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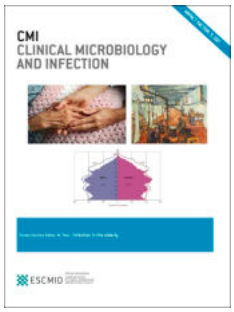

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PII: S1198-743X(25)00127-2

DOI: https://doi.org/10.1016/j.cmi.2025.03.009

Reference: CMI 3953

To appear in: *Clinical Microbiology and Infection*

Received Date: 18 October 2024

Revised Date: 12 March 2025

Accepted Date: 16 March 2025

Please cite this article as: Okwu DG, Manego RZ, Duparc S, Kremsner PG, Ramharter M, Mombo-Ngoma G, The non-artemisinin antimalarial drugs under development: a review, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2025.03.009.

The non-artemisinin antimalarial drugs under development: a review

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Abstract:

Background

In 2022, malaria caused approximately 249 million cases and 608000 deaths, primarily in Africa. Current treatments target asexual blood-stage parasites, gametocytes, and liver hypnozoites. Standard guidelines recommend a 3-day course of artemisinin-based combination therapies as first-line treatment of uncomplicated malaria and parenteral artesunate for severe malaria. However, emergence of partial resistance to artemisinin derivatives threatens the treatment efficacy, highlighting the urgent need for novel antimalarial drugs.

Objectives

This review summarizes recent progress in the clinical development of antimalarials particularly non-artemisinin compounds under target product profile (TPP)-1.

Sources

Data were gathered from the medicines for malaria venture (MMV) portfolio and clinical trial databases between 2020 and 2024.

Content

Sixteen clinical trials were reviewed, including safety and efficacy studies involving healthy volunteers, experimentally infected volunteers, asymptomatic *P. falciparum* carriers, and malaria patients. Six trials evaluated the safety and tolerability of MMV533, ZY19489, INE963, GSK701/MMV367, and intravenous KAE609 in healthy volunteers. Efficacy trials involving experimentally infected volunteers assessed ZY19489 and GSK701/MMV367, while studies on asymptomatic carriers tested ZY19489/ferroquine and cabamiquine/pyronaridine. Trials on malaria patients investigated combinations of ganaplacide/lumefantrine-SDF, cabamiquine/pyronaridine, both oral and intravenous cipargamin, and INE963.

Implications

Although attrition remains a possibility, several promising candidate drugs with novel modes of action are advancing through clinical development. Many are expected to become available for treating uncomplicated and severe malaria within the next decade. These new antimalarials could significantly enhance malaria treatment, reduce resistance, and support global health effort toward malaria control, elimination, and, potentially, eradication.

Keywords

Non-artemisinin antimalarial drugs, clinical development, medicines for malaria venture, target product profile, target candidate profile, uncomplicated malaria, severe malaria

Introduction

Despite major progress made in reducing malaria incidence and mortality over the last two and half decades, the latest malaria reports from the World Health Organisation (WHO) indicate that progress has stalled (1). *Plasmodium falciparum* and *P. vivax* are the two major parasitic species affecting humans and can cause uncomplicated and severe malaria. Relapsing malaria, where a form of the parasite remains dormant in the liver and can reactivate later, is caused by *P. vivax* and *P. ovale* (2). To date, the most effective way of preventing an uncomplicated case of malaria from developing into severe disease and death is through early diagnosis, prompt and efficacious treatment.

Recommended antimalarial drugs for the treatment of malaria

The development of new antimalarial therapy forms part of the WHO global technical strategy for malaria 2016—2030. Since 2006, the WHO malaria treatment guidelines recommended artemisinin-based combination therapies (ACTs) as first-line treatment against uncomplicated malaria caused by *P. falciparum* parasite (WHO, 2006). A 3-day course of these ACTs covers two asexual parasite life cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug after exposure to the artemisinin component for 48 hours. Shorter treatment courses (1—2 days) are currently not recommended as they appear less efficacious, have a smaller impact on gametocytes, and provide less protection for the slowly eliminated partner drug. However, the effectiveness of ACTs in real-world practice is substantially lower than the efficacy observed in research settings, due to multiple factors such as non-adherence to prescribed treatment regimens, including dosage, duration, and dietary requirements, as well as incomplete administration.

