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Global Accelerator for Paediatric formulations
WHO Hosted Network

World Health Organization

Paediatric drug optimization for malaria

Meeting report, 24-26 June 2025

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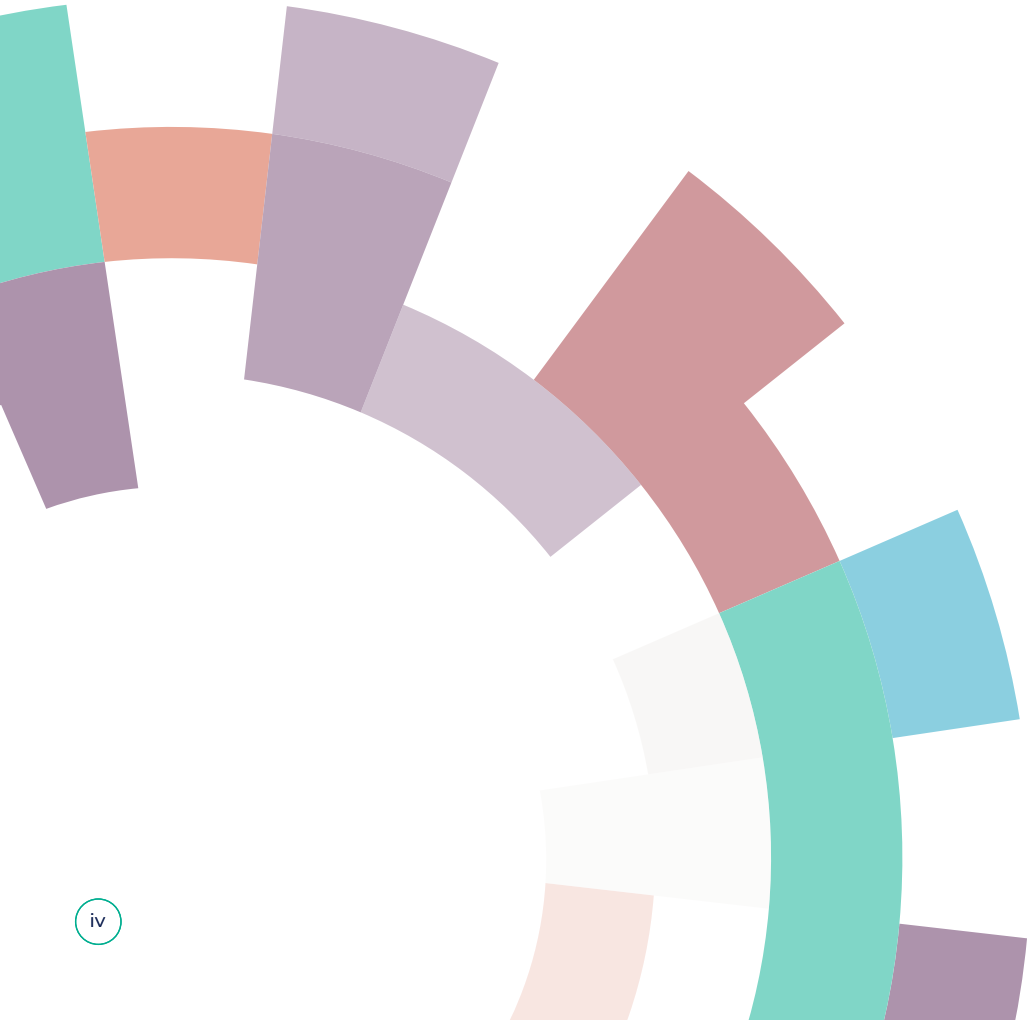


The need for paediatric drug optimization

The development of medicines for children lags unacceptably behind that for adults by nearly a decade

Following the resolution at the Sixty-ninth World Health Assembly on promoting innovation and access to quality, safe, efficacious and affordable medicines for children, WHO and partners have increased their efforts to deliver on this global commitment and have scaled up activities to ensure that age-appropriate formulations are available for children *(1)*. The Global Accelerator for Paediatric Formulations Network (GAP-f), a WHO-hosted network, works across the life cycle of drug development to accelerate the investigation, development and introduction of optimal formulations for children *(2)*. Priority-setting is the first step to enable a targeted approach to research and development. Developing a priority drug portfolio of the most needed formulations for children is essential to streamline researchers' and suppliers' efforts and resources around specific dosage forms and formulations that address the most urgent needs of children. This is especially important since the market for medicines for children is often small and/or fragmented, resulting in limited volumes with potential market failures.

Paediatric drug optimization (PADO) exercises to identify key priority products and their preferred product characteristics for research and development have been successfully undertaken for human immunodeficiency virus (HIV), hepatitis C, tuberculosis, coronavirus disease 2019 (COVID-19), antibiotics, neglected tropical diseases and childhood cancer, demonstrating their potential and impact to accelerate access to optimal formulations in the context of fragmented, small markets for medicines for children. To provide further guidance to support similar processes for optimizing drugs for children in other disease areas, GAP-f has published a guidance document to undertake a PADO process and adapt it to the specific needs of each disease area *(3)*.

PADO processes are not processes for developing guidelines and as such are not intended to endorse the use of products that have not been fully assessed by a WHO guidelines development group. However, prioritization provides a clear signal that specific formulations and products are of interest in the short-, medium- or long term and that stakeholders should work together towards completing investigation and development of age-appropriate formulations.

PADO for malaria

Of all the causes of childhood mortality, malaria is among the top killers.

Globally in 2023, there were an estimated 263 million malaria cases and 597 000 malaria deaths in 83 countries, with the WHO African Region carrying the highest share of the global malaria burden (94% cases, 95% deaths). Children under 5 years of age accounted for about 76% of all deaths due to malaria in the Region. This translates into a daily toll of over 1000 children under the age of 5 years *(4)*. Children may go on to suffer up to 13 episodes of malaria a year, after one episode of *Plasmodium falciparum* malaria *(5)*. The other main species of the malaria parasite, *Plasmodium vivax*, can remain dormant in the liver only to reawaken even in the absence of a new mosquito bite. This species is prevalent in South America and South-East Asia, and causes relapsing malaria, which contributes significantly to global malaria morbidity *(6)*.

