A young child with dark skin and short hair is shown in profile, looking towards the right. The child is wearing a light-colored t-shirt with some faint text. In the background, there is a large, abstract artwork with warm, orange and yellow tones, possibly made of wood or a similar material. The lighting is soft and focused on the child and the artwork.

# Global Portfolio of antimalarial medicines

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Dr Tim Wells, CSO, MMV  
September 19th Vienna

Defeating Malaria Together

**MMV**   
Medicines for Malaria Venture

# Global Portfolio of Antimalarial Medicines

Research Lead Optimisation		Translational			Development		
		Preclinical	Phase I	Phase IIa	Phase IIb/III	Registration	Phase IV
Oxaboroles Anacor	1 Project Novartis	P218 DHFR (Biotec/Monash/ LSHTM)	DSM265 (UTSW/UW/ Monash)	OZ439 (Monash/UNMC/ STI)	Tafenoquine GSK	Mefloquine Artesunate Farmaguinhos/DNDi	Coartem® Novartis <b>APPROVED</b>
DHODH UTSW/UW/Monash	3 Projects GSK	ELQ-300 (USF/ OHSU-VAMC)	Antimalarial Actelion	KAE609 Novartis	Pyramax Paediatric Shin Poong/ University of Iowa	Artesunate i.r. WHO/TDR	Artesunate for injection Guilin <b>APPROVED</b>
OSDD Univ Sydney	Orthologue Leads Sanofi	21A092 (DrexelMed/UW)	CDRI 97-78 Ipsca	KAF156 Novartis	Eurartesim® Paediatric Sigma-Tau	Arterolane/PQP Ranbaxy	Eurartesim® Sigma-Tau <b>APPROVED</b>
Heterocycles Dundee	Whole cell leads AstraZeneca	MMV390048 (UCT)	DF02 Dilafor	Ferroquine Sanofi	ArtiMist™ Proto Pharma	ARCO Naphthoquine/ Artemisinin	Pyramax Shin Poong University of Iowa <b>APPROVED</b>
Long Duration Leads Merck Serono	Tetraoxane Liverpool STM/Liverpool Uni	SJ557733 St Jude/Rutgers	N-tert butyl isoquine Liverpool STM/GSK	Fosmidomycin Piperaquine Jomaa Pharma GmbH			ASAQ Winthrop sanofi /DNDi <b>APPROVED</b>
HKMT IC/ CNRS	Aminopyridines UCT	NPC-1161-B University of Mississippi	AQ13 Immtech	Methylene Blue AQ Uni. Heidelberg			SP-AQ Guilin <b>APPROVED</b>
dUTPase inhibitors Medivir	NDH2 Liverpool STM/Liverpool Uni	RKA182 Liverpool STM		SAR97276 Sanofi			
Imidazolidinediones WRAIR	DOS Broad Institute	SAR116242 Palumed		Artemisone UHKST			

 Included in MMV portfolio post registration

Non MMV 

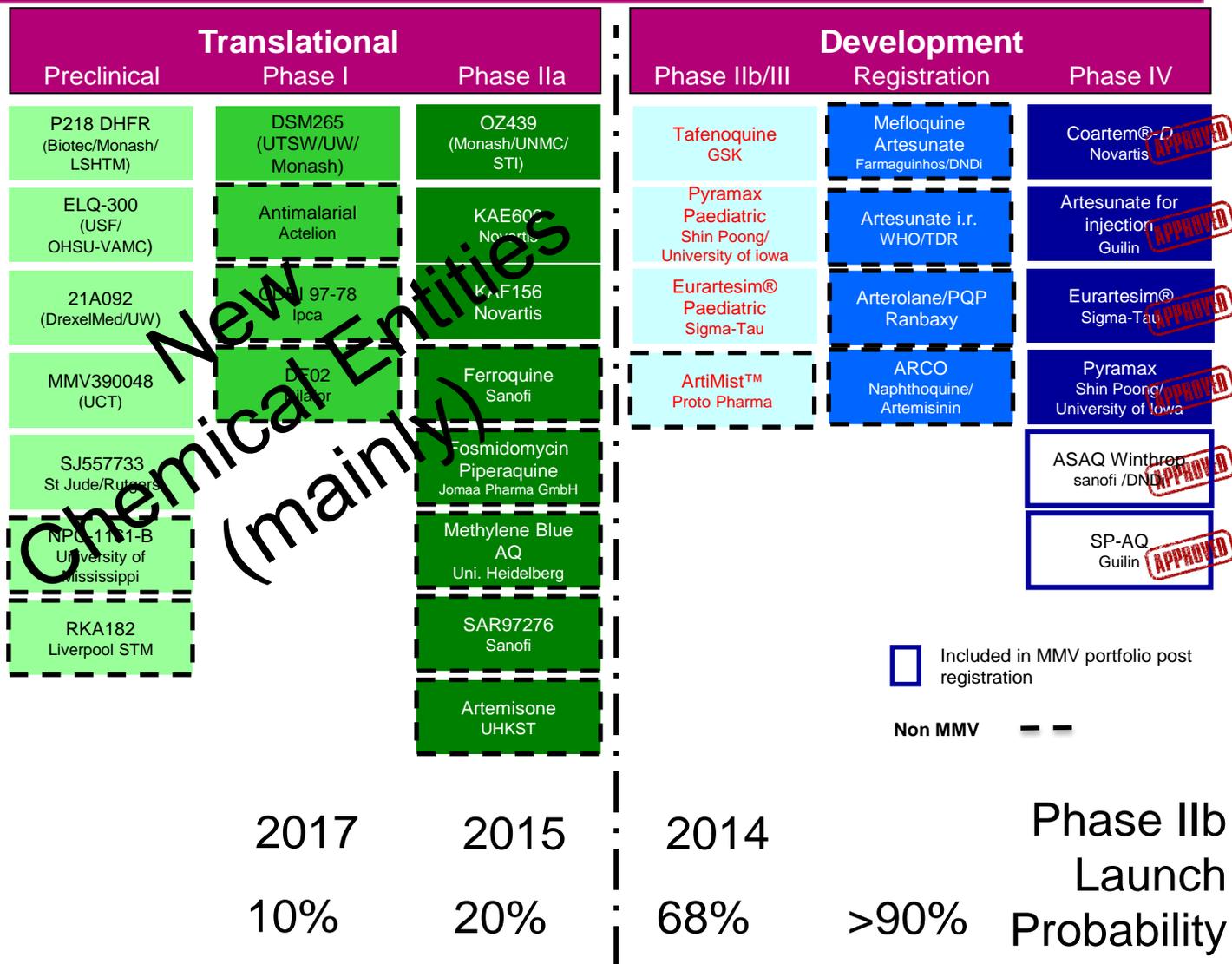
*Nauclea  
pobeguinii*  
DRC/Antwerp

*Argemone  
mexicana*  
Mali/Geneva

# Global Portfolio of Antimalarial Medicines

## Clinical Perspective 2014-2017

2-3  
new  
clinical  
cand-  
idates  
per  
year



New Chemical Entities (mainly)