Besides ACTs, other currently licensed antimalarial treatment options for uncomplicated malaria include atovaquone-proguanil, and combination therapy of quinine or artemisinins with antibiotics clindamycin or tetracyclines. No further non-artemisinin drugs are currently recommended for the treatment of malaria.

Concerning severe malaria, WHO recommends intravenous or intramuscular administration of injectable artesunate until the patient can tolerate oral medication. The treatment must be completed with the sequential administration of three days of an ACT. Rectal artesunate can be used as a pre-referral intervention administered at the community level until reaching the healthcare facility.

Relapsing malaria can be prevented by radical cure of *P. vivax* and *P. ovale* species through the administration of a combination therapy using chloroquine or an ACT for the blood stage, and primaquine to clear the relapsing form of the parasite in the liver. An alternative to primaquine is tafenoquine, a drug registered in the US and in Australia since 2018 and used in combination with chloroquine for the treatment of blood stages of the parasite.

Malaria chemoprevention programs

Malaria chemoprevention involves using antimalarial drugs to prevent malaria in vulnerable populations. For pregnant women, intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) given monthly from the second trimester onwards is recommended for all high transmission settings. In the African Sahel region where malaria is highly seasonal, seasonal malaria chemoprevention (SMC) with SP and amodiaquine (AQ) involves a monthly administration of SP-AQ (single-dose SP and AQ once a day for 3 days) to children from 6 months to 5 years of age. Finally, other preventive treatment programs are discussed and partly recommended including school-based intermittent preventive treatment of malaria and intermittent preventive treatment in young children.

Current challenges to effective antimalarial therapy

A challenge to effective treatment has been the emergence of parasites with resistance, and partial resistance to artemisinin derivatives, the latter manifested by delayed parasite clearance after therapy, as seen over the past years in the Greater Mekong sub-region in Southeast Asia (3,4). Importantly, partial artemisinin resistance has been reported from several countries in the Central and Eastern African region (5). The spread of drug resistant isolates needs to be contained and novel drug regimens need to be developed to ensure high cure rates for malaria in the coming years. Another significant

challenge is the risk of (severe) haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency when treated with primaquine and tafenoquine. Therefore, G6PD screening is recommended before treatment but such testing facilities are often unavailable in many regions.

Besides this, there is also an urgent need for simpler antimalarial regimens , such as a single-dose cure (6). Not only would such a medicine facilitate “directly observed therapy”, but it would also reduce the cost of treatment (7,8).

One ultimate goal for the development of next-generation antimalarial drugs is a combination of new compounds that blocks all developmental stages and is potent enough to work as a curative single-dose, described as a single encounter, radical cure, and prophylaxis (SERCaP) treatment. This combination will also have to be affordable to the population in need of these drugs (9–11).

In this review, we describe non-artemisinin antimalarial drugs that are currently under clinical development to face multidrug-resistant malaria, strains with partial artemisinin resistance, and the need to provide simplified treatment regimens.

Search strategy

The medicines for malaria venture (MMV) ’s portfolio of antimalarial drug research, development, and access was used together with clinical trial databases for this review. MMV is a not-for-profit organization instrumental in the clinical development of new antimalarial drugs by collaborating with academic and pharmaceutical partner institutions.

The compounds in clinical development phases were identified and categorized according to the target product profile (TPP), that is whether the product is for uncomplicated malaria, severe malaria, prevention of relapse, prereferral intervention, intermittent preventive treatment, and chemoprophylaxis. Only the non-artemisinin TPP-1 – case management compounds were selected for this review as these classes include drugs with truly novel modes of action. Further categorization included the target candidate profile (TCP), meaning whether the target was aiming for transmission

reduction, relapse prevention, paediatric formulation, chemoprevention or asexual stages. A search for clinical trials conducted between 2020 and 2024 was done on the MMV's website, clinical trials databases (clinicaltrial.gov, ISRCTN, PACTR, ICTRP, EU Clinical trials registry, ANZCTR), and PubMed.