Infants and children under 5 years of age are also at higher risk of severe malaria. Severe anaemia, hypoglycaemia and cerebral malaria are features of severe malaria, more commonly seen in children than in adults. Without treatment, severe malaria can rapidly become fatal.

Although children are the main age group affected by malaria, historically, few antimalarial medicines have been developed with their needs in mind. Moreover, most active pharmaceutical ingredients of malaria medicines are bitter, potentially causing children to vomit and thereby impacting the effectiveness of treatment and adherence. Furthermore, only the first dose is given by a health-care worker under direct observation.

Parents or caregivers must continue to treat their sick children at home. This makes it hard to guarantee that children will complete their treatment course, which is critical to ensure a complete and efficacious cure. Incomplete dosing can also contribute to a larger problem – the development of drug resistance.

Following resolution 60.20 on better medicines for children at the Sixtieth World Health Assembly in 2007, several stakeholders joined forces to promote child-friendly medicines that would meet the requirements for dosing, tolerability and ease of administration *(7)*. The most updated WHO Essential Medicines List for children (WHO EMLc) (2025, 10th edition) now includes child-friendly formulations of many antimalarial medicines, including fixed-dose combinations (FDCs) *(8)*. The manufacturing of these formulations continues to be fostered through the WHO Prequalification Expression of Interest (PQ EOI) *(9)*.

Despite this progress, several gaps remain. Child-friendly formulations need to be available for all antimalarial medicines to ensure that children can have access to the medicines they need. Moreover, paediatric formulations typically cost more than tablets for adults.

Meanwhile, the pipeline for antimalarial medicines has been strengthened in recent years to tackle drug resistance and include new treatment options, with a focus on new mechanisms of action and simplified regimens *(10)*.

Objectives

The objectives of PADO for malaria were as follows:

- to review the options available for the treatment and prevention of malaria and discuss whether age-appropriate formulations that need to be given priority for development (PADO priority list, 3–5 years) are missing. These included:
  - medicines and formulations listed in the antimalaria section of the WHO EMLc and for which gaps in age-appropriate formulations had been flagged (*11*);
  - medicines and formulations recommended in WHO guidelines;
- to review candidates for the treatment or prevention of malaria that are being investigated clinically, including new chemical entities as well as combinations of medicines approved for use in children as individual medicines but not yet evaluated as a combination by WHO, and identify promising candidates that should be prioritized for investigation and development for children (PADO watch list, 5–10 years);
- to review products that have been developed, approved and recommended by WHO and discuss the challenges related to their access, uptake and roll out to identify those that require specific actions towards increased access (PADO access list);
- to develop a clear research agenda to support and enable future optimization work, with the goal of ensuring that the unique needs of children are effectively addressed.

The PADO–malaria exercise enables alignment between funders, procurers, market coordination entities, researchers, innovators, generics manufacturers, product development partnerships and regulators on priority products to be investigated and developed. Increasing efforts are needed to tackle challenges in access to available and upcoming interventions for malaria in low- and middle-income countries (LMICs).

Methods

Available resources published by WHO for malaria were reviewed, including the latest WHO guidelines *(12)*, and the WHO publication on implementation of multiple first-line therapies (MFT) as part of the response to antimalarial drug resistance *(13)*. Relevant resources published by other partners were also reviewed, including target product profiles and target candidate profiles published by the Medicines for Malaria Venture *(14)*, as well as the global portfolio of antimalarial medicines *(10)*.

For the priority-setting exercise of approved and recommended medicines, the 9th WHO EMLc (2023) and the 2024 WHO guidelines for malaria *(12)* were used as reference documents. Medicines discussed included those for which gaps in availability of age-appropriate formulations were identified as part of a previously conducted review of age-appropriateness of formulations on the WHO EMLc *(11)*. Such a review had been conducted by designing and applying a quality target product profile tool that considered various paediatric-centric attributes, including the target population, dose flexibility and acceptability for younger and older children, administration and excipients, storage and shelf-life and market authorizations *(15)*. The specific needs of, and challenges associated with, medicine supply in LMICs were considered. Targets for each of the proposed attributes were then defined based on regulatory guidance documents, taking into consideration the needs of paediatric patients as well as LMICs. A qualitative scoring method was proposed to assess each medicine dosage form against the target for the predefined attribute. For medicines recommended by WHO but not yet included in the WHO EMLc (tafenoquine), the quality target product profile tool was applied to assess age-appropriateness *(15, 16)*.

For ease of discussion, the priority-setting exercise was conducted by grouping medicines depending on the indication (severe malaria, prevention of relapse, uncomplicated malaria, chemoprophylaxis), followed by a final consolidation of all priorities.

For new chemical entities and new combinations of existing medicines not yet reviewed by WHO in guidelines, the global portfolio of antimalarial medicines published by the Medicines for Malaria Venture was used as a starting point *(10)*. Only candidates in late-stage clinical development (Phase II or III) were considered for priority-setting. The information was complemented by a targeted literature review and reach out to developers, to assess whether candidates were still being actively investigated and collect additional information. Compounds for which development had stalled were included in the discussions if developers provided insight into the reasons for discontinuation and they were considered worthy of further examination.

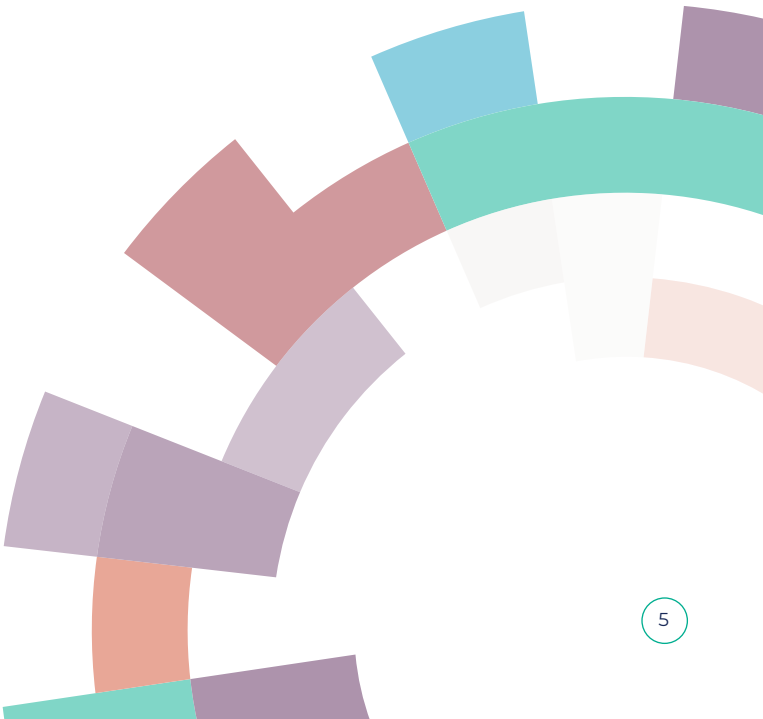
Adjuvant therapies, compounds with unknown status of development and no updates in the past two years, as well as monoclonal antibodies were outside the scope of the PADO–malaria meeting. A priority-setting exercise for monoclonal antibodies was deemed premature at this stage, given the current stage of development and the uncertainty of their role and potential in malaria management in the future.