# Global Portfolio of Antimalarial Medicines

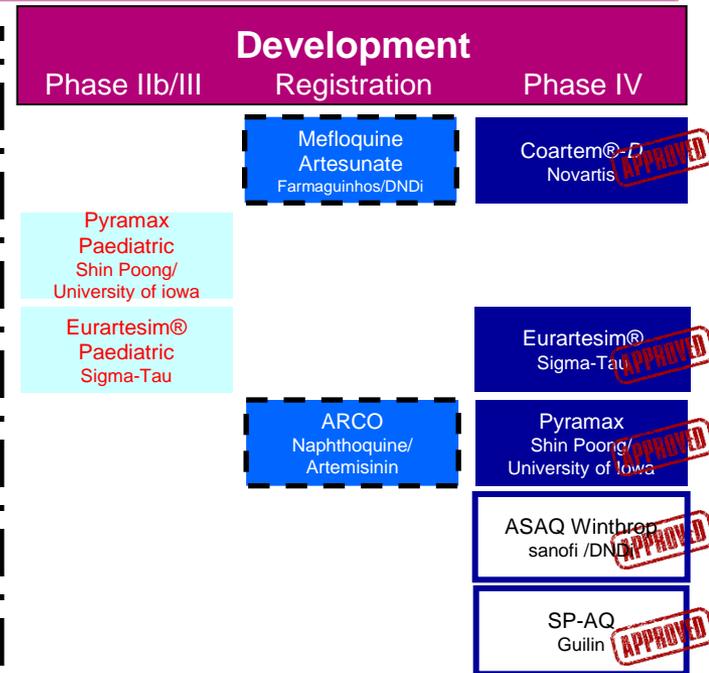
## Priorities for late stage in Africa

Development		
Phase IIb/III	Registration	Phase IV
Tafenoquine GSK	Mefloquine Artesunate Farmaguinhos/DNDi	Coartem®-D Novartis <b>APPROVED</b>
Pyramax Paediatric Shin Poong/ University of Iowa	Artesunate i.r. WHO/TDR	Artesunate for injection Guilin <b>APPROVED</b>
Eurartesim® Paediatric Sigma-Tau	Arterolane/PQP Ranbaxy	Eurartesim® Sigma-Tau <b>APPROVED</b>
ArtiMist™ Proto Pharma	ARCO Naphthoquine/ Artemisinin	Pyramax Shin Poong University of Iowa <b>APPROVED</b>
		ASAQ Winthrop sanofi /DNDi <b>APPROVED</b>
		SP-AQ Guilin <b>APPROVED</b>

# Global Portfolio of Antimalarial Medicines

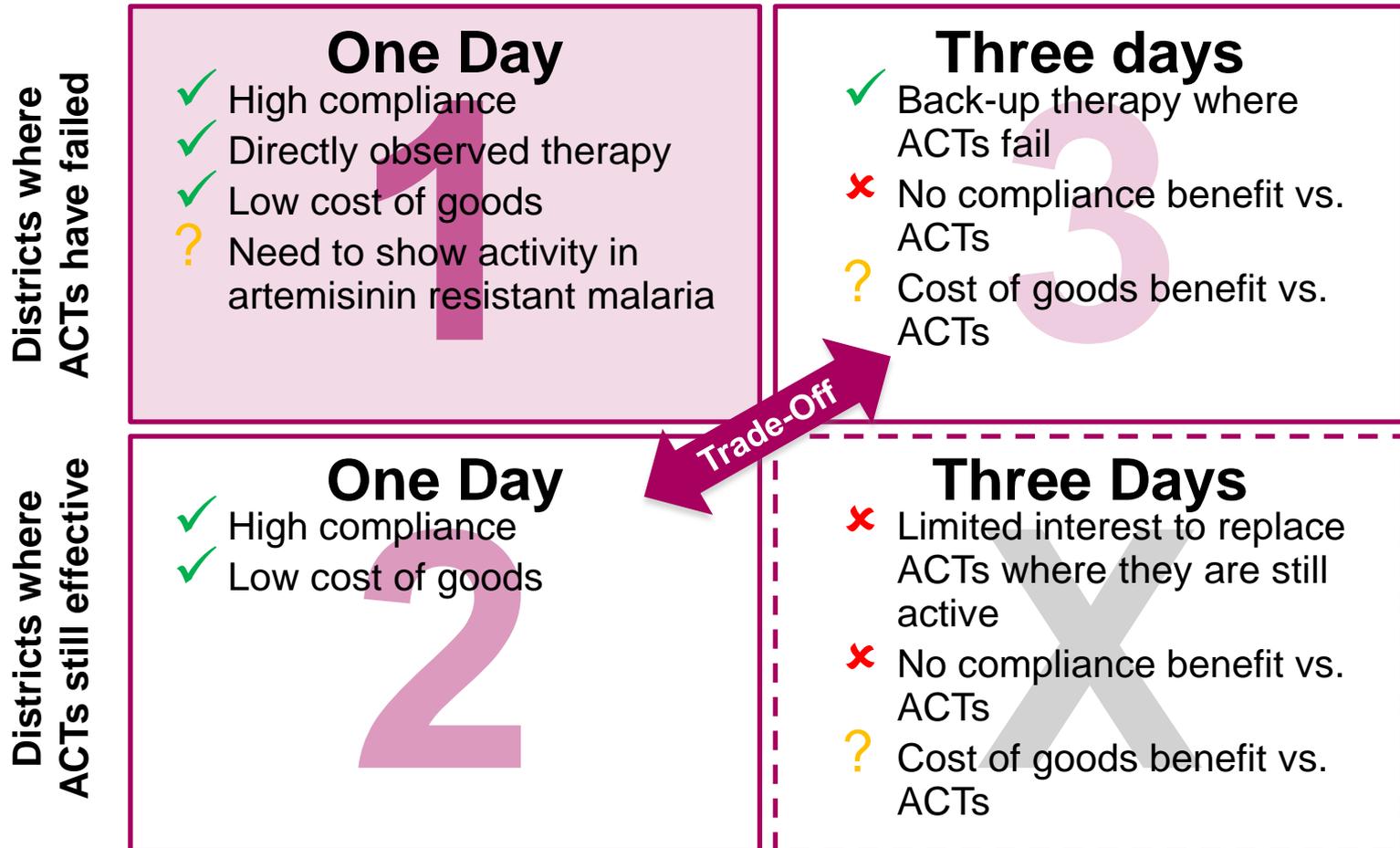
## Workstream 1: Making Medicines Available for all

- Safety studies of new ACTs
  - Cardiac
  - Hepatic
- Pediatric FDCs for ACTs
- Pediatric Primaquine (transmission); Tafenoquine (relapse)
- Studies of ACTs in pregnancy
- Studies in co-infection, drug interactions
- Capacity building for these studies in African centres



