Key needs and challenges in the development of new drugs for treatment of malaria

**highly efficacious, preferably single-dose treatment (SERC*)**

**Aim:**
replace 3-day treatment regimens due to poor compliance, and prepare tools for malaria elimination

**Challenge:**
potent molecules to deliver a single efficacious dose safely and to provide post-treatment protection

**combination drugs with fixed-dose formulations**

**Aim:**
reduce likelihood of resistance and increase patient compliance by co-formulating 2 drugs

**Challenge:**
drug-drug compatibility and suitable formulation availability early in clinical development

**for children and pregnant women**

**Aim:**
address most vulnerable populations as best and quickly as possible

**Challenge:**
safety data package generation and inclusion of the target population early in clinical development

**addressing drug resistance**

**Aim:**
provide new treatment options for countries to combat drug resistance

**Challenge:**
geographical and population variability in clinical development

Dialogue and agreement with regulatory authorities

*Single encounter radical cure*
Strong pipeline of molecules in development

Footnotes: 🌟 Included in MMV portfolio after product approval; 🌟 Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. 🌟 WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers. MMV support to projects may include financial, in-kind, and advisory activities.

Strength in discovery

Research

- Lead optimisation
- Candidate Profiling

 Injectable Prodrug Calibr
- Miniportfolio 3 series GSK
- SFK59 series H3D Cape Town
- DHODH backups UTSW/UW/Monash
- Pantothenates TropiG/GRMC
- Phenotypic Lead Broad/Eisai
- Open Source Series University of Sydney
- Phe tRNA lygase Broad Institute/Eisai
- Purines Celgene
- DHODH Broad/Eisai
- Phenotypic Lead Eisai
- Molecular Target DDU Dundee

Translational

- Preclinical
- Human volunteers

 OZ609 Nebraska, Monash, STHI

Product development

- Patient exploratory
- Patient confirmatory
- Regulatory review

- Post approval

2-3 new candidates per year

Access

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- Brand names 1: Coartem® Dispersible; 2: Artesun®; 3: Eurartesim®; 4: Pyramax® tablets or granules; 5: ASAQ/Winthrop®; 6: SPAQ-COTM; * For infants 3 – 12 months, ** for children 13-60 months
Simplify therapy and fight resistance

All development compounds:

- Active against all clinical isolates
- Difficult to raise resistance in vitro
- No breakthrough in clinical studies

Fast clearance of parasitaemia
Long-acting post treatment prophylaxis
Kills hypnozoites
Transmission blocking

SERCaP
single exposure radical cure and prophylaxis

1. Building on an existing template

**OZ03**
- Reduce logP
- Improve solubility

**OZ277/ RBx11160**
- Decrease interaction with ferrous iron (single electron)

**OZ439**
- Less potent on embryos and on granulocytes
- Active vs artemesunate resistance

McCarthy JS, *Antimicrob Chemother*;71(9):2620–7 (OZ439)
2. Molecular Design: DHODH

**DSM1**
EC$_{50}$ 3D7 79 nM
No oral efficacy

**DSM191**
EC$_{50}$ 3D7 220 nM
ED$_{90}$ *Pf* SCID 57 mg/kg

**DSM265**
EC$_{50}$ 3D7 8 nM
ED$_{90}$ *Pf* SCID 8.1 mg/kg

3. Ask the parasite

Chemistry: All available molecules

HTS Whole parasite

Hits to leads

Identify resistance

New candidate molecules for development

Portfolio potential combination partners

Research
- Lead optimisation
- Candidate Profiling

Translational
- Preclinical
  - M5717: Merck KGaA
  - MMV253: Zydus Cadila
  - AN13762 (Anacor)
  - UCT943: H3D Cape Town
  - SAR121: Sanofi

Human volunteers
- P218: Jansen, (Biotec Thailand)
- SJ733: Kentucky/Eisai

Product development
- Patient exploratory
  - Artefenomel/ Ferroquine: Sanofi
  - KAF156/ Lumefantrine: Novartis
  - Cipargamin: Novartis
  - DSM265: Takeda (UTSW/UW/ Monash)
- Patient confirmatory
- Regulatory review
- Post approval

Access

10 new candidates, 7 new targets

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Key translational platforms (1/2)

Humanized SCID mouse model

- Human blood inoculation to mice
- *P. falciparum* infection
- Administer drug
- Data collection & modelling (PK/PD)
  - Pharmacokinetics (PK): drug concentration vs time
  - Pharmacodynamics (PD): parasitaemia versus time
  - Modelling: growth/kill rate vs time in response to drug concentration

Data help predict the human dose and support compound selection
Controlled human malaria infection (CHMI) model
Collaboration with QIMR-Berghofer