Before the meeting, two dedicated priority-setting frameworks were developed (Table 1) and populated with information collected from relevant WHO documents, scientific publications, clinical trial databases and ad-hoc outreach to relevant developers.

After the PADO–malaria meeting, a public consultation was launched and disseminated via relevant networks and social media to solicit broader community feedback on the PADO-malaria meeting outcomes *(17)*.

Table 1. Attributes of antimalarial agents included in the priority-setting frameworks of PADO for malaria

Antimalarial agents approved and recommended by WHO	Antimalarial agents under clinical investigation (new chemical entities, new combinations)
Indication	New chemical entity
Use in low- and middle-income countries	Mechanism of action
Safer, more effective alternatives available for the same indication	Indication
Flexibility of indication across *P. falciparum* and *P. vivax*	Efficacy
Activity against resistant parasites	Safety and toxicity (including signals from preclinical studies, in vitro and animal models; side-effects; tolerability and effect of organ impairment on drug metabolism and excretion; used in children before [for other indications])
Resistance potential	Activity against malaria parasites with difficult-to-treat resistance profiles
Drug–drug interactions	Need for clinical or laboratory monitoring for signs of efficacy or toxicity
Acceptability of currently available formulations	Screening required before initiating treatment
	Drug–drug interactions
	Previous use in children
	Paediatric formulation under development



Meeting proceedings

The PADO for malaria meeting was held virtually on 24–26 June 2025 (Annex 1) and brought together academics, researchers, clinical experts, regulators, funders and other key stakeholders involved in research and development related to malaria (Annex 2). Of the 12 participants who declared potential conflicts of interest, none were considered significant enough to warrant exclusion from the priority-setting process. Funders, regulators, UN agencies (UNITAID, UNICEF) and GAP-f partners (Medicines for Malaria Venture, Medicines Patent Pool, University of Liverpool, European Paediatric Formulation Initiative) attended the meeting in an observer capacity.

Consensus on priority antimalarial agents to be further investigated and/or developed for infants and children was reached through group discussions informed by the pre-populated frameworks described above. The PADO access, priority and watch lists for malaria and corresponding research agendas were consolidated during a final plenary session.

Summary of discussions

Existing products

Among the medicines listed on the WHO EMLc and/or recommended by WHO in relevant guidelines, the PADO for malaria Group focused their discussions on those for which gaps in age-appropriate formulations had been identified in the context of a comprehensive review of the WHO EMLc conducted between 2021 and 2024, with the antimalarial sections of the WHO EMLc reviewed in Phase 2 of the project (2023–2024) *([11])*.

The PADO-malaria meeting also considered medicines for which no gap in age-appropriate formulation was noted, but access-related issues had been flagged during the preparatory work ahead of the PADO-malaria meeting, namely tafenoquine and artesunate–pyronaridine.

Table 2 provides the final list of antimalarial agents discussed during the PADO-malaria meeting.

Table 2. Medicines recommended by WHO and/or listed on the WHO EMLc reviewed during the PADO-malaria meeting.

	Indication	Drug or drug combination recommended in WHO guidelines	Drug included in the WHO EMLc	Paediatric formulation included in the WHO EMLc	
				2023	2025
Artemether	Treatment of severe malaria	●	●	●	●
Primaquine	Prevention of relapse *(P. vivax)*	●	●	●	●
Tafenoquine[a]	Prevention of relapse *(P. vivax)*	●	●	●	●
Artesunate–amodiaquine	Treatment of uncomplicated malaria	●	●	●	●
Artesunate–mefloquine	Treatment of uncomplicated malaria	●	●	●	●
Sulfadoxine–pyrimethamine (+ artesunate)[b]	Treatment of uncomplicated malaria	●	●	●	●
Artemether–lumefantrine (<5 kg)[c]	Treatment of uncomplicated malaria	●	●	●	●
Artesunate–pyronaridine[a]	Treatment of uncomplicated malaria	●	●	●	●
Mefloquine	Chemoprophylaxis for travellers	●	●	●	●
Atovaquone–proguanil	Chemoprophylaxis for travellers	●	●	●	●

Legend: green: recommended in WHO guidelines or included in the WHO EMLc; red: not recommended in WHO guidelines or not included in the WHO EMLc.

[a] Tafenoquine and artesunate–pyronaridine were discussed during the PADO-malaria meeting, given access issues identified prior to the meeting.

[b] In the 2023 WHO EMLc, sulfadoxine + pyrimethamine was listed alone, with a footnote specifying its mandatory use alongside artesunate. In the 2025 WHO EML and EMLc, the listing was updated to co-packaged scored tablets: artesunate 50 mg and sulfadoxine + pyrimethamine 500 + 25 mg.

[c] Artemether–lumefantrine is recommended by WHO across the paediatric age spectrum (including in children <5 kg). Artemisinin-based combination therapy (ACT) is included in the WHO EMLc in an age-appropriate formulation for children (dispersible tablets). However, the specific formulation for neonates weighing <5 kg (with the optimized drug ratio of 2.5/30 mg) that was discussed during the PADO-malaria meeting is not yet included in the WHO guidelines nor in the WHO EMLc

The PADO for malaria Group's discussions focused on several key aspects, including the suitability of available formulations for children, the use of drugs or drug combinations in LMICs, and the availability – or expected availability – of products considered superior from both the clinical and public health perspectives. The priority-setting exercise took into consideration the approach of MFT implementation to prolong the lifespan of artemisinin-based combination therapies (ACTs) by using currently available drugs in ways that minimize the risk of resistance *(13)*.