# Single dose cure is a priority: Three day therapy role where ACTs fail

## Therapeutic efficacy safely achieved



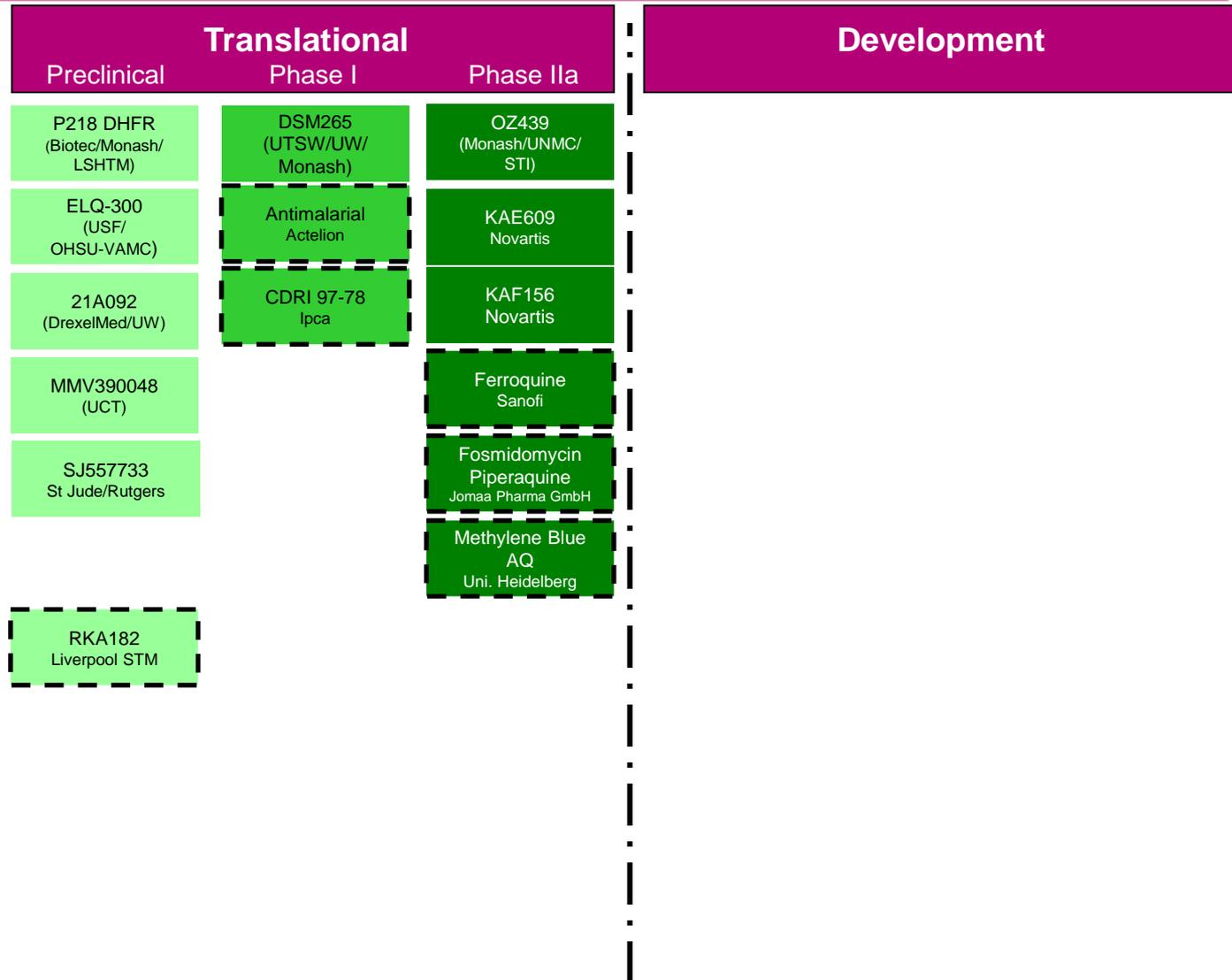
# Target Candidate Profiles

1. Fast killers/blood stage
2. Long persisters/blood stage
- 3a. Relapse prevention,
- 3b. transmission blocking
4. Chemoprotection



# Global Portfolio of Antimalarial Medicines

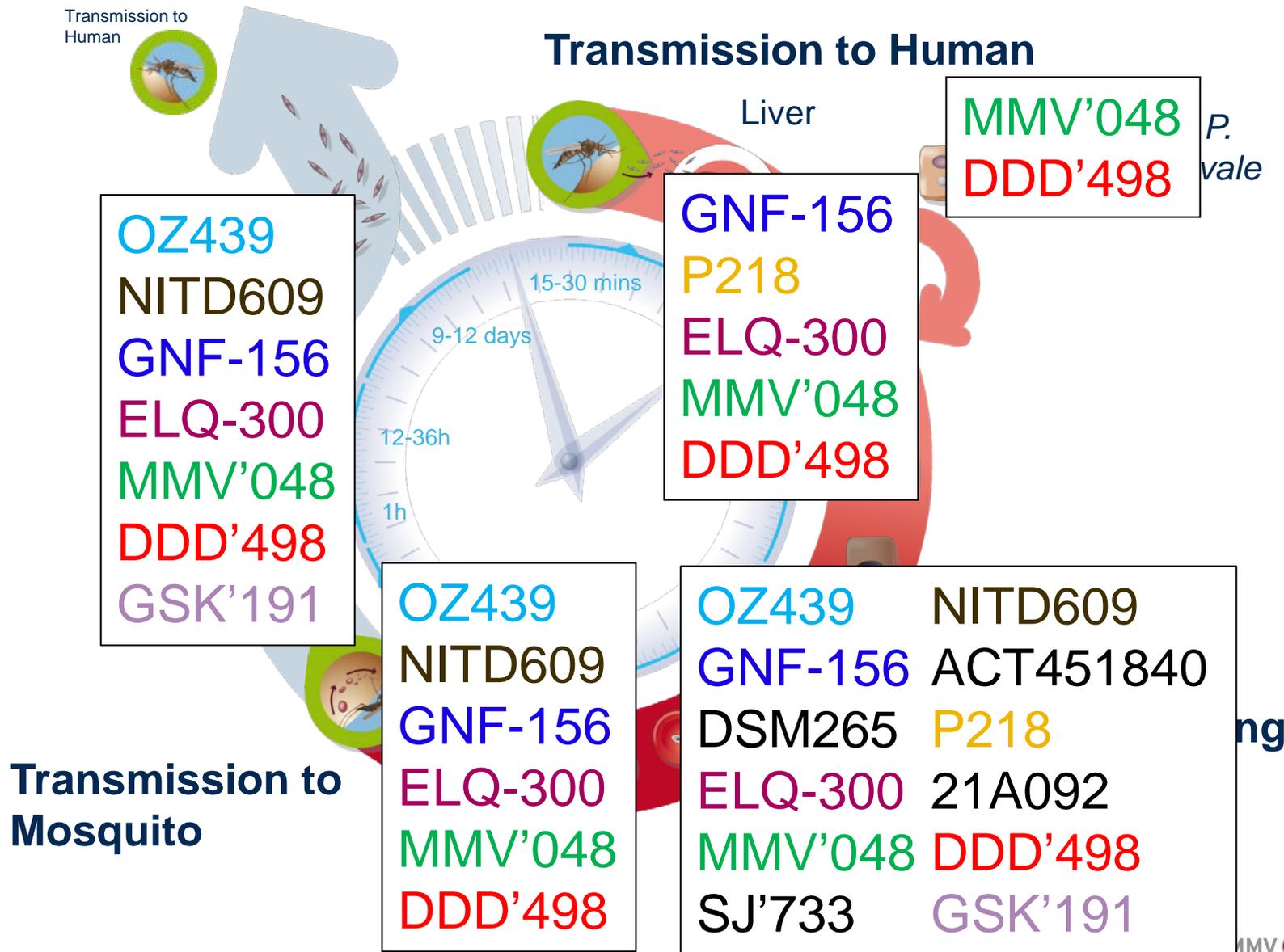
## Workstream 2: Uncomplicated Falciparum Malaria



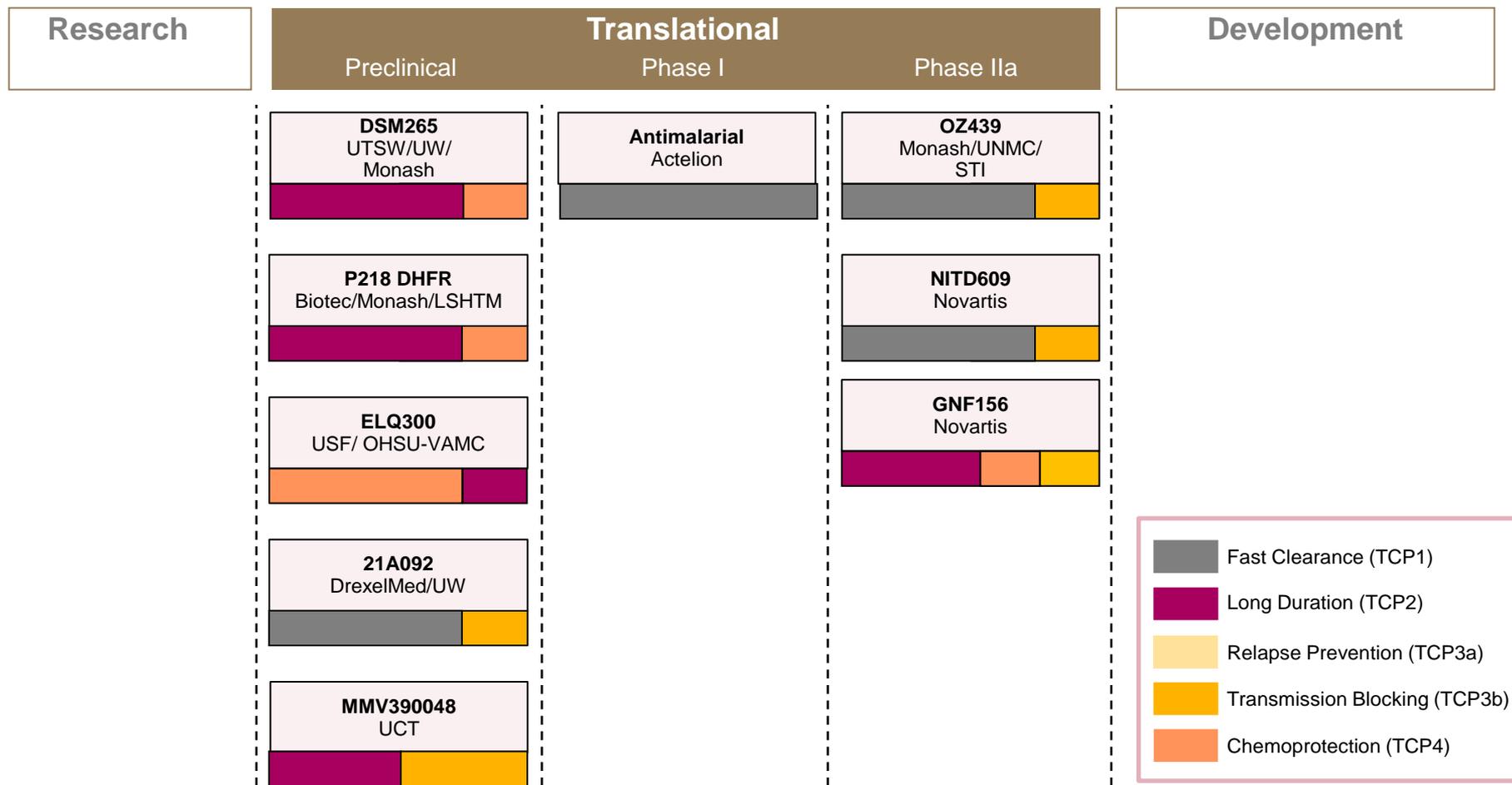
# Picking the winners: what capacity do we need