Antimalarial product development partnership and drugs discovery

Following the stalling of drug development against neglected diseases in the 1990s (12), an innovative collaborative approach to research and development of medicines emerged in the form of public-private partnerships that were designated as product development partnership (PDP). The leading PDP in antimalarial drug research, MMV was founded in 1999. MMV's mission is to reduce the burden of malaria in endemic countries through the discovery, development, and delivery of new, effective, and affordable antimalarial drugs. Globally, the largest portfolio of antimalarial drug research and development and access projects ever assembled is managed by MMV and its partners (Figure 1).

Concerns about drug resistance have led to this antimalarial PDP that has brought together universities, research institutions, the pharmaceutical industry, funding agencies, governments, non-governmental organizations, and the military, with collaboration from the global North and from the South working together to find possible replacement medicines.

The strategies for the development of new antimalarial medicines include the quest to improve existing success by expansion of the medicinal arsenal, but also a better design by identification of new molecular targets, and lastly by a renaissance and expansion of phenotypic screening of large compound libraries. The past decade has seen the development of new and more sophisticated phenotypic screens resulting in new drug candidates and targets. Potency, cost, ease of synthesis, known limitations to their use, and toxicity, in particular teratogenicity, are aspects on which further selection is based (13). Many of these compounds have now entered the clinical development program.

Target product profiles and target candidate profiles

Several changes in antimalarial target candidate profile (TCP) and TPP have occurred over the past years. New foci include new drugs and drug combinations to treat uncomplicated malaria and prevent transmission, and drugs used for chemoprevention. Finally, parenteral formulations are developed for the treatment of severe disease. As described in a review by Burrows and collaborators, with the ultimate goal to eliminate malaria, medicines that are well-tolerated to be used in vulnerable populations such as pregnant women, malnourished or co-infected patients, are required (14). TCPs and TPPs are summarized in Table 1. While this TCP and TPP strategy has been in place since 2017, a revision has been discussed over the past year and a new strategy will be published soon.

TPP-1 non-artemisinin antimalarial drug candidates in the early and product development stages of the pipeline

Human volunteers phase

As of May 2024, there were five candidates that were listed as TPP-1 in early development in human volunteer studies as shown in Table 2. Malaria human volunteer studies, also known as Controlled Human Malaria Infection (CHMI) studies, are a phase of research that involves infecting healthy volunteers with malaria parasites to study the disease and test new treatments.

MMV533 has undergone a clinical phase 1a study to assess the safety, tolerability, and pharmacokinetic profile of a single dose, enrolled 72 healthy volunteers from 2020 to 2022 (NCT04323306)(15) in Melbourne, Australia. A phase 1b study was conducted in 2022 to assess the safety, tolerability, and antimalarial activity of MMV533 against *P. falciparum* 3D7 blood stage infection in 9 healthy volunteers (NCT05205941)(16). Its key features include the rapid parasite killing *in vitro* and clearance in induced blood stage, the long half-life in human volunteers, and the potential for single-dose cures (17), and for use in pregnancy. The next step in its development is the identification of a combination partner and conduct of phase 2 clinical studies.

INE963 Phase 1 trial to assess safety, tolerability, and pharmacokinetics, placebo-controlled, in healthy volunteers was conducted in Nottingham, UK from 2021 to 2022, and enrolled 64 individuals

(NCT04896632)(18). It is being evaluated in the PLATINUM study that started in 2024 (NCT05750628)(19), a platform trial evaluating the parasiticidal effect and potential for cure with different antimalarial agents. INE963 is administered as monotherapy and in combination therapy with other antimalarial agents in adult and adolescent patients with uncomplicated *P. falciparum* malaria.

GSK701 or MMV367 first-in-human trials, which were designed as placebo-controlled studies to assess the safety, tolerability, and pharmacokinetics were conducted from 2022 to 2023 in Nottingham, UK, in 47 healthy volunteers (NCT05507970)(20). The Phase 1b study to characterize pharmacokinetic/pharmacodynamics relationship and safety was conducted in Australia in 2023 in 18 healthy adults experimentally infected with blood-stage *Plasmodium* (NCT05979207)(21).

Patient exploratory phase

The TPP-1 non-artemisinin antimalarial drug candidates in the exploratory and confirmatory stages are listed in Table 3. The patient exploratory phase includes compounds that are in phase 2 and phase 3 clinical trials.