The Group also acknowledged that formulation consolidation (defined as development of a higher-strength, flexible formulation that can allow administration of different doses across the paediatric population, for example, through the addition of a scoring line) is typically not considered for antimalarial medicines, and that several strengths of paediatric formulations are typically developed to ensure that dosing can be appropriately administered across the paediatric age spectrum and that no manipulation is being done that could potentially compromise dose accuracy, given that antimalarial medicines are typically given by a parent or caregiver in low-resource settings.

Artemether oily injection is recommended by WHO for the treatment of severe malaria in both adults and children when injectable artesunate is unavailable, and it should be preferred over quinine for this indication. While the 2023 WHO EMLc includes an 80 mg/mL formulation, a proposal has been submitted to replace this with lower-strength formulations (20 mg/mL and 40 mg/mL), which are more suitable for paediatric dosing, also considering that artemether should be administered without dilution. None of the strengths of artemether oily injection reviewed are registered by stringent regulatory authorities/WHO-listed authorities (SRA/WLA), nor are they prequalified by WHO despite being listed on the WHO PQ EOI for antimalarials. While artesunate – administered either intravenously (IV) or intramuscularly (IM) – remains the preferred treatment for severe malaria according to WHO guidelines, the PADO-malaria meeting participants acknowledged that artemether is still used in some countries, particularly in remote areas, as an option for IM administration. This is considered as being more practical in low-resource settings, whereas artesunate is predominantly administered intravenously, though it is also recommended for intramuscular use. Recognizing this gap and given the WHO-recommended dose of artemether (initial dose: 3.2 mg/kg IM; maintenance dose: 1.6 mg/kg IM without dilution), the 20 mg/mL formulation was prioritized for inclusion in the PADO access list.

Primaquine plays a critical role in malaria control and elimination strategies. It is recommended by WHO, alongside an ACT, as a single low dose (0.25 mg/kg) to reduce transmission of *P. falciparum* malaria, particularly in low-transmission areas, without the need for glucose-6-phosphate dehydrogenase testing. It is also used at higher doses for the radical cure of *P. vivax* and *P. ovale* malaria. Primaquine dispersible tablets (2.5 mg, 5 mg, 7.5 mg) are under development and being evaluated by WHO prequalification. The PADO-malaria Group prioritized the 2.5 mg dispersible tablet for inclusion in the PADO access list, recognizing its importance for achieving accurate low-dose administration for reduction of transmission. The formulation is also suitable for radical cure, as multiple tablets can be dispersed in water, improving usability. Despite discussions on the possibility of consolidating the demand around one dosage strength, which could provide 2.5 mg dose increments (i.e. the scored 7.5 mg tablet), this was not considered a priority and the Group agreed that availability of three individual tablets at different strengths is preferred. Alternative dosage forms that enable administration of primaquine to younger age groups unable to swallow tablets can be considered, provided they also maximize affordability, programmatic suitability, and access.

Tafenoquine is recommended by WHO in South America as an alternative to primaquine for preventing relapses of *P. vivax* in patients aged 2 years and above, who have ≥70% G6PD activity and who receive chloroquine treatment. These recommendations currently pertain only to South America, while studies to facilitate the potential extension of its use to other regions are encouraged.

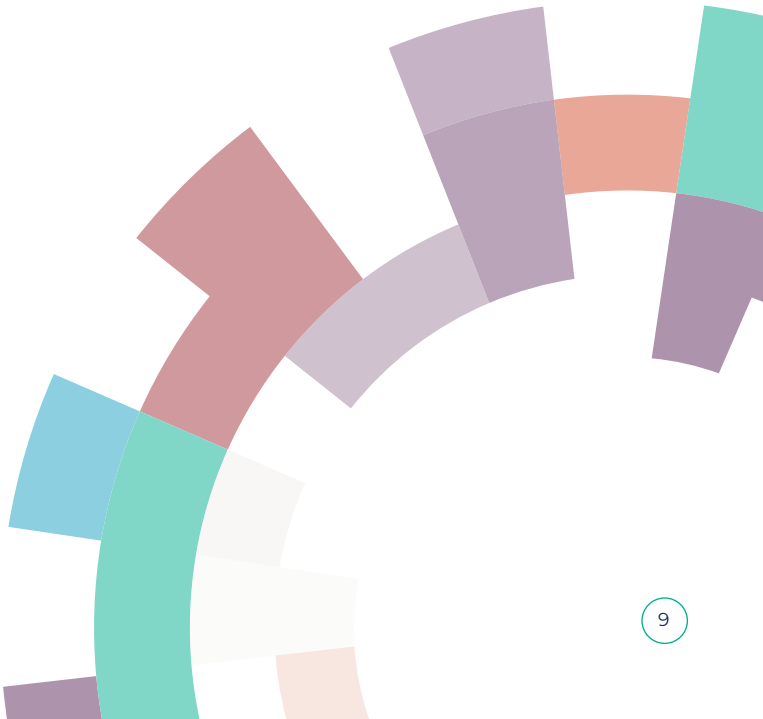
Tafenoquine 50 mg dispersible tablets are approved by the Australian Therapeutic Goods Administration and prequalified by WHO and are appropriate to deliver the WHO-recommended dose in the indicated paediatric population. The Group acknowledged the added value of tafenoquine as a single-dose option for radical cure, offering an alternative to the standard 7-day or 14-day regimen of primaquine. It also discussed the potential long-term coexistence of both tafenoquine and primaquine, agreeing that tafenoquine is not expected to completely replace primaquine. However, the Group noted that key research gaps need to be addressed to clarify market size and stimulate demand for tafenoquine implementation, including efficacy and safety of tafenoquine outside South America, dose optimization (by investigating higher tafenoquine doses), as well as comparative efficacy and safety with primaquine at the recommended total dose of 7.0 mg/kg. To highlight these issues, the Group decided to add tafenoquine to the PADO access list.

Despite acknowledging the 100 mg minimum dose of tafenoquine for the recommended indication, it was also recognized that a dose lower than 100 mg may be needed for children below 2 years of age, should the required evidence be generated and lead to an extension of the WHO recommendation. However, formulation consolidation with a scored 100 mg dispersible tablet was not deemed a priority. This decision reflects existing evidence gaps on tafenoquine, including dosing for children younger than 2 years of age and its use with ACTs. Addressing these key research gaps will be essential to supporting broader use of tafenoquine and potentially improving its market viability.