- Inoculate parasites
- Administer drug candidate
- Count parasites in the mosquito
- Monitor parasitaemia in volunteers
- Rescue drug administered, if needed
- Rescue drug administered at the end
- Mosquito feeds (direct and indirect)
- Clearance of asexual parasitaemia
- Sexual parasitaemia
- End of study
# Cipargamin

**Novartis**

## Product vision
- Part of single exposure radical cure
- Potential for use in severe malaria

## MoA
- *Pf*ATP4 inhibitor

## Key features
- First validated new molecular target in 20 years: very rapid killing of parasites
- 75mg human dose gives concentrations above Minimal Parasiticidal Concentration for >8 days
- Potential for transmission blocking in Standard Membrane Feeding Assay

## Challenges
- Safety profile to be further characterized in malaria patient study

## Status
- Completed first phase IIa (short-duration monotherapy PoC in patients)

## Next milestone
- Dose escalation study in patients

## Previously
- Names NITD609, KAE609: discovery partnership with Novartis, STPHI and Wellcome

## MMV Project Director
- Dr Marc Adamy

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31 July 2017 – Interim
| **Product vision** | • Part of a single exposure radical cure  
| | • Potential for chemoprotection  |
| **MoA** | • Plasmodial dihydroorotate dehydrogenase (DHODH) inhibitor  |
| **Key features** | • Novel mechanism of action  
| | • 400mg human dose gives concentrations above Minimal Parasiticidal Concentration for >8 days  |
| **Challenges** | • Cost of goods for API, and formulation  
| | • Reduced relative activity against *P. vivax*  
| | • Single enzyme target; potential for resistance  |
| **Status** | • Phase IIa in Peru in patients with *P. falciparum* or *P. vivax* malaria complete  
| | • Controlled Human Malaria Infection Study of combination with OZ439 complete  |
| **Next milestone** | • Complete human challenge models with *P. falciparum* sporozoites  
| | • Prioritise combination partner for phase IIb  |
| **Previously** | • Discovery Partnership with University of Texas Southwestern, Washington University and Monash University  |
| **MMV Project Director** | • Dr Jörg Möhrle  |
# MMV048 (UCT)

| **Product vision** | • Part of a single exposure radical cure
  • Potential for chemoprotection |
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<td><strong>MoA</strong></td>
<td>• <em>PfPI4K</em> inhibitor</td>
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| **Key features** | • 80mg dose predicted to give coverage above Minimal Parasiticidal Concentration for >8 days
  • Good prophylactic activity against *P. cynomolgi*, *in vivo* after single dose
  • Long half-life in human |
| **Challenges** | • Development of new formulation reducing exposure variability |
| **Status** | • Phase I and human volunteer challenge model with new formulation |
| **Next milestone** | • Start of Phase IIa protocol in Ethiopia (2017) |
| **Previously** | • Name MMV390048: Discovery and Phase I partnership with H3D, University of Cape Town and South African Technology Innovation Agency |
| **MMV Project Director** | • Dr Cristina Donini |

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![Chemical structure of MMV048](image)
**SJ733**
Kentucky/Eisai

| **Product vision** | *Part of a single exposure radical cure*  
| **MoA** | *PfATP4 inhibitor* |
| **Key features** | *Novel chemotype for clinically validated pathway; First validated new molecular target in 20 years: very rapid killing of parasites*  
| **Challenges** | *Cost of goods: chiral molecule*  
| **Status** | *First in Human study recruiting*  
| **Next milestone** | *Complete first in human studies with three day multiple rising dose*  
| **Previously** | *Name (+)-SJ000557733; Discovery Partnership with St Judes Children’s Research Hospital, Rutgers University and US NIH*  
| **MMV Project Director** | *Dr Lidiya Bebrevska* |
## Product vision
- Potential for Chemoprotection

## MoA
- *P. falciparum* dihydrofolate reductase (DHFR) inhibitor

## Key features
- Clinically validated pathway
- Activity against wild type, and antifolate resistance-conferring quadruple mutants

## Challenges
- Human half-life difficult to predict
- 10 fold difference between *P. falciparum* and *P. vivax* IC50 in ex-vivo field isolates

## Status
- First in human study recruiting

## Next milestone
- Go/no go decision to initiate controlled human malaria infection cohort

## MMV Project Director
- Dr Emilie Rossignol

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**Product:** P218 (BIOTEC Thailand)