Cipargamin (also known as KAE609), a PfATP4 inhibitor is being developed for the management of uncomplicated and severe malaria. Following clinical phase 1 studies of the oral cipargamin, a Phase 2a study was conducted to examine the efficacy, safety and tolerability in Iquitos, Loreto, Peru from 2021 to 2022 in 22 adult patients with acute uncomplicated malaria (NCT04709692)(22,23). This novel drug is part of the PLATINUM study (19). Intravenous cipargamin has been evaluated in a phase 1 placebo-controlled study for its safety and tolerability of single and multiple ascending intravenous doses in 2020 in 57 healthy volunteers (NCT04321252)(24,25). A phase 2 study evaluating the efficacy, safety, tolerability, and pharmacokinetics of intravenous cipargamin in adult and paediatric participants with severe *P. falciparum* malaria (KARISMA) is ongoing since 2022 (NCT04675931)(26). Importantly this study is also evaluating a new composite endpoint, that could replace the regulatory mortality endpoint in phase 3 studies. It is based on patient survival, parasite clearance, and the

absence of key complications of severe malaria and may prove instrumental to accelerate drug development for severe malaria in the future.

The combination ZY19489+ferroquine is being evaluated in a phase 1 single center, placebo-controlled dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and parasite clearance in adult asymptomatic carriers of *P. falciparum* in Gabon (NCT05911828)(27). A phase 1 placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics of ZY19489 in healthy adults was conducted from 2021 to 2022 in India (NCT05206201)(28). Another Phase 1 study using the *P. falciparum* induced blood stage malaria (ISBM) model to determine the safety and tolerability and to characterize the antimalarial activity of a single-dose oral administration of ZY19489 in 24 healthy adult volunteers was conducted in Australia from 2019 to 2020 (ACTRN12619001215112) (29).

Following a first-in-human volunteer infection study and a trial evaluating its chemoprophylactic activity (30,31), a Phase 2 study assessing the safety, efficacy, and pharmacokinetics of the combination M5717+pyronaridine in adults and adolescents with acute uncomplicated *P. falciparum* malaria (CAPTURE-1) is ongoing (NCT05689047)(32). Another study investigates the potential of this drug combination as chemoprevention in adults and adolescents with asymptomatic *P. falciparum* (CAPTURE-2) and is also currently ongoing (NCT05974267)(33).

The combination of ganaplacide (also known as KAF156) with lumefantrine-solid dispersion formulation LUM-SDF (a new formulation of lumefantrine with an improved bioavailability that allows once daily dosing), developed for the case management of uncomplicated malaria was evaluated in a clinical phase 2 trial to determine the most effective and best tolerable dose at the shortest dosing regimen (NCT03167242)(34). It has just completed a phase 2 study to evaluate efficacy, safety, and tolerability in paediatric population with uncomplicated malaria (KALUMI) (NCT04546633)(35), and in parallel it has started a Phase 3 study of its efficacy, safety, and tolerability in adults and children with uncomplicated *P. falciparum* malaria (KALUMA) (NCT05842954)(36). This drug combination is part of

the platform trial evaluating the efficacy and safety of antimalarial agents in patients with uncomplicated *P. falciparum* malaria (PLATINUM) (NCT05750628)(19).

Discussion

Based on the highly successful collaboration of MMV with academic and pharmaceutical partners over the past 20 years, there is a robust pipeline of preclinical drug candidates and clinically developed drugs. Among them, there are several non-artemisinin antimalarial drug candidates for case management that are currently in the clinical development pipeline.

Rational clinical development of antimalarial drugs increasingly relies on the concepts of TCP and TPP. Given the latest updates, new drugs will require to fulfil a set of features to be successfully developed for registration. This includes favourable safety – including the absence of teratogenicity – and tolerability that allows the use of drugs in all patient populations including vulnerable groups such as pregnant women and children. Shorter treatment durations than the current 3-day regimens will improve patient adherence and thus reduce the selective pressure for antimalarial drug resistance. Whether single-encounter treatment or multiple-dose, single-day treatments as proposed recently will prove more beneficial in real-life settings, it will only be known after registration and large-scale implementation (7,8). Next-generation antimalarials will most likely constitute combinations of two or more drugs that will ideally have independent modes of action, similar pharmacokinetic profiles, and a low propensity to induce specific drug resistance. Activity on sexual developmental forms has the added benefit of reducing onward transmission of malaria.