Among the ACTs reviewed (Table 2), the Group agreed to add **artesunate–amodiaquine** (25/67.5 mg and 50/135 mg child-appropriate oral dosage forms such as coated micropellets, dispersible tablets) and **artemether–lumefantrine** (2.5/30 mg dispersible tablets) to the PADO priority list.

There is a need to increase the armamentarium of ACTs to enable countries to implement MFTs to prolong their lifespan in ways that minimize the risk of resistance. Considering that artesunate–amodiaquine is widely used in LMICs, especially in sub-Saharan Africa, the availability of a child-friendly formulation of this was deemed a priority for development. Two oral strengths were prioritized for development to match WHO-recommended dosing. The Group acknowledged that micropellet formulations in stick packs for direct administration into the mouth are under development, offering improved stability and taste. The Group also encouraged exploring other age-appropriate formats and stressed that the final cost should remain affordable to avoid limiting its inclusion in national MFT programmes.

Artemether–lumefantrine 2.5/30 mg dispersible tablets represent the first malaria treatment designed and approved specifically for newborns and young infants weighing less than 5 kg. This formulation is acceptable for the indicated population, as the tablets are designed to be dispersed in a very small volume of water. The Group recognized the need to develop appropriate access strategies due to the very limited market size for this indication, and acknowledged that this specific artemether–lumefantrine ratio is not yet included in WHO guidance documents. To highlight the importance of promoting access to this formulation, the Group agreed to add artemether–lumefantrine 2.5/30 mg dispersible tablets to the PADO-malaria priority list.



The Group acknowledged the availability of age-appropriate formulations of **artesunate –pyronaridine** and its increasingly important role in the treatment of uncomplicated malaria. However, it noted that the uptake of this medicine – including the paediatric formulation listed on the WHO EMLc – has been limited primarily due to its high price (as it is a single-source medicine). Therefore, the Group agreed to add artesunate–pyronaridine granules: 20 mg + 60 mg to the PADO access list, to advocate for and support stakeholders' actions to increase the uptake of this product. In the short term, this includes efforts such as volume negotiations and volume guarantees. In the medium term, initiatives may need to focus on encouraging generic manufacturers to enter the market by supporting more efficient manufacturing and process chemistry. This strategy, combined with the introduction of generic competition, is expected to drive down the final cost. The Group acknowledges that at least five manufacturers are developing generic artesunate–pyronaridine products, with plans to submit to WHO prequalification within the next two years.

Despite identifying gaps in age-appropriate formulations of **sulfadoxine–pyrimethamine (with artesunate)** and **artesunate–mefloquine** for children, the Group decided not to add them to the PADO priority list. The Group acknowledged that sulfadoxine–pyrimethamine dispersible tablets are available, but artesunate dispersible tablets are not available, which would make the use of this combination challenging in children. However, this drug combination is used in only a few countries where resistance to sulfadoxine–pyrimethamine is not widespread. In general, resistance of *P. falciparum* to sulfadoxine–pyrimethamine is common, and this drug combination is also less effective than other options against *P. vivax* malaria. Artesunate–mefloquine was not added to the PADO priority list as this ACT is used in a limited number of countries, mainly in South-East Asia. Although currently available formulations are not labelled as dispersible tablets and acceptability may be an issue because of taste and aftertaste, the tablets can be placed on a teaspoon containing clean water and allowed to disintegrate before oral administration. Overall, the Group concluded that this ACT is not a global priority for development, noting that its use is likely to decline even more in the future as newer ACTs or non-ACTs emerge, and therefore did not propose its inclusion in the PADO priority list.

For chemoprophylaxis, the Group discussed **mefloquine** and **atovaquone–proguanil**. While proguanil was previously listed in the WHO EMLc (and WHO EML), it was proposed for removal in both the 2025 WHO EMLs, with an encouragement to submit an application for inclusion of atovaquone–proguanil as an FDC in the 2027 update of the list. Currently, atovaquone–proguanil is available only as a non-dispersible, costly tablet that must be swallowed whole or crushed, which poses challenges for children. To address the lack of suitable paediatric options and improve dosing accuracy and adherence, the Group recommended inclusion of a dispersible formulation in the PADO priority list, recognizing it as an unmet public health need, including for travellers across endemic countries in LMICs. Other agents were not discussed due to the absence of formulation gaps. Mefloquine was considered but not prioritized, despite a formulation gap, due to concerns about its future use for this indication.

PADO-malaria access list	PADO-malaria priority list
Artemether oily injection 20 mg/mL	**Artemether–lumefantrine** 2.5/30 mg dispersible tablet
Primaquine 2.5 mg dispersible tablet	**Artesunate–amodiaquine** 25/67.5 mg and 50/135 mg child-appropriate oral dosage forms such as coated micropellets, dispersible tablets
Tafenoquine 50 mg dispersible tablet	**Atovaquone–proguanil** 62.5/25 mg dispersible tablets
Artesunate–pyronaridine Granules: 20 mg + 60 mg	

Antimalarial agents not yet considered for WHO guidelines

The PADO-malaria Group reviewed and discussed several drugs and drug combination candidates that are being investigated and developed, including new combinations of existing products as well as new chemical entities being investigated in late-phase clinical trials (Table 3).

The availability of dispersible tablets of artesunate–piperaquine would expand the range of ACTs available for use in MFT strategies. However, the Group noted that this drug combination is functionally similar to dihydroartemisinin–piperaquine, since artesunate is metabolized into dihydroartemisinin in vivo. This raises questions about its added value over dihydroartemisinin–piperaquine, especially given that dihydroartemisinin–piperaquine is already available in WHO-prequalified dispersible tablet formulations. As a result, the Group considered age-appropriate formulations of artesunate–piperaquine to be of relatively lower priority compared to other new combinations of existing products on the PADO watch list. The Group acknowledged that human bioequivalence/bioavailability studies against dihydroartemisinin–piperaquine are ongoing and that dispersible formulations are being developed (50/320 mg, 35/160 mg, 12.5/80 mg dispersible tablets). However, the timeline for submission to WHO prequalification is unknown.

