opportunity to test new approaches to dose optimisation for combination therapy such as factorial design. There are a number of advantages to this approach:

- Enables dose optimisation in the combination in one experiment.
- It may avoid unnecessary patient exposure to ineffective drug levels.
- The doses indicated from monotherapy studies may have little relevance to those needed in the combination. Factorial design would examine dose regimens outside those that are 'expected'. For example, it would allow for unexpected drug interactions, e.g. synergy, antagonism.
- Monotherapy still needs to be tested to prove that both agents contribute to the combination and that it is superior, and to provide safety information, e.g. the maximum tolerated dose.

Recommendation: Factorial design should be considered for Phase IIb combination therapy dose finding as a pioneering methodology in antimalarial drug development.

Cost: The cost of a factorial Phase II study would be comparable to conducting Phase II on individual components and then Phase II on the combination. However, a factorial study would be more expensive if the development plan was to progress straight from Phase II with individual components to combination therapy in Phase III (considered a high-risk option).

Resource issues: Obtaining access to a suitably qualified statistician would have to be addressed within MMV. Also, the study would be complex and the practicalities of conducting a study of this type would have to be examined carefully.
Recommendation: The statistical and practical input to conduct factorial Phase IIb dose-finding studies is considerable and MMV needs to examine how this could be best obtained.

Regulatory issues

- The statistical capabilities of the larger regulatory agencies would be sufficient to provide feedback on a finalised factorial study design.
- With an appropriate protocol the MHRA would have an open mind on factorial design for antimalarial combination therapy dose finding. The MHRA are receiving more proposals on factorial design in other therapeutic areas.
- Although factorial design includes various assumptions, this is true of any Phase IIb study. Phase III data will show regulators whether the dose finding was actually correct.
- If registered drugs are included in the combination, it cannot be assumed that the dose used previously is the correct dose for the new combination. There may be drug–drug interactions. There must be a rational basis for the dose used in the combination.

Recommendation: Regulatory discussion and positive feedback on a factorial design can be helpful and is recommended (though it is not a guarantee that the completed study will be acceptable).

Actions

Responsible	Action
Pascal Ringwald	• To forward comments on FDA document regarding ACPR definitions to Renata Albrecht or communicate the general points made in those comments.
MMV	• Examine statistical resources in regard to factorial trials.

Further information and links

Analysis and Reporting of Factorial Trials: A Systematic Review
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World Health Organisation. Methods for surveillance of antimalarial drug efficacy. WHO: Geneva, 2009.
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Participants list

Chair: David McGibney

Invited participants:

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Chantal Laburte	Expert Scientific Advisory Committee (ESAC)
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