Fortunately, several of the above-mentioned drugs and drug combinations currently in clinical development tick many of the boxes required for next-generation antimalarials. While this situation seems comforting, we currently observe a race between the rapidly evolving development of drug resistance in the most highly endemic regions of sub-Saharan Africa and the often slow-appearing pace in the clinical development of drugs until reaching regulatory approval. While diligence is required in

the regulatory pathways, we herewith highlight the urgent need for new antimalarial drugs entering the routine medical practice in the highly endemic regions of sub-Saharan Africa in the next few years.

This review based on the MMV antimalarial portfolio might not show the full picture of drugs in clinical development as the Global portfolio of antimalarial medicines shows more drug candidates including non-artemisinin TPP-1 compounds such as fosmidomycin or AQ-13 among many others.

Conclusion

While the occurrence of partial resistance against artemisinins in sub-Saharan Africa has led to an urgent need for new, highly efficacious antimalarial drug regimens, the current clinical development pipeline includes several highly promising drugs. Though attrition cannot be ruled out until the end of the clinical development pathway, we are confident that new drug regimens with novel modes of action will become available for the treatment of uncomplicated malaria and severe malaria within a decade. Given the ever-evolving propensity for antimalarial drug resistance, no complacency is to be put in place, and measures to speed up the clinical development pathway for new antimalarial drugs are needed.

Conflict of interest disclosure

The authors have declared no competing interests.

Contribution of authors

Writing-original draft: DGO and GMN; Writing-review and editing RZM, SD, PGK and MR; Conceptualization GMN, RZM and MR.; Methodology: RZM, PGK, MR, and GMN; Investigation: RZM, DGO and GMN; Visualization: DGO, RZM and GMN; Project administration: RZM, MR, and GMN.

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Table 1| Target Product Profiles and Target Candidate Profiles of antimalarial drugs

Profile	Intended use
TPP-1	Case management; treatment of acute uncomplicated malaria in children or adults. Uses a combination of two or more molecules with TCP-1 activity, plus TCP-5 for reducing transmission and TCP-3 for relapse prevention, when such molecules become available For severe malaria, a parenteral formulation of a single fast-acting TCP-1 would be appropriate
TPP-2	Chemoprotection: given to subjects migrating into areas of high endemicity, or during epidemics. Uses a combination of TCP-4 activity, potentially with TCP-1 support for emerging infections
TCP-1	Molecules that clear asexual blood-stage parasitemia
TCP-2	(profile retired, see article Burrows et al. 2017)
TCP-3	Molecules with activity against hypnozoites (mainly *P. vivax*)
TCP-4	Molecules with activity against hepatic schizonts
TCP-5	Molecules that block transmission (targeting parasite gametocytes)
TCP-6	Molecules that block transmission by targeting the insect vector (endectocides)

Table 1| Antimalarial compounds in the human volunteers stage of development

Product name	TPP / TCP	MOA	Key features	Clinical trials phases
MMV533 (Sanofi)	TPP-1 TCP-1	Unknown, inability to select resistance mutants	• Rapid parasite killing *in vitro* and clearance in induced blood-stage • Long half-life in human volunteers • Potential for single-dose cures (Murithi et al. 2021) • Potential for use in pregnancy	Phase 1 study to assess the safety, tolerability, and pharmacokinetic profile of a single dose of MMV533 conducted from 2020 to 2022 (NCT04323306). Volunteer infection Phase 1b study to assess the safety, tolerability and antimalarial activity of MMV533 against *Plasmodium falciparum* 3D7 blood stage infection in healthy volunteers completed in 2022 (NCT05205941). Next milestone: identification of a combination partner and conduct Phase 2 clinical study
INE963 (Novartis)	TPP-1 TCP-1	Novel and unknown	• No cross-resistance • No resistant mutant identified • Low predicted dose, long half-life in human (60 h) • Fast killing	Phase 1 study in healthy volunteers successfully completed in 2022 (NCT04896632). Phase 2 study, PLATINUM (NCT05750628), started in 2024, estimated completion by 2026.
MMV367 / GSK701 (GSK)	TPP-1 TCP-1	Novel, interference with *P. falciparum* Acyl-CoA synthetase 10/11	• Novel chemical class • Highly potent and active against sensitive and resistant strains • Fast killing • Potential single-dose cure	Phase 1a completed in 2023 (NCT05507970), Phase 1b (healthy volunteer infection) completed (NCT05979207) Next milestone: start of Phase 2 studies
GSK484 (GSK)	TPP-1 TCP-1	Novel and unknown	• Fast killing • Very low propensity to select for resistance	Phase 1a study underway (NCT06171113)