Table 3. Antimalarial candidates discussed by the PADO-malaria Group, which have not yet been reviewed by WHO for guidelines[a]

New combinations of existing products	New chemical entities being investigated in late-phase clinical trials
Artesunate–piperaquine	Ganaplacide–lumefantrine
Artemether + lumefantrine + amodiaquine	Cipargamin
Sulfadoxine–pyrimethamine + artesunate–pyronaridine	ZY 19489 + ferroquine
	M5717 + pyronaridine
	Fosmidomycin + piperaquine

[a] Scientific evidence reviewed by WHO so far from studies investigating artesunate + piperaquine was not deemed sufficient for guideline consideration.

Artemether–lumefantrine remains the most widely used antimalarial treatment globally and is currently being developed into an FDC with amodiaquine. This formulation aims to improve adherence by addressing the challenges associated with loose-tablet regimens. Recent randomized controlled trials have demonstrated the excellent safety and efficacy of the resulting triple ACT, artemether–lumefantrine–amodiaquine *(18, 19, 20)*. In light of this, and recognizing the potential of triple ACTs as a promising strategy to counter the declining efficacy of current treatments due to multidrug-resistant malaria, the Group decided to include artemether–lumefantrine–amodiaquine in the PADO priority list as 20/120/40 mg taste-masked dispersible tablets. The combination of sulfadoxine–pyrimethamine and artesunate–pyronaridine has been evaluated as a potential single-dose cure for uncomplicated malaria in a randomized controlled trial conducted in Gabon, with artemether–lumefantrine serving as the standard of care (Pan African Clinical Trial Registry reference number: PACTR202405571736678). Although the results of the trial are still unpublished, preliminary data indicate promising efficacy and no safety concerns. Notably, the study population included over 40% children under the age of 10 years, highlighting the relevance of this combination for paediatric use. Plans are under way to develop this regimen into an FDC, including an age-appropriate formulation for children. A single-dose cure for malaria could simplify treatment delivery, reduce overall treatment costs, and play a critical role in limiting the emergence and spread of drug resistance. Therefore, the Group decided to add this FDC to the PADO watch list. In relation to the new chemical entities in late-phase clinical development discussed during the PADO-malaria meeting (Table 2), the PADO-malaria Group agreed that all four products should be added to the watch list, signalling that ongoing studies will be monitored for emerging evidence. These candidates have the potential to be used in drug-resistant uncomplicated malaria, as they have novel mechanisms of action that have shown activity against parasites that are resistant to current drugs (Table 4). Cipargamin is also being investigated as an IV treatment for severe malaria, to tackle the spread of artemisinin partial resistance in *Plasmodium falciparum*, especially in Asian countries. The Group emphasized that child-appropriate formulations of any compounds emerging from the pipeline should be developed concurrently with ongoing studies to avoid delays in providing children with access to new treatment options.

Table 4. Summary of key characteristics of new chemical entities under investigation

	Ganaplacide–lumefantrine	Cipargamin	ZY 19489 + ferroquine	M5717 + pyronaridine
New chemical entity	YES (ganaplacide)	YES	YES (ZY 19489 and ferroquine)	YES (M5717)
New mechanism of action	YES (ganaplacide: not fully determined, effect on parasite internal protein secretory pathway)	YES (it acts by inhibiting P-type transporter Na+–ATPase)	ZY 19489: unknown Ferroquine: similar to chloroquine (it prevents the polymerization of toxic haem released during proteolysis of haemoglobin)	M5717: *P. falciparum* EF2 inhibitor
Main indication	Treatment of uncomplicated malaria (P. falciparum, *P. vivax*)	Treatment of uncomplicated malaria (as an add on to Gan/Lum as a single-dose cure) and severe malaria	Treatment of uncomplicated malaria (single-dose cure)	Treatment of uncomplicated malaria (single-dose cure). Interest in exploring it as chemoprevention and potential for prophylaxis
Phase completed	Phase 2b combination study Phase 2b study in paediatric population (KALUMI) (down to 5 kg)	Phase 2 malaria patient study and parenteral good laboratory practice safety study First-in-human study with IV formulation completed	ZY 19498: Phase 1 multiple ascending dose completed Ferroquine: phase 2 studies in combination with OZ439 completed	M5717: first-in-human study (blood-stage) volunteer infection study and (sporozoite) volunteer infection study completed Phase 2a combination study in patients with acute uncomplicated malaria completed
Phase ongoing	Phase 3 (recruitment completed)	Phase 2 monotherapy study in patients with severe malaria, including children (currently recruiting)	Phase 2 combination study ongoing (planned for completion in 2026)	Top line data for Phase 2a expected in Q2 2025
Drug–drug interactions	Both ganaplacide and lumefantrine are substrates of CYP3A4; they also inhibit CYP2D6, CYP3A4 and CYP2C8 to various extents	Cipargamin is a CYP3A4 substrate hence CYP3A4 modulators, both inhibitors and inducers, may alter the exposure levels of cipargamin. It acts as a moderate inhibitor of CYP2C19 enzyme. Consequently, it is expected to increase the exposure levels of sensitive CYP2C19 substrates. Due to low solubility at higher pHs, it may potentially interact with acid-reducing agents.	No information	No information

Table 4. (continued) Summary of key characteristics of new chemical entities under investigation

	Ganaplacide–lumefantrine	Cipargamin	ZY 19489 + ferroquine	M5717 + pyronaridine
Activity against difficult-to-treat resistance profiles / resistance potential	Active against parasites that are resistant to current drugs Decreased susceptibility to ganaplacide is associated with mutations in three *P. falciparum* genes, CARL (cyclic amine resistance locus), UDP-galactose and acetyl-CoA transporters	Novel mechanism of action (MoA), potential for use in resistance management Resistance potential noted based on in vitro results, thus the planned use as an add on to Gan/Lum	ZY19489: No stable resistance detected in in vitro or clinical studies Ferroquine: long duration of plasma exposure, fully active against amodiaquine- and piperaquine-resistant strains Refractory to resistance, less prone to resistance than M5717 + pyronaridine	Positive interaction demonstrated in preclinical model on killing rate and resistance protection Potential for resistance against M5717
Administration	Oral (once daily for three days)	Oral (uncomplicated malaria, potentially simplified dosing schedule), IV (severe malaria)	Oral (potentially simplified dosing schedule)	Oral (potentially simplified dosing schedule)
Paediatric formulation	Granules (in stickpack) for direct administration into the mouth. A specific formulation for <10 kg is being developed to improve palatability	Clinical service formulation used in the phase 2 trial based upon loose combination of the components (i.e. Gan–Lum as granules in stickpack and cipargamin as capsules). Work is ongoing on a child-friendly formulation for phase 3	Dispersible granules supplied as capsules in Phase 2 studies Dispersible tablet to be developed for Phase 3	
Next steps	Submission to US FDA by the end of 2025	Plans to study it in combination with INE963 for uncomplicated malaria and severe malaria	Completion of phase 2 combination study by 2026	Top line data for Phase 2a expected by 2025