- Safety and Pharmacokinetics preclinically
- Pharmacology platforms
- Formulation development
  
- In the clinic 'platform technologies'
  - Safety: cardiology, hepatology in the right populations
  - Drug interactions in the right populations
  - Transmission blocking assays ...
  - Ways of assessing drugs for severe malaria: speed and formulation

# New preclinical portfolio having eradication fingerprint



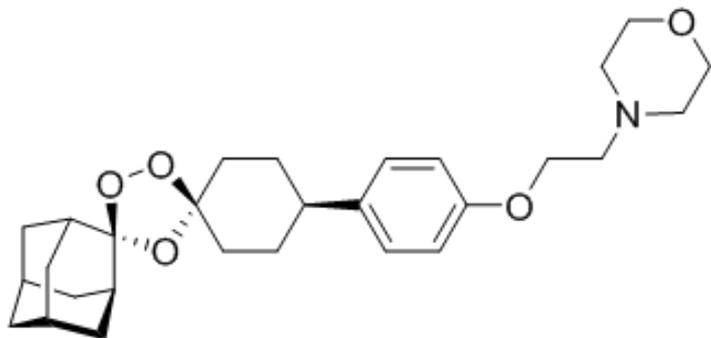
# Translational portfolio is richer than it has ever been



**Most NCEs in translational portfolio have potential against multiple features (1-5 molecules per key feature)**

# OZ439 trioxalane

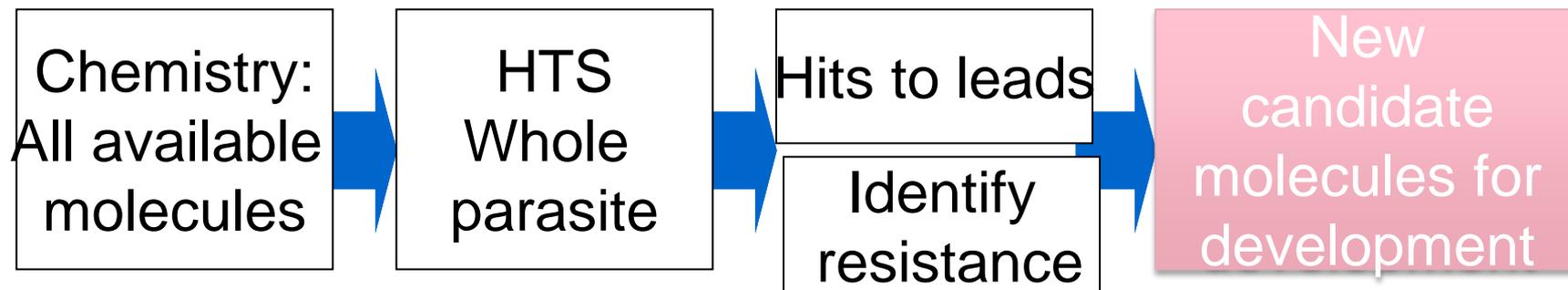
Nebraska, STPHI, Monash, MMV



Phase II  
combination  
1H 2014

- Fast killer; PRR =  $10^3$ - $10^4$  /48h
- Time above MPC: potentially >120h
- Transmission blocking
- Mechanism: oxidative > Fe<sup>2+</sup> mediated radical
- Active against all primary isolates (including Cambodia)
- Phase IIa completed 2012 200mg-1200mg
- Phase IIb with Piperaquine: Protocol submission 4Q'13

# A transformation in drug discovery



- New business model
- Screened five million compounds: 25'000 hits (1 uM)
- Fast: screen to human trials in less than four years
- Seven molecules already in clinical or preclinical
- Identifies *previously overlooked* new targets

Rottman M., *et al*, Science 325 1175-1180 (2010)

Meister S., *et al* Science 334 1372-1377 (2011)

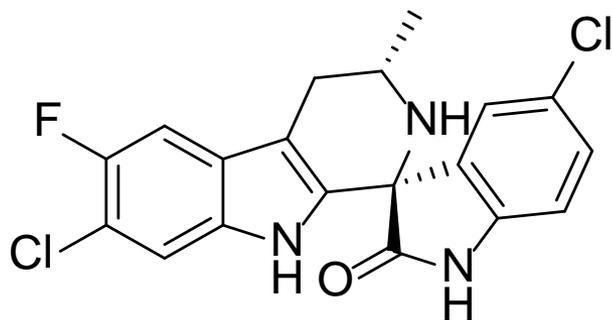
Gamo FJ, *et al.*, Nature 465 (7296): 305–310 (2010)

Guiguemde WA, *et al.*, Nature 465, 311–315 (2010)

Wells TNC Science 329 1153-1154 (2010)

# KAE609 Spiroindolone

## Novartis ITD, GNF, STPHI

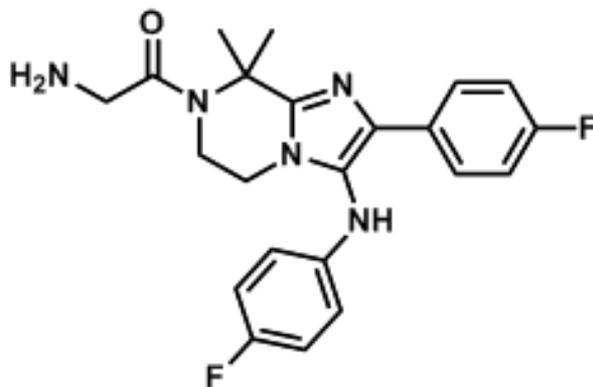


Phase II  
combination  
2H 2014

- Extremely Fast killer; PRR =  $>10^5$  /48h
- Time above MPC: potentially  $>120$ h
- Transmission blocking
- Mechanism: PfATP4 – sodium channel
- Active against all primary isolates (including Cambodia)
- Phase IIa first cohorts 2012; second cohorts ongoing
- Phase IIb with 4-aminoquinoline?
- Funded: Wellcome Trust, MMV, now Novartis AG

# KAF156 imidazolopiperazine

## Novartis GNF, NITD, BPRC, STPHI

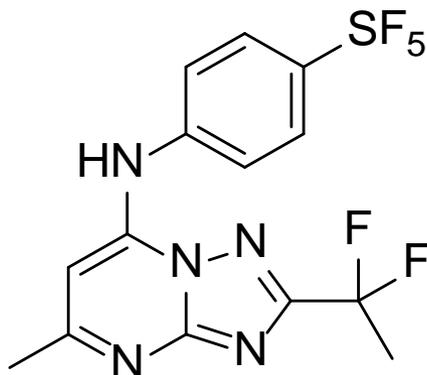


Chemo-  
protection?