			• Low predicted dose and long predicted half-life	
IWY357 (Novartis)	TPP-1 TCP-1	Novel and unknown	• No cross-resistance • No resistant mutants identified • Low predicted dose and long predicted half-life • Fast killing	Next milestone: first-in-human Phase 1 clinical study

TPP: Target Product Profile; TCP: Target Candidate Profile; MOA: Mode of Action

Table 1| Antimalarials in the patient exploratory and confirmatory stages of clinical development

Product name	TPP	MOA	Key features	Clinical trials phases
Cipargamin (Novartis)	TPP-1 TCP-1,5,6 Uncomplicated and severe malaria	PfATP4 inhibitor	• Novel mechanism of action for resistance management • Potentially simplified dosing schedule • Very rapid killing of parasites • Potential for transmission-blocking activity	• Phase 2 oral malaria patient study completed (Schmitt et al. 2022) • First-in-human study with intravenous formulation completed (Venishetty et al. 2024) • Phase 2 monotherapy study in severe malaria patients ongoing (NCT04675931) • Phase 2 study, PLATINUM (NCT05750628), started in 2024, estimated completion by 2026.
ZY19489+ferroquine (Zydus)	TPP-1 TCP-1	ZY19489 new class of inhibitors, mechanism of action unknown Ferroquine (FQ), a aminoquinoline, inhibitor of haem detoxification	• ZY19489: No stable resistance detected in *in vitro* or clinical studies • FQ: long duration of plasma exposure, fully active against amodiaquine and piperaquine resistant strains*	• ZY19489: First Phase 1 Multiple Ascending Dose completed in 2022 (Barber et al. 2022) • FQ: Two phase 2 studies in combination with OZ439 completed in 2020; • ZY19489+ferroquine combination to be evaluated in asymptomatic carriers of *P. falciparum* (NCT03911828)

M5717+pyronaridine (Merck KGaA / Shin Poong)	TPP-1 TCP-1,4,5,6	• M5717: *P. falciparum* EF2 inhibitor • Pyronaridine: pleotropic effect including inhibition of hematin formation, and haem degradation. Interferes with the digestive system of the parasite by modifying food vacuoles	• M5717: long half-life and comparable activity across all stages of the malaria parasite lifecycle; transmission blocking activity, active against schizonts • Pyronaridine: fast acting and long duration	M5717: First-in-human study volunteer infection studies completed (McCarthy et al. 2021); and study of chemoprophylactic activity (Plas et al. 2023) M5717+pyronaridine: ongoing Phase 2a study in adults and adolescents with uncomplicated Plasmodium falciparum malaria – CAPTURE 1 (NCT05689047); and as chemoprevention in adults and adolescents with asymptomatic plasmodium falciparum infection – CAPTURE 2 (NCT05974267).
Ganaplacide-lumefantrine-SDF (Novartis)	TPP-1 TCP-1,4,5,6	Ganaplacide: Effect on parasite internal protein secretory pathway Lumefantrine-SDF: New formulation of lumefantrine with improved bioavailability, inhibits the parasite conversion of toxic haem to non-toxic hemozoin	• Rapid killing of parasites (PCT<48h) • Potential transmission blocking activity • Early liver stage activity	Phase 2b combination study completed Phase 2b study in paediatric population (KALUMI) ongoing (NCT