**Chemical Structure:**

![Chemical Structure](image-url)
| **Product vision** | • Part of single exposure treatment of uncomplicated malaria  
• Potential for chemoprotection |
|-------------------|--------------------------------------------------------------------------------|
| **MoA** | • *P. falciparum* EF2 inhibitor Novel 
Mechanism of Action |
| **Key features** | • Comparable activity across all stages of the malaria parasite lifecycle  
• Predicted dose to give coverage above Minimal Parasiticidal Concentration for over 8 days is 16-145mg  
• Excellent transmission blocking potential |
| **Challenges** | |
| **Status** | • Approved by Merck for progress as pre-clinical candidate 1Q 2016 |
| **Next milestone** | • Initiate First in Human studies 2017 |
| **Previously** | • Names DDD107498; DDD498, MMV121; Discovery collaboration with the University of Dundee Drug Discovery Unit |
| **MMV Project Director** | • Dr Lidiya Bebrevska |
MMV’s SERC combination drug development strategy aims at early de-risking

Classical drug-combination development strategy

- Converging development pathways between drug A and B
- Priority on adults (formulations, participants in clinical trials)

MMV’s SERC combination drug development strategy

- Integrated development plan and testing of multiple drug-combos in pre-clinical and phase I
- Priority on vulnerable populations (treatment of children in Phase II, child-friendly formulation)
- Use of translational tools, modelling & simulation

- Potential for late-failure → high sunk costs
- FDA drug combination rule satisfied with large Phase II trials

- Saves time & resources via early de-risking
- Satisfies FDA drug combination rule using non-clinical and early clinical data (to be agreed)
Find the right partner

Trusted friend or beautiful stranger? Can you afford to wait for perfection?

https://plus.maths.org/content/kissing-frog-mathematicians-guide-mating
Older

Newer

Newest
Drug combination scoring tool to select drug combinations for further testing in translational models
We can help choose the right one

- Combination Selection Tool
- SCID mouse data – in vivo: additivity /synergy
- Metabolic interactions: Simcyp
- Human Challenge Model
Putting the combination together

**Drug A – Individual Agent**
- **Phase 1a**
  - SAD + FE
- **Phase 1b**
  - Challenge
- **Phase 1a**
  - Combo safety
- **Phase 1b**
  - Combo challenge

**Drug B – Individual Agent**
- **Phase 1a**
  - SAD + FE
- **Phase 1b**
  - Challenge

**SINGLE STUDY: PHASE 2a/2b**
- Drug A / Drug B Combination
- **Phase 2a**
  - Confirm minimum efficacy at maximum feasible* dose
- **Phase 2b**
  - Confirm tolerability & efficacious doses/exposures across age / weight range & dosing weight bands
- **PONV**
  - No Go if probability of combination efficacy >95% ACPR is low at maximum feasible* dose
- **Safety Satellite**
  - in 2–12y
  - in 0.5–2y

**Dose selection rationale for Phase 3**

**Ph3**: Pivotal efficacy for filing

**Ph3/4**: Safety & Efficacy on re-dosing

**Ph3 / 4 Multiple exposures study**

**Phase 3 Studies in Africa, Asia & LATAM**
- Optimal Combination Dose vs SOC in adults & children

**Pre-clinical**
- Healthy Volunteers
- **Ph2b**
- Satellite Study
- **Ph3**

**PopPK & PKPD**
- Go/No Go (or Combination selection)
- Go/No Go

*Highest clinically feasible dose includes tolerability, Toxicology margins, dose size and potential for commercial formulation
** alternative age minimum depending on local regulations
*** Dose with optimal balance of efficacy, duration & tolerability
PONV – Proof of non-viability
MMV’s development strategy will allow early de-risking based on translational science*

* to be discussed & agreed with regulatory authorities; assuming predictive translational models & PKPD modelling
Leveraging the potential of translational science, modelling & simulation will de-risk

**Historic**
- Limited translational tools for prediction of efficacy
- Decision making after Phase IIb futility

**Current**
- Combo partner ranking at pre-clinical & Ph Ib
- Earlier evidence of clinical efficacy with lower investment Ph II (Part 1) drop combos with low probability of success
- M&S to aid dose setting & scaling in children

**Future**
- Estimation of dose efficacy via translational methods
- Identify combos with highest prob. of success
- Earlier derisking & lower probability of failure due to efficacy in Ph II and III
- FDA combination rules satisfied using SCID mouse &/or human challenge model*

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* To be confirmed
Model-informed drug development at MMV

Non-clinical or clinical data

- Preclinical package
- SCID mouse data
- First in human data
- Human challenge model data
- PBPK
- Dose-concentration-effect relationship. Est. Day28 ACPR
- Drop non-viable combos. Dose-selection for Phase III
- Ph II Efficacy highest feasible dose & dose ranging
- PBPK/PD model for extrapolation to other population (e.g. children)
- Confirmation of safety & efficacy
- Translation from mouse to human
- Est. Day28 ACPR

Modelling & simulation
If you want to go fast, go alone
If you want to go far, go together
The aspiration for PK/PD modelling is to be able to predict (single and combo) drug efficacy in humans.

- Predict parasitemia profile in humans
- Prioritize combinations for testing in humans
- Predict drug-drug interactions