- Fast killer; PRR =  $10^4$  /48h
- Time above MPC: >48h
- Active against liver schizonts (chemoprotective)
- Mechanism: PfCARL – unannotated channel
- Active against all primary isolates
- Phase IIa first cohorts 2013
- Funding Wellcome Trust MMV

# DSM265 Triazolopyrimidine

## UTSW (Dallas), STPHI, Monash

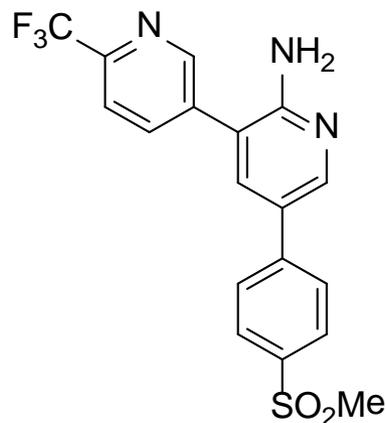


Phase II  
combination  
1H 2015

- Medium speed killer; human challenge Nov '13
- Time above MPC: > 96h predicted
- Active against liver schizonts
- Mechanism: dihydroxyorotate dehydrogenase
- Active against all primary isolates
- Phase I ongoing
- Phase IIa planned for Peru 2014; **Africa phase IIb 2015**
- Funding partnership MMV, US NIH

# MMV '048 Aminopyridine

## University of Cape Town led

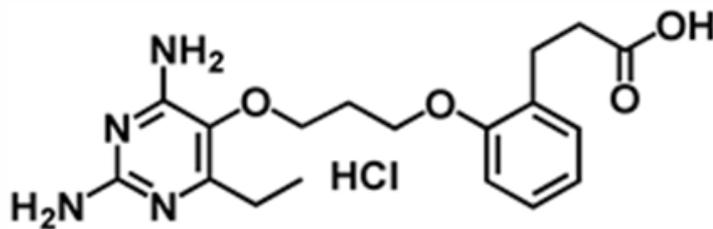


Phase II  
combination  
1H 2015

- Medium speed killer? Phase I 1Q'14
- Time above MPC: >96h predicted
- Active against liver schizonts
- Mechanism: novel lipid kinase
- Active against all primary isolates
- Phase I 1Q'14 in Cape Town
- Phase II – **Direct to phase II in Africa?**
- Funding Partnership MMV, TIA South Africa

# P218 2,4-diamino pyrimidine

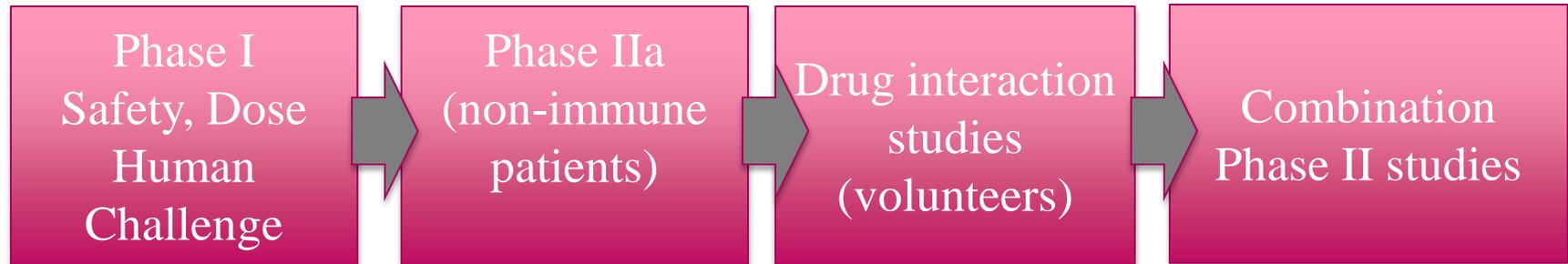
## Biotec Thailand, Monash, MMV



Chemo-  
protection?

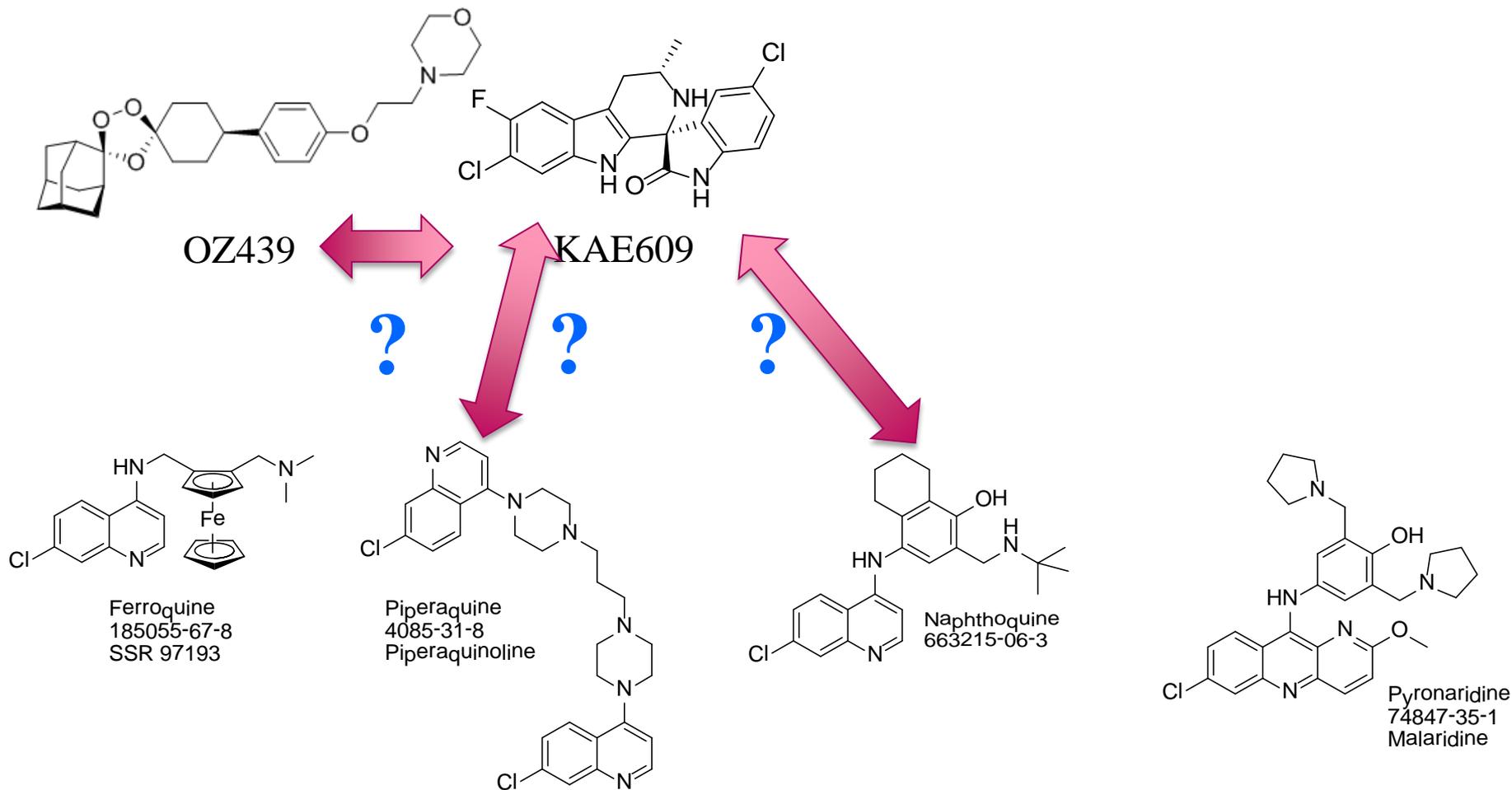
- Medium speed killer?
- Time above MPC: >96h target
- Chemoprotection: pyrimethamine replacement in SMC?
- Mechanism: PfDHFR inhibitor
- Active against all primary isolates, DHFR mutants
- Preclinical
- Phase I 2014? Sporozoite challenge?
- Funding Partnership MMV, Biotec Thailand