TPP: Target Product Profile; TCP: Target Candidate Profile; MOA: Mode of Action

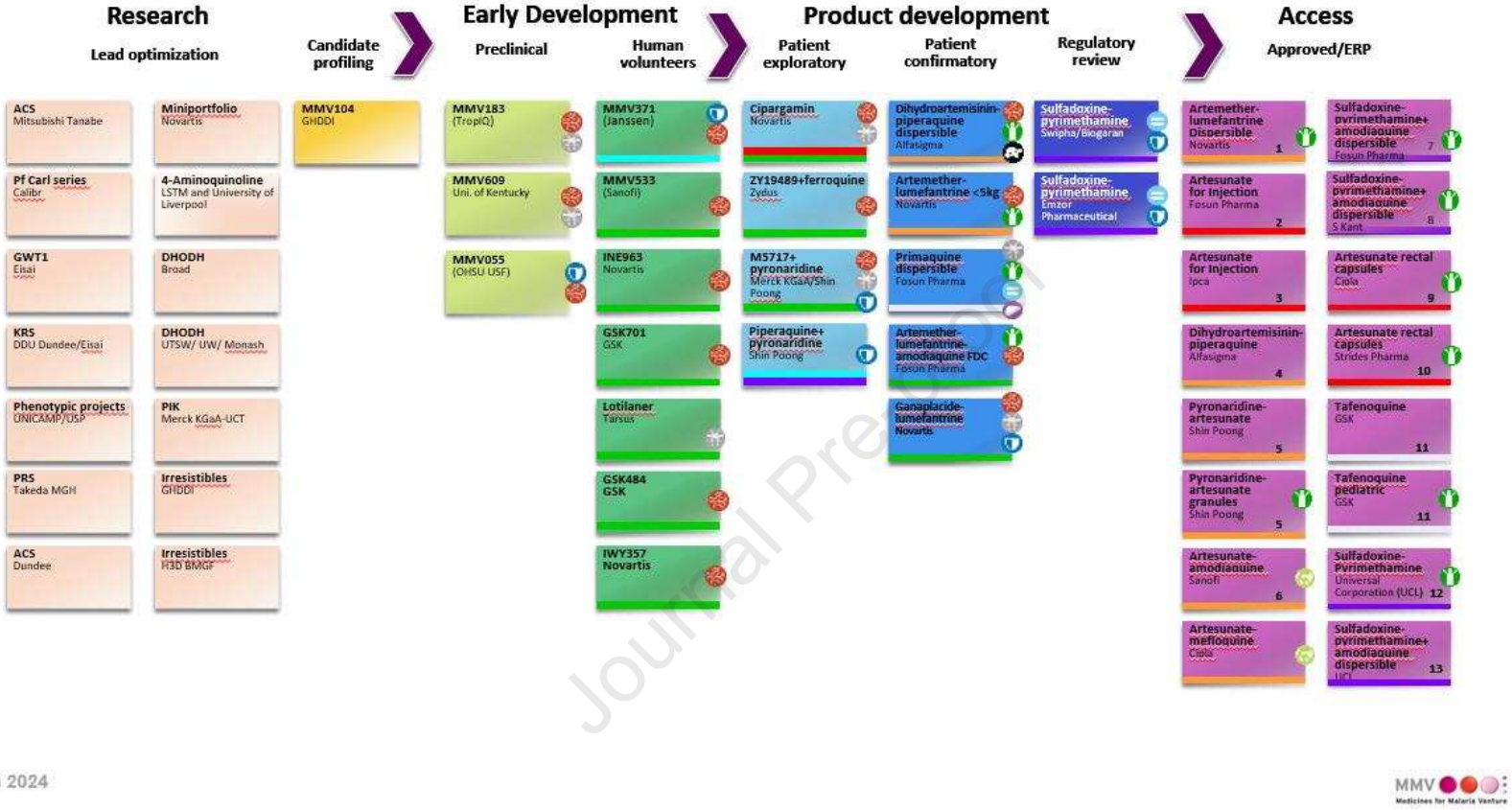

Figure 1| Medicines for Malaria Venture supported projects (From MMV website www.mmv.com)

MMV support to projects may include financial, in-kind, and advisory activities.
Footnotes: Included in MMV portfolio after product approval and/or development. DND*i* and partners completed development and registration of ASMQ and ASAQ. | Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing | Pediatric formulation. | Via a bioequivalence study. Past partners are in brackets (-).

Brand names 1: Coartem® *Dispersible*; 2: Artesun®; 3: Larinate® 60 mg; 4: Eurartesim®;
5: Pyramax® tablets or granules; 6: ASAQ Winthrop®; 7: SPAQ-CO™; 8: Supyra®
9: 100 mg Artesunate Rectocaps; 10: Artecap™; 11: *Kozenis or Krintafel* (Trademarks owned or licensed by GSK); 12: Wiwal®