The Group decided not to add fosmidomycin + piperaquine to the PADO watch list. Even though a proof-of-concept study conducted in Gabon showed promising results *(21)*, the development of this drug combination as a non-artemisin-based combination for uncomplicated *P. falciparum* malaria was halted due to a funding gap for a comparative study versus artemether–lumefantrine. The Group agreed that further investigation of this candidate is not warranted, as other combinations currently in clinical development appear more promising for the same indication.

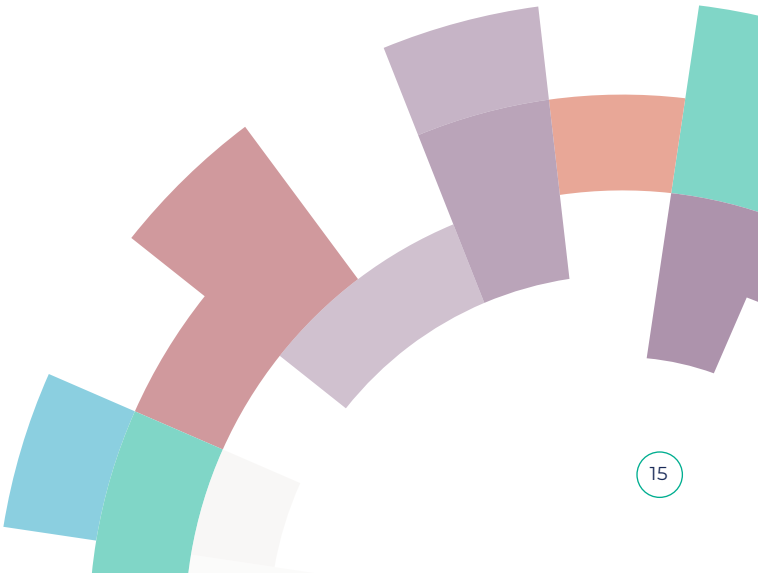
Lastly, the Group discussed how long-acting technologies can potentially be transformative in malaria management, including for children. In particular, these help to tackle the growing resistance to sulfadoxine–pyrimethamine and increase adherence. The Group also discussed how several-use cases should be explored, including (but not limited to) chemoprevention. The Group acknowledged that two candidates in early-stage development are currently being explored *(10)*. A derivative of atovaquone is being clinically tested in an injectable form that could provide up to 3 months of protection with a single intramuscular dose, when administered in combination with a suitable partner drug to reduce the likelihood of inducing resistant strains of the malaria parasite. A potential partner drug candidate that has the same target as atovaquone but at a different binding site is currently in clinical development.

Results emerging from ongoing studies should be closely monitored in the future, given that these interventions have the potential to be a game changer in malaria management offering a long-lasting option to protect people of all ages from malaria. Therefore, the Group decided to add long-acting technologies to the PADO-malaria watch list.

The Group also discussed the need to prioritize appropriate-use cases and target age groups for long-acting injectables, especially those with mechanisms of action on blood-stage activity. Early consensus on priority-use cases and target ages is essential to guide trial design and formulation development, including considerations for broader implementation in school-age children.

PADO-malaria watch list	
Artesunate–piperaquine [a]	Ganaplacide–lumefantrine
Artemether + lumefantrine + amodiaquine	Cipargamin
Sulfadoxine–pyrimethamine + artesunate–pyronaridine	ZY 19489 + ferroquine
	M5717 + pyronaridine
Long-acting technologies	

[a] Lower priority compared to other new combinations of existing antimalarials on the PADO–malaria watch list



Priority research questions

The Group highlighted the importance of investigating medicines in children under 6 months, including those weighing less than 5 kg. While a formulation of artemether–lumefantrine (2.5/30 mg dispersible tablet) specifically designed for infants and newborns under 5 kg is now approved, the Group discussed the need to have alternative options available for this vulnerable group in case artemether–lumefantrine becomes ineffective in the future. Acknowledging the challenges of recruiting infants and newborns into clinical studies, the Group agreed on the value of identifying 1–2 promising candidates, based on robust criteria, to guide focused investigation and ensure that children under 5 kg are not left without appropriate treatment options in the future.

The Group also encouraged further discussion – including with regulators – on how to streamline studies in younger children (under 6 months) while ensuring the generation of appropriate evidence. This includes developing strategies to facilitate enrolment for this specific population, but also optimizing study design and clarifying regulatory requirements for approval, including the role and methodologies of modelling studies to help minimize the number of subjects needed for recruitment.

Another group that was indicated as needing specific attention was children with sickle cell disease in malaria-endemic countries. In some settings, this group constitutes a high proportion of children at risk for malaria. As they require lifelong chemoprevention, the Group emphasized the importance of designing regimens tailored to their specific needs.

Alongside long-acting technologies, the Group noted the relevance of exploring other innovative delivery methods, especially for chemoprevention, where dosing is more standardized, such as microarray patches.

In general, the Group stressed the value of continuing drug optimization discussions to address the specific needs of children with or at risk for malaria to help inform a more targeted approach to research and development of antimalarials in this population. It would also help to support the optimization of study design to account for some of the challenges faced, especially in neonates and infants. There is a need to reflect on these aspects as the global community decides how to better focus research and development programmes that have the highest chances of addressing urgent paediatric unmet needs.

Additional areas of work flagged for attention included:

- streamlining outcome definitions, especially for severe malaria, when evaluating the efficacy of antimalarials in clinical trials, so as to streamline evidence review, including by WHO;
- providing guidance on how to compare novel chemopreventive therapies under investigation to sulfadoxine–pyrimethamine–amodiaquine, given the non-malaria effects of sulfadoxine–pyrimethamine (i.e. identification of non-malaria outcomes for novel chemopreventive therapies being investigated).