# Clinical development of combination medicines for uncomplicated falciparum malaria



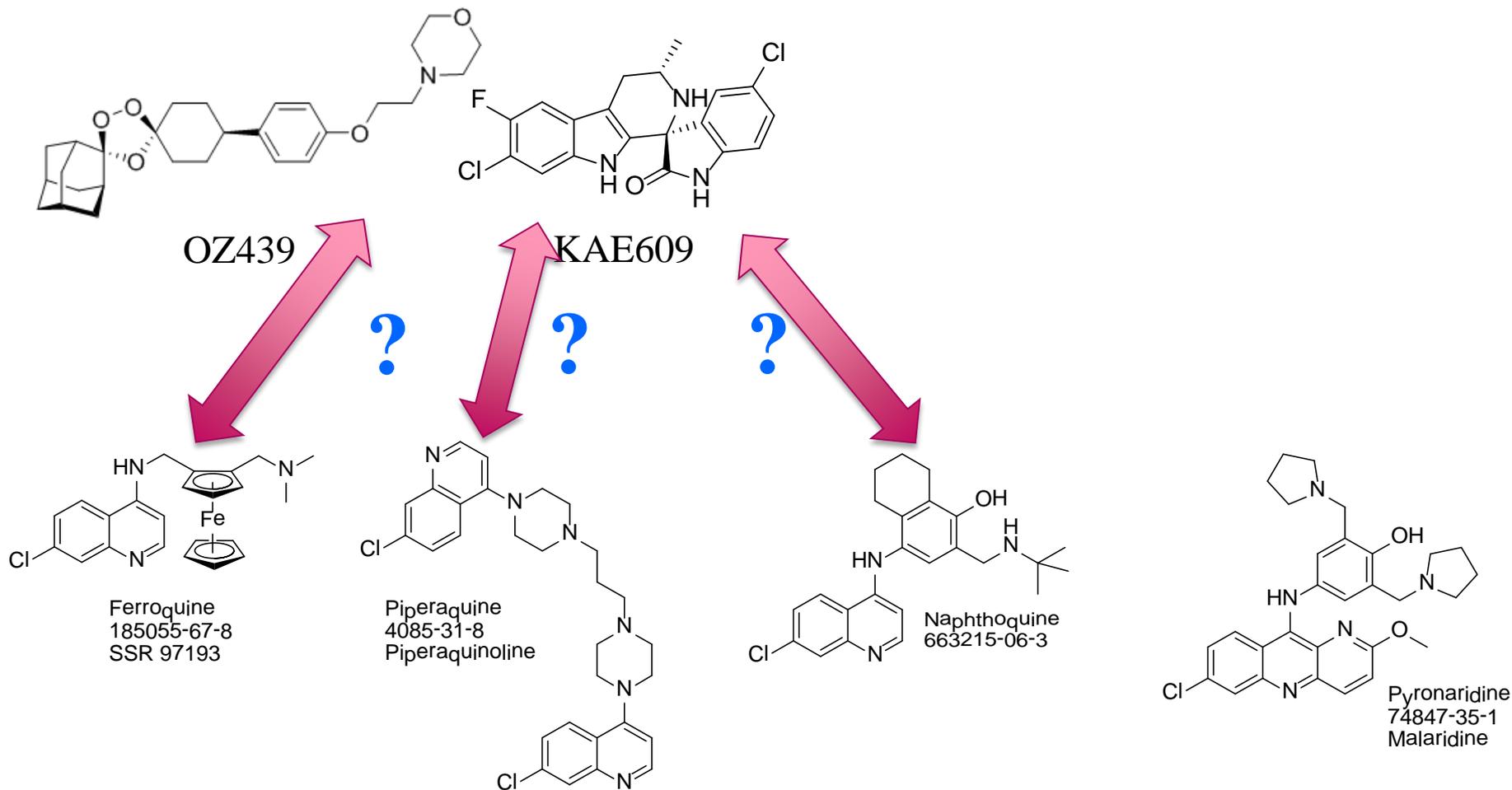
- Phase I defines safe dose, parasite reduction rate, PK
- (Phase IIa in non-immunes confirms data at high parasitaemia – usually in *P.vivax*)
- Drug interaction studies - in the right population?
- Combination phase IIb studies: 3 doses, different age groups, African children

# Partnering strategy in Phase IIb 2013 perspective



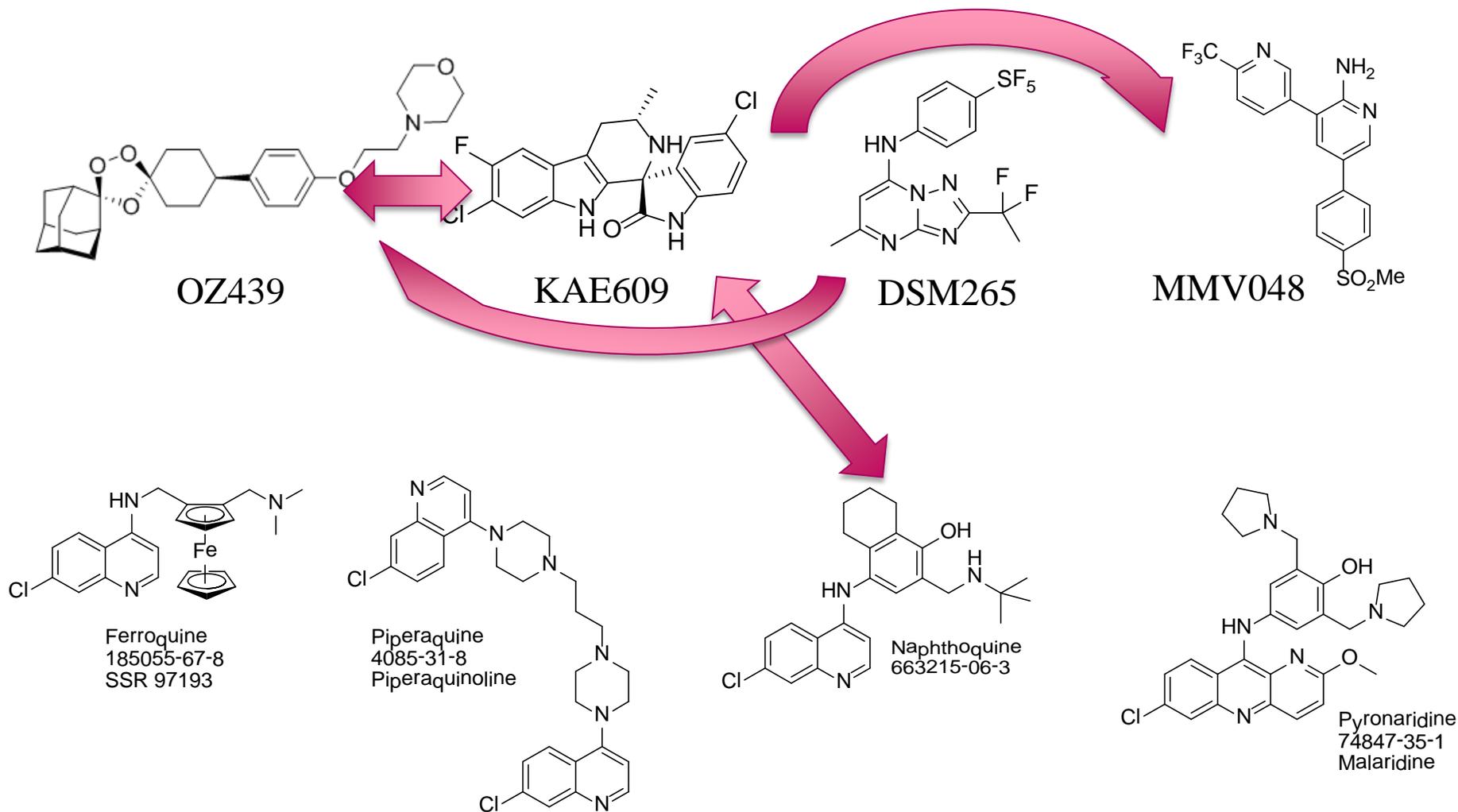
New molecule pairs with matched pharmacokinetics and overlapping properties

# Partnering strategy in Phase IIb 2013 perspective



New molecule pairs with matched pharmacokinetics and overlapping properties

# Partnering strategy in Phase IIb 2014 perspective for EDCTP2



ANThEM: Match the properties of rapidly expanding combinations with the needs of African patients

# Managing the risk of attrition

- 3 new clinical candidates per year
- Target convergence PFATP4
  - 21A092 (Drexel) Preclinical; phase I 2014 ?
  - SJ733 (St Judes) Preclinical; phase I 2015?
- Back-up compounds, de-risking frontrunner
  - MMV'048 follow up; preclinical 2014
  - DSM265 follow up; preclinical 2014
- New classes of molecule
  - DDD498 (Dundee) Preclinical; phase I 2015

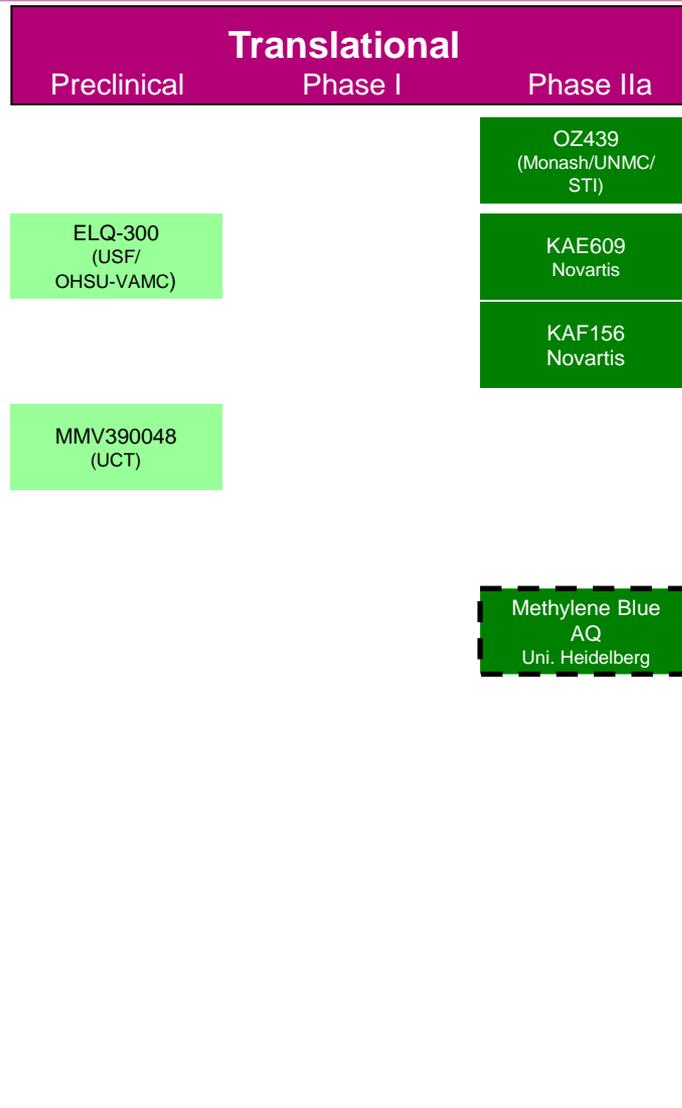
# Global Portfolio of Antimalarial Medicines

## Workstream 3: transmission blocking

Translational		
Preclinical	Phase I	Phase IIa
P218 DHFR (Biotec/Monash/ LSHTM)	DSM265 (UTSW/UW/ Monash)	OZ439 (Monash/UNMC/ STI)
ELQ-300 (USF/ OHSU-VAMC)	Antimalarial Actelion	KAE609 Novartis
21A092 (DrexelMed/UW)	CDRI 97-78 Ipca	KAF156 Novartis
MMV390048 (UCT)	DF02 Dilafor	Ferroquine Sanofi
SJ557733 St Jude/Rutgers		Fosmidomycin Piperaquine Jomaa Pharma GmbH
NPC-1161-B University of Mississippi		Methylene Blue AQ Uni. Heidelberg
RKA182 Liverpool STM		SAR97276 Sanofi
		Artemisone UHKST

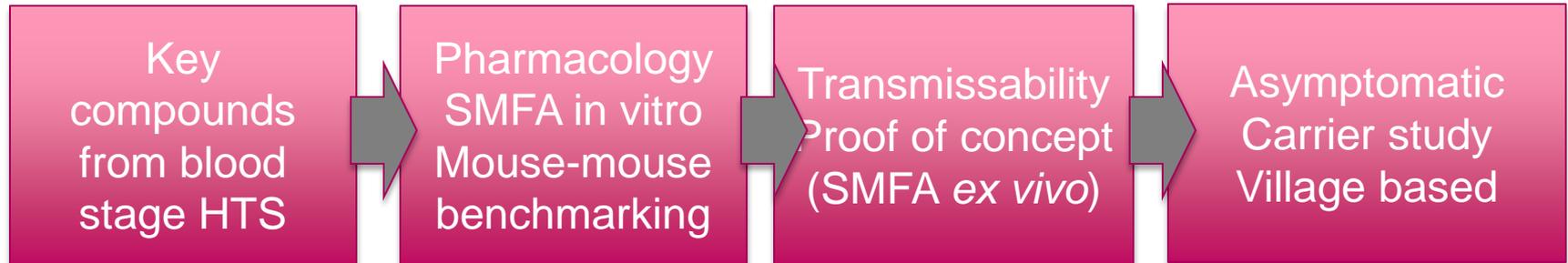
# Global Portfolio of Antimalarial Medicines

## Workstream 3: transmission blocking



# Global Portfolio of Antimalarial Medicines

## Workstream 3: transmission blocking



- All compounds can be registered based on blood schizonticide activity
- EMA/WHO informal feedback
  - Prove concept for blockade of transmission
  - Threshold of parasite free mosquitoes
- Standardized platform for SMFA, DFA

# Global Portfolio of Antimalarial Medicines

## Workstream 4: pregnancy

Translational			Development	
Preclinical	Phase I	Phase IIa	Registration	Phase IV
P218 DHFR (Biotech/Monash/ LSHTM)	DSM265 (UTSW/UW/ Monash)	OZ439 (Monash/UNMC/ STI)		Coartem® Novartis <b>APPROVED</b>
ELQ-300 (USF/ OHSU-VAMC)		KAE609 Novartis		
21A092 (DrexelMed/UW)		KAF156 Novartis		Eurartesim® Sigma-Tau <b>APPROVED</b>
MMV390048 (UCT)				Pyramax Shin Poong University of Iowa <b>APPROVED</b>
SJ557733 St Jude/Rutgers				
		Methylene Blue AQ Uni. Heidelberg		

Accelerate standard ICH reproductive toxicity to identify new 'front runners'

Safety database on ACTs in first trimester, N=600

Key safety data on differential toxicity for artesunate between rats and humans

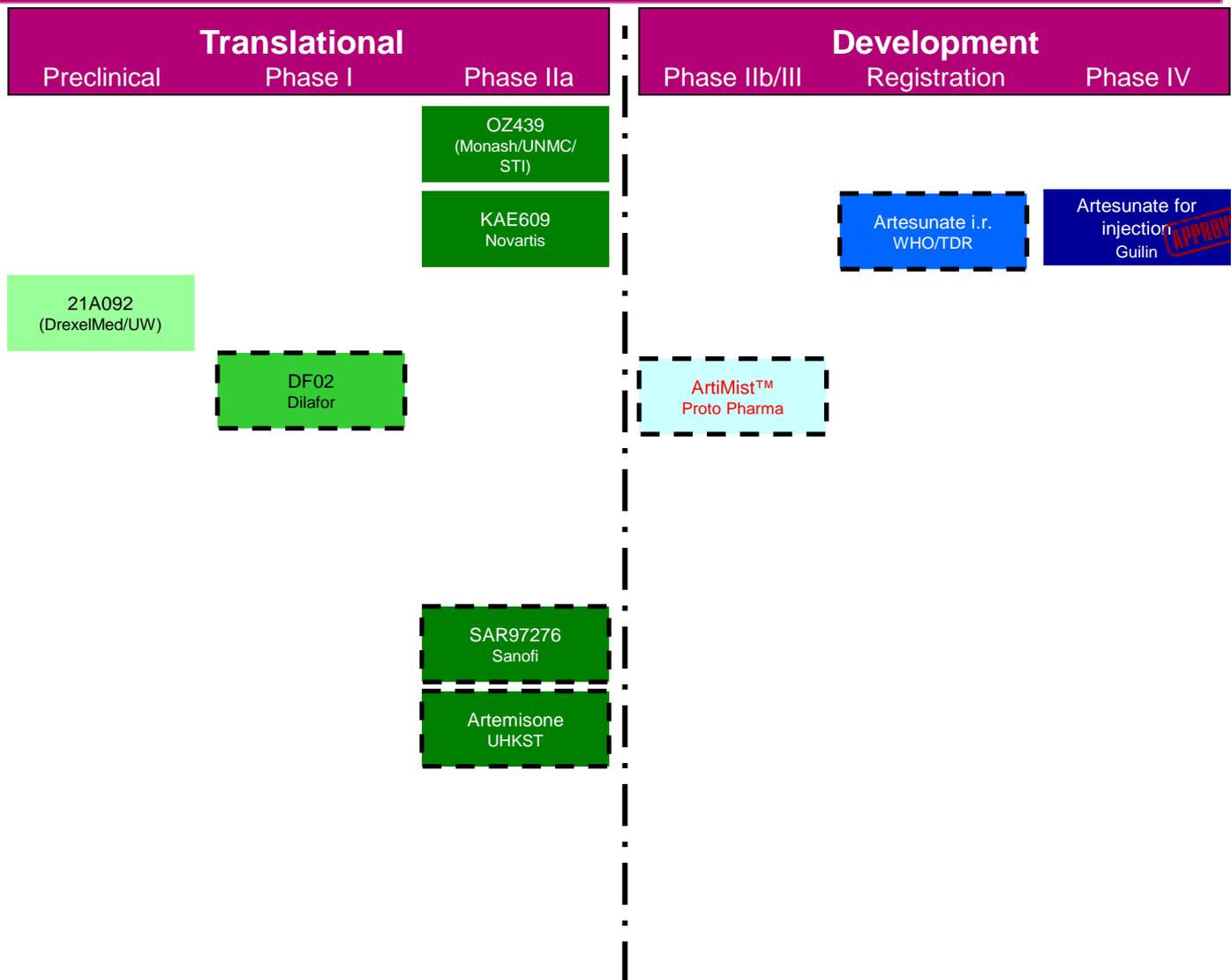
# Global Portfolio of Antimalarial Medicines

## Workstream 5: severe malaria

Translational			Development		
Preclinical	Phase I	Phase IIa	Phase IIb/III	Registration	Phase IV
P218 DHFR (Biotec/Monash/ LSHTM)	DSM265 (UTSW/UW/ Monash)	OZ439 (Monash/UNMC/ STI)	Tafenoquine GSK	Mefloquine Artesunate Farmaguinhos/DNDi	Coartem®-D Novartis <b>APPROVED</b>
ELQ-300 (USF/ OHSU-VAMC)	Antimalarial Actelion	KAE609 Novartis	Pyramax Paediatric Shin Poong/ University of iowa	Artesunate i.r. WHO/TDR	Artesunate for injection Guilin <b>APPROVED</b>
21A092 (DrexelMed/UW)	CDRI 97-78 Ipca	KAF156 Novartis	Eurartesim® Paediatric Sigma-Tau	Arterolane/PQP Ranbaxy	Eurartesim® Sigma-Tau <b>APPROVED</b>
MMV390048 (UCT)	DF02 Dilafor	Ferroquine Sanofi	ArtiMist™ Proto Pharma	ARCO Naphthoquine/ Artemisinin	Pyramax Shin Poong University of Iowa <b>APPROVED</b>
SJ557733 St Jude/Rutgers		Fosmidomycin Piperaquine Jomaa Pharma GmbH			ASAQ Winthrop sanofi /DNDi <b>APPROVED</b>
NPC-1161-B University of Mississippi		Methylene Blue AQ Uni. Heidelberg			
RKA182 Liverpool STM		SAR97276 Sanofi			
		Artemisone UHKST			SP-AQ Guilin <b>APPROVED</b>

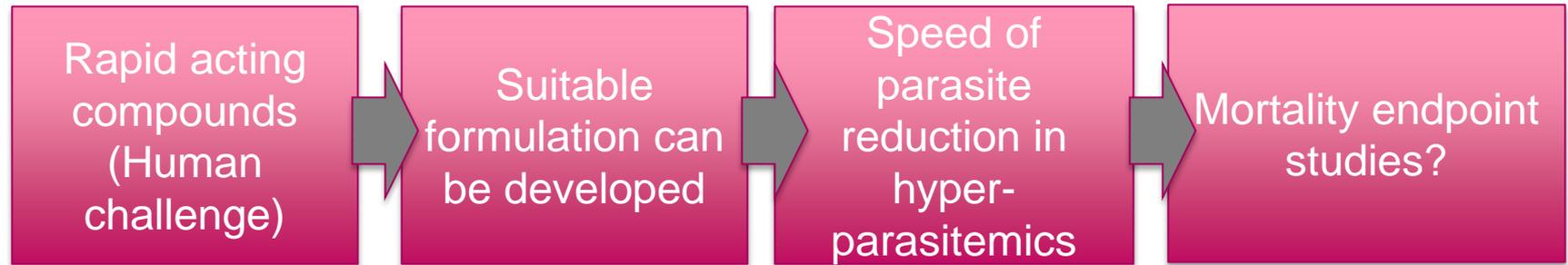
# Global Portfolio of Antimalarial Medicines

## Workstream 5: severe malaria



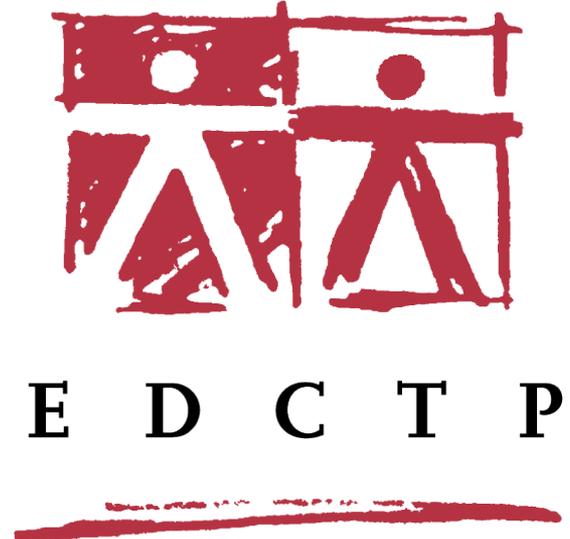
# Global Portfolio of Antimalarial Medicines

## Workstream 5: severe malaria



- Target Profile: rapid onset, active against artemisinin insensitive strains
- Formulation: parenteral, sub-lingual (spray?), suppository
- Need standardized testing cascade
- Cast the net wide: piperazine has a PRR as fast as artesunate.

# Suggested priority workstreams for malaria medicines



1. Making medicines safe for all
2. Unparalleled opportunities in uncomplicated malaria
3. Transmission blocking: parallel track with vaccines
4. Picking the winners for pregnancy
5. Severe malaria: parasite reduction platform