Conclusions and next steps

The PADO for malaria meeting brought together academic researchers, clinical experts, implementing partners and other key stakeholders involved in research and development to reach consensus on the first-ever PADO lists for malaria. These contain three key antimalarial agents to be developed in the short term (PADO priority list) and to be monitored in the longer term (PADO watch list), with a clear message on the need to continue investigating long-acting injectables, given their potential role in future malaria management. Additionally, the PADO-malaria access list will support all stakeholders to advocate for greater access to, uptake and roll out of the products included, through multiple activities.

The overall outcome of the exercise will be widely disseminated via multiple opportunities for engagement with regulators, industry, funders, civil society and the general public.

Finally, the WHO Global Malaria Programme will use existing mechanisms to follow up on some of the technical discussions in the areas given priority, including identified research priorities. Where needed, GAP-f and its working groups will be leveraged to advance and accelerate the investigation, development and introduction of priority products.

PADO-malaria access list	PADO-malaria priority list
Artemether oily injection 20 mg/mL	**Artemether–lumefantrine** 2.5/30 mg dispersible tablet
Primaquine 2.5 mg dispersible tablet	**Artesunate–amodiaquine** 25/67.5 mg and 50/135 mg child-appropriate oral dosage forms such as coated micropellets, dispersible tablets
Tafenoquine 50 mg dispersible tablet	**Atovaquone–proguanil** 62.5/25 mg dispersible tablets
Artesunate–pyronaridine Granules: 20 mg + 60 mg	

PADO-malaria watch list	
Artesunate–piperaquine	Ganaplacide–lumefantrine
Artemether + lumefantrine + amodiaquine	Cipargamin
Sulfadoxine–pyrimethamine + artesunate–pyronaridine	ZY 19489 + ferroquine
	M5717 + pyronaridine
Long-acting technologies	

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Note: All references were accessed on 4 September 2025.

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Annex 1. Agenda

Tuesday, 24 June 2025 Introductory session		
Welcome and introduction	Martina Penazzato (WHO)	13:00–13:05
Paediatric drug optimization (PADO) for malaria: meeting objectives	Tiziana Masini (WHO)	13:05–13:15
WHO policies and update	Peter Olumese (WHO)	13:15–13:30
A perspective from the field: remaining gaps in paediatric formulations	Olugbenga Mokuolu (University of Ilorin, Nigeria)	13:30–13:40
TPP for antimalarials	Hanu Ramachandruni (MMV)	13:40–13:55
Market analysis and trajectory	Dale Halliday (UNITAID)	13:55–14:10
Q&A	WHO	14:10–14:25
Closing	Martina Penazzato (WHO)	14:25–14:30
Wednesday, 25 June 2025 Existing products and access considerations		
Welcome and review of objectives for day 2	Martina Penazzato (WHO)	13:00–13:10
Existing products. Summary of background work to inform the PADO exercise	Tiziana Masini (WHO)	13:10–13:25
Facilitated discussion on PADO priority formulations through the prioritization framework	Moderators: Tiziana Masini and Peter Olumese (WHO)	13:25–15:00
Break		15:00–15:10
Facilitated discussion on access priorities	Moderator: Jan Kolaczinski (UNITAID)	15:10–15:50
Wrap up of PADO priorities and end of day 1	Martina Penazzato (WHO)	15:50–16:00

Thursday, 26 June 2025 Pipeline products		
Welcome and review of objectives for day 3	Martina Penazzato (WHO)	13.00–13:10
Pipeline products: summary of background work to inform the PADO exercise	Conor Cahill (MMV)	13:10–13:30
Q&A	All	13.30–13:40
Facilitated discussion on PADO watch list	Moderators: Martina Penazzato and Peter Olumese (WHO)	13:40–14:50
Break		14:50–15:00
PADO research priorities – finalization of the list	Olugbenga Mokuolu (University of Ilorin, Nigeria)	15:00–15:30
Summary of PADO priorities	Tiziana Masini (WHO)	15:30–15:45
Closing and next steps	Martina Penazzato (WHO)	15:45–16:00

Annex 2. List of participants

Jane Achan	Malaria Consortium, United Kingdom
Ida Marie Ameda	UNICEF, Switzerland
Evelyn Korkor Ansah	University of Health and Allied Sciences, Ghana
Gideon Asamoah	University College London, United Kingdom
Marta Busana	European Medicines Agency, Netherlands (Kingdom of the)
Conor Cahill	Medicines for Malaria Venture, Switzerland
Laurence Delcros	The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
Paul Domanico	Clinton Health Access Initiative (CHAI), United States of America
Laura Fregonese	European Medicines Agency, Netherlands (Kingdom of the)
Elizabeth George	University College London, United Kingdom
Dale Halliday	UNITAID, Switzerland
Anitta Kamara	National Malaria Control Programme, Sierra Leone
Jan Kolaczinki	UNITAID, Switzerland
Peter Kremsner	German Center for Infection Research, Germany
Christine Mayando	Tropical Disease Centre, Ndola, Zambia
Olugbenga Mokuolu	College of Health Sciences, University of Ilorin, Nigeria
Sebastien Morin	Medicines Patent Pool (MPP), Switzerland
Bernhards Ogutu	East African Chapter of the Association of the Clinical Research Professionals, Kenya
Mary Atieno Ojoo	UNICEF, Switzerland
Andrew Owen	Centre of Excellence for Long-acting Therapeutics (CELT), United Kingdom
Melissa Penny	The Kids Research Institute Australia, Australia
Hanu Ramachandruni	Medicines for Malaria Venture, Switzerland
Smita Salunke	European Paediatric Formulation Initiative (EuPFI), United Kingdom
Htin Kyaw Thu	The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
Charles D. Wells	The Gates Medical Research Institue, United States of America
Dyann Wirth	Harvard T.H. Chan School of Public Health, United States of America

WHO	
Bernadette Cappello	WHO Department of Health Products Policy and Standards
Ray Corrin	WHO Regulation and Prequalification Department
Tiziana Masini	GAP-f, Science for Health, Science Division
Peter Olumese	WHO Global Malaria Programme
Martina Penazzato	GAP-f, Science for Health, Science Division
Jackson Sillah	WHO African Region
Wilson Were	Department of Sexual, Reproductive, Maternal, Child and Adolescent Health & Ageing (LHR)

World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland