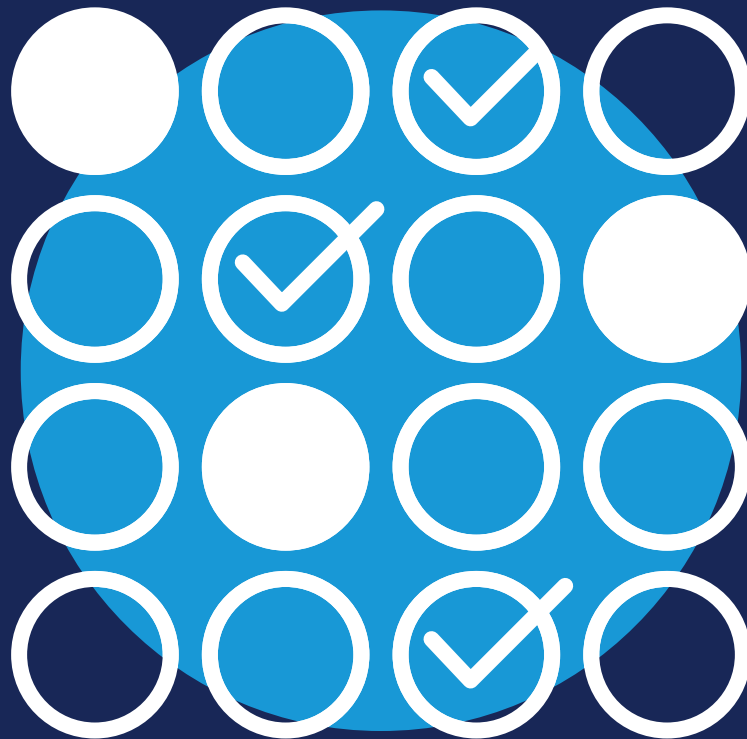# Monoclonal antibodies for malaria prevention

Preferred product characteristics and clinical development considerations

World Health Organization

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ACKNOWLEDGEMENTS

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ABBREVIATIONS

ACD	active case detection
ADA	anti-drug antibody
CHMI	controlled human malaria infection
CHO	Chinese hamster ovary
CSP	circumsporozoite protein
Fc	fragment crystallizable
GTS	Global technical strategy for malaria
IPTi	intermittent preventive treatment of malaria in infants
IPTp	intermittent preventive treatment of malaria in pregnancy
LMIC	low- and middle-income country
LS	leucine-serine
mAb	monoclonal antibody
PCD	passive case detection
PDMC	post-discharge malaria chemoprevention
PDVAC	Product Development for Vaccines Advisory Group
PMC	perennial malaria chemoprevention
PPC	preferred product characteristic
R&D	research and development
RSV	respiratory syncytial virus
SMC	seasonal malaria chemoprevention
WHO	World Health Organization

OVERVIEW

The *Global technical strategy for malaria 2016–2030* (GTS) *(1)* seeks to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threat of drug and insecticide resistance. It encourages innovation and the development of new tools and strategies to maintain progress in malaria control and advance towards elimination. To accelerate implementation of the GTS, in 2018, the World Health Organization's (WHO) Global Malaria Programme reviewed its policy-making process to ensure that it is transparent, consistent, efficient and predictable. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) as a tool to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve communication about public health needs and to facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;

- stimulate the development of relevant new products to meet those needs; and

- facilitate the timely, effective assessment of new products, and the formulation of relevant policy recommendations and prequalification listings.

The PPCs published here aim at promoting the development of malaria monoclonal antibodies (mAbs) with high public health impact and suitability for use in low- and middle-income countries (LMICs). This document has been jointly developed by the WHO Global Malaria Programme, the WHO Department of Immunization, Vaccines and Biologicals and a scientific development committee of experts. The malaria mAbs PPCs address several considerations, including indication, target population, safety and efficacy, formulation and presentation, dose regimen, co-administration, route of administration, product stability and storage, and access and affordability. These preferences are shaped by the unmet public health needs in priority disease areas and by the realities of malaria epidemiology and delivery systems in the target geographies.

Malaria PPCs are aligned with and complementary to guidance developed by other WHO departments, such as the WHO Product Development for Vaccines Advisory Group (PDVAC) and the WHO Prequalification Team. PDVAC is a WHO committee of experts providing external advice to WHO related to priority infectious disease pathogens, associated vaccine and monoclonal antibody product development approaches, and related manufacturing and delivery technologies *(2)*. The WHO Prequalification Team has detailed the prequalification process for therapeutic mAbs in the document *Pilot prequalification of biotherapeutic products (3)*. WHO encourages developers to consult these documents, alongside malaria PPCs, particularly if they intend to seek a WHO recommendation for use or prequalification of their products.

The preferred product characteristics for malaria monoclonal antibodies were developed in accordance with the WHO Standard Procedure for Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles (V1.02, 3 August 2020).

Assessment and management of conflicts of interest

Declarations of any competing interests were received from all experts. WHO processes were used to assess declared interests and to manage any conflicts of interest. Three experts declared potential competing interests. After review and due diligence by the WHO Secretariat, it was concluded that these interests were not significant with respect to the specific topics discussed in the development of this report.

TERMINOLOGY

Preferred product characteristics (PPCs) are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers including researchers, regulatory agencies, procurement agencies, and funders of research and development (R&D). PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve global health impact.

Target product profiles (TPPs) in the context of public health are planning tools used to set R&D targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process.

1. BACKGROUND AND PURPOSE

While major reductions in malaria have been achieved in the last two decades, recent trends show that progress with disease control has stalled *(4)*. The widespread use of insecticides for vector control and drugs for treatment and prevention form the foundation of malaria control. However, the emergence of drug and insecticide resistance *(5)*, challenges in achieving high coverage *(4,6)* and suboptimal adherence to existing interventions *(7–9)* present significant hurdles for sustained progress. Future strategies to combat malaria will require an expanded set of tools.

Major milestones have already been achieved in malaria vaccine R&D and the use of drugs for chemoprevention. Chemoprevention has been used in the form of perennial malaria chemoprevention (PMC, formerly intermittent preventive treatment of malaria in infants [IPTi]), intermittent preventive treatment of malaria in pregnancy (IPTp) and, more recently, seasonal malaria chemoprevention (SMC) in children in areas of seasonal malaria transmission in the Sahel subregion. However, the complex drug regimens required to achieve duration of protection can result in adherence issues. In October 2021, RTS,S/AS01 was the first malaria vaccine to be recommended by WHO for widescale use in moderate- to high-transmission settings in sub-Saharan Africa. Work is ongoing to develop next-generation vaccines and drugs for chemoprevention. However, both face several challenges. The currently available vaccine, RTS,S/AS01, has moderate efficacy and duration of protection due to the difficulty in maintaining high levels of antibodies and T-cells to mediate durable protection. Vaccine efficacy against malaria is also influenced by age, parasite diversity, baseline disease incidence and pre-existing immunity in naturally exposed individuals. As with all vaccines, the time and cost of development are substantial. In parallel, work is ongoing to develop new drugs for malaria chemoprevention, but they are unlikely to be available in the short term.

Alongside the development of new malaria vaccines and chemoprevention drugs, there have been recent R&D advances in the development of mAbs for malaria prevention. Passive immunization with mAbs through direct administration of functional antibodies could potentially overcome some of the limitations of vaccines by providing immediate protection. In addition, given that mAbs do not depend on the immune system for production, the serum antibody concentration following passive immunization is expected to be far less variable than the immune responses generated by vaccines. Future malaria mAbs could potentially be used as prophylaxis for several months, providing short-term protection in populations at high risk of clinical malaria or individuals who are less able to develop robust immune responses, such as malnourished children or HIV-infected and other immunocompromised populations. Furthermore, the development of mAbs with simplified dose regimens (e.g. a single directly observed dose) could potentially circumvent some of the coverage and adherence issues faced by vector control and chemoprevention.

Technical innovations in candidate identification, optimization and manufacturing have reduced the time required to isolate, characterize and produce antibodies, increasing the possibility of developing more affordable mAbs. New methods have also been designed to increase the potency of mAbs and extend their half-life *(10,11)*. As of 2022, several mAbs for the prevention of malaria are in Phase 1 and 2 clinical trials. These include two anti-circumsporozoite protein (CSP) mAbs, CIS43LS and L9LS, which have been shown to be highly effective in preventing infection in mouse models and Phase 1 human challenge studies *(12,13)*. CIS43LS began Phase 2 clinical evaluation in Mali in 2021 (NCT04329104) and Kenya in 2022 (NCT05400655), and L9LS began Phase 2 evaluation Mali in 2022 (NCT05304611). Transmission-blocking mAbs include TB31F, which has been tested in a Phase 1 clinical trial *(14)*. Additional mAb candidates targeting sporozoite, blood-stage and sexual stage antigens are also in preclinical development.

As of 2022, over 130 mAbs have been approved globally or are under regulatory review, but only 11 of these products are for infectious diseases, including mAbs for respiratory syncytial virus (RSV), anthrax, prevention of recurrent *Clostridium difficile*, HIV, Ebola virus disease, rabies and coronavirus disease (COVID-19) *(15,16)*. Updated guidelines for the clinical evaluation and manufacturing of infectious disease mAbs are under development, and pilot procedures for WHO prequalification have been developed for therapeutic mAbs. However, specific guidelines for preventive mAbs have yet to be developed. Global access to mAb products remains severely limited in many countries; very few mAbs are registered in low-income countries, and those registered in middle-income countries remain prohibitively expensive or are not optimized for use by populations in LMICs *(16)*.

To support this quickly developing R&D area, the WHO Global Malaria Programme and Department of Immunization, Vaccines and Biologicals convened a scientific development group to consider the PPCs for mAbs to be used for malaria prevention.

2. WHO STRATEGIC GOALS FOR MALARIA MABS

In the current landscape of malaria control, mAbs for malaria prevention may offer several advantages over existing tools, as standalone products or in combination with existing tools. The ultimate aim of any malaria mAb is to reduce morbidity and mortality, which can be achieved either directly by preventing blood-stage infection and/or reducing blood-stage parasite density, or indirectly by reducing community-level transmission. mAbs with very high efficacy against sporozoites could prevent blood-stage infection and subsequent clinical disease, and, if delivered to a sufficient proportion of the individuals representing the infectious reservoir, could potentially reduce community-level transmission.

This document represents the first WHO PPCs for mAbs for malaria prevention. Given the current state of R&D in this area, the considerations for PPCs and clinical development outlined will focus on the most urgent public health priority: reduction of morbidity and mortality in infants and children due to *Plasmodium falciparum.*

2.1 Priority use case scenario: reduction of morbidity and mortality in children

Infants and children living in endemic settings are in the age groups at highest risk of severe disease and death. mAbs able to maintain a high level of protection for the duration of a transmission season or high-risk period (e.g. 3–6 months) are a potential alternative to SMC. Single-dose mAbs may enable improved adherence over current chemoprevention regimens, which require three to four doses in a transmission season *(11)*. mAbs could provide protection in the first year of life, particularly if increased resistance leads to reduced effectiveness of SMC or PMC *(5)*. However, it will be important to understand the differences in efficacy and safety in young infants compared to older children. Depending on the target age group and feasibility of administration in local health systems, mAbs can potentially be delivered through the Expanded Programme on Immunization (EPI), other routine contacts with the health system or mass immunization campaigns.

2.2 Other use case scenarios for future consideration

As the malaria mAb R&D space evolves, reduction of morbidity and mortality in other target populations such as adults may be of interest, especially in high-risk or vulnerable adult populations. Prevention of infection in pregnant/lactating women and/or women of childbearing age is of particular interest, especially if increased drug resistance reduces the effectiveness of IPTp. Passive immunization during pregnancy may have a significant impact on both women and infants, particularly if delivered to primigravid women during the first trimester, a period of high risk. If a single administration of mAbs can provide protection for six months or more, it may also avoid the adherence issues encountered with the more complex drug regimens currently used for IPTp.

However, the feasibility of delivery in adults will depend on the dose and volume required to achieve protective efficacy, whether it can be administered intramuscularly or subcutaneously, and, for pregnant women, the feasibility of intravenous administration in antenatal clinics. Given that the concentration of mAbs can range from 12 µg/mL to 200 mg/mL *(17)*, reducing the volume to enable intramuscular or subcutaneous administration in adults (ideally < 2 mL) may require mAb formulations that have higher concentration or potency than the formulations used in children.

Another potential use case for malaria mAbs in children could be as post-discharge prophylaxis for children admitted to hospital with severe anaemia. These patients have a marked increase in mortality in the six months following discharge, and studies have shown that post-discharge malaria chemoprevention (PDMC) with sulfadoxine-pyrimethamine and artemisinin-based combination therapies substantially reduces that risk. Therefore, there may be interest in developing malaria mAbs as a similar preventive intervention.

Highly efficacious mAbs may also have application in emergency situations to prevent outbreaks of malaria or to reduce the burden of febrile disease on the health system. In regions that have already cleared or locally eliminated malaria, mAbs could be used as an alternative to mass drug administration or drug-based prophylaxis for high-risk travellers or workers to prevent outbreaks or reintroduction. In addition, mAbs targeting gametocytes or sexual/mosquito stages could potentially be used to reduce transmission at the community level. However, to interrupt transmission, these applications would require mAbs to be suitable for administration in both children and adults, and should be deliverable at scale to cover a sufficient proportion of the population.

2.3 Use of mAbs with other malaria control interventions

The use of multiple interventions and delivery strategies can maximize the impact of available malaria prevention tools. For example, an evaluation of RTS,S/AS01 and SMC in West Africa has shown the potential benefits of combining malaria prevention tools *(18)*.

Similarly, the use of mAbs for preventing malaria infection could potentially be combined with malaria chemoprevention and/or vaccines. Preclinical mouse models suggest that there are biological synergies when malaria mAbs and vaccines are combined. Administration of anti-CSP mAbs in mice immunized with the malaria vaccine candidate R21 led to enhanced protection against sporozoite challenge compared to vaccine or mAbs alone *(19)*. While further research is required, the administration of mAbs combined with other interventions, such as vaccines and/or chemoprevention drugs, may be a potential future strategy.

3. STATE OF THE ART

Most mAbs for malaria prevention are currently in the discovery and optimization phase. The majority of antibody candidates target sporozoite stage antigens, particularly the CSP antigen due to its immunodominance on the sporozoite surface and its high conservation. The focus on the liver stage is due to the small number of parasites, allowing for a favourable mAbs-to-parasite ratio to achieve neutralization of the pathogen. Elimination of parasites in this critical stage can prevent blood-stage infection, disease and transmission.

There is also the potential for combinations of mAbs targeting liver-stage antigens and blood-stage antibodies to block breakthrough parasites downstream. Combining liver-stage and blood-stage mAbs could deliver particularly high potency if the number of parasites entering the blood is dramatically reduced first with liver-stage mAbs. However, improved preclinical models are still needed to test the efficacy against blood-stage infection. mAbs targeting the sexual stage with longer duration than current transmission-blocking drugs may also be promising, but may need to be combined with anti-infection or disease-reducing mAbs, as they would not provide direct benefit to the individual.

As of 2022, three malaria mAb candidates are being tested in clinical trials. These include two CSP-targeting antibodies (CIS43LS and L9LS) and one antibody (TB31F) targeting the gametocyte surface protein Pfs48/45 to block human-to-mosquito transmission. CIS43LS is based on the human monoclonal antibody CIS43[1], modified to include leucine-serine (LS) mutations in the fragment crystallizable (Fc) region to increase antibody half-life through binding to the neonatal Fc receptor. In 2020, CIS43LS was tested in a Phase 1 dose-escalation trial in healthy malaria-naïve adults to assess safety, efficacy and pharmacokinetics following CHMI (NCT04206332) *(12)*. This study also aimed to estimate the serum concentration required for protective efficacy against malaria in naïve adults and evaluate the efficacy of subcutaneous administration. In 2021, a Phase 2 dose-escalation trial also began in Mali (NCT04329104) to evaluate the safety, protective efficacy and pharmacokinetics of CIS43LS administered intravenously in adults under conditions of natural exposure in a seasonal setting *(22)*. L9LS is a second-generation anti-CSP mAb candidate that has been found to be protective in mice with two- to three-fold increased potency compared to CIS43. A Phase 1 CHMI dose-escalation study was conducted in 2021 to evaluate the safety, protective efficacy and pharmacokinetics of L9LS by intravenous and subcutaneous administration in malaria-naïve adults (NCT05019729) *(23)*. This study showed high-level protection at low doses of L9LS by the subcutaneous route in a small number of subjects, providing the necessary data to advance to studies of subcutaneous administration in infants and young children in Africa *(13)*. Two Phase 2 studies are ongoing to evaluate the safety, protective efficacy and pharmacokinetics of subcutaneous administration in seasonal and perennial settings in Africa. These include a randomized trial evaluating efficacy of two subcutaneous administrations over a 12-month period in infants and children aged 5 months to 5 years in a perennial setting in Kenya (NCT05400655) *(24)* and a dose-escalation randomized trial evaluating efficacy of a single subcutaneous administration in children aged 6 to 10 years in a seasonal setting in Mali (NCT05304611) *(25)*, both evaluating L9LS compared to placebo.

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1   The CIS43 mAb was isolated from a clinical trial participant protected against controlled human malaria infection (CHMI) following immunization with an attenuated *P. falciparum* whole-sporozoite vaccine (Sanaria), whose serum also exhibited high anti-*Pf*CSP antibodies and in vitro functional inhibition of sporozoite invasion of hepatocytes *(20)*. CIS43 preferentially binds to a unique junctional NDNP epitope between the N-terminus and the central repeat domains of the *Pf*CSP protein *(21)*.

The most advanced transmission-blocking mAb candidate is TB31F, a humanized form of the rat mAb 85RF45.1, targeting the male gametocyte surface protein Pfs48/45. In 2020, a Phase 1 dose-escalation study evaluated the safety, pharmacokinetics and functional activity of TB31F administered intravenously and subcutaneously in healthy malaria-naïve adults in the Netherlands (NCT04238689) *(14)*.

Research is ongoing to identify and develop new malaria mAbs,[2] including efforts to standardize preclinical assays to enable improved evaluation and selection of mAb candidates. Challenges remain in the translatability of results from preclinical models to human studies,[3] as well as from CHMI to field studies under conditions of natural exposure (e.g. in terms of the minimum dose or antibody concentration required for protection). Overall, the harmonization of assays and study designs across research groups would enable better comparability of studies, laboratories and settings (see Annex 1).

While early identification of mAb candidates typically select for binding affinity and specificity for target antigens, other factors such as a product's biophysical properties and the ability for further engineering are also critical for formulation and ease of manufacturing. A combination of increased potency and extended antibody half-life will impact the dose and regimen. Enhanced potency that can achieve antigen neutralization with fewer antibodies can allow for lower dosage (i.e. reduced antibody concentration and volume) and easier administration (i.e. intramuscular or subcutaneous injection rather than intravenous), while extended antibody half-life would enable a longer duration of protection and less frequent dosing.

A number of technical advances are enabling the engineering of mAbs to improve their potency, breadth, half-life and biophysical properties. These include modifications to increase half-life or Fc effector function, as has been done with mAbs for malaria (CIS43LS, L9LS) *(27)* and RSV (MEDI8897) *(28)*. Other innovations include multi-specific antibodies, antibodies designed to bind and neutralize several antigens, or multi-valent antibodies designed to have multiple binding domains to increase avidity and potency, although these mAbs may require a more complex downstream manufacturing process *(29)*.

Nucleic acid delivery of mAbs (e.g. RNA, viral vectors) has also been suggested as a way to overcome some of the complex production and purification processes associated with cell-based mAb manufacturing and to address challenges related to potency, efficacy and half-life. However, these products will likely require different R&D and regulatory considerations.

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2   New technology platforms, such as the Berkeley Lights Beacon, have enabled large-scale, high-throughput single B-cell sorting to screen for parasite-stage or antigen-specific antibodies. Methods are also being explored to generate more potent mAbs, including the use of human B-cell knock-out mice and yeast display platforms to evaluate a range of single amino-acid mutations in existing mAb candidates, or modifications to the Fc region to increase effector functions *(26)*.

3   In vitro assays of functional activity are currently used to prioritize and select candidates for in vivo studies, but improved assays are needed (e.g. with a greater dynamic range) to better predict in vivo responses in mouse models. The use of humanized mouse models (FRG-huHep) infected with wild-type *P. falciparum* is one method that has been used to improve the translatability of preclinical results to CHMI.

4. CLINICAL RESEARCH AND DEVELOPMENT CONSIDERATIONS

4.1 End-points, case definitions and analytical strategies in late-stage clinical development

The optimal approach to measuring the efficacy and public health impact of mAbs for malaria prevention will vary according to the evaluation phase. End-points that are closer to the point of biological action can be useful in early-stage evaluation, whereas end-points that are further downstream may be increasingly useful in later development, depending on a product's indication for use (Fig. 1). For example, evidence of efficacy in smaller CHMI Phase 1/2a studies can build confidence for investment in larger Phase 2b studies under conditions of natural infection. Initial assessments in malaria-naïve subjects enable measurement of efficacy without the influence of naturally acquired immunity unrelated to the intervention. End-points may also differ depending on the mode of action, for example, focusing on the number of individuals protected for pre-erythrocytic mAbs, parasite density or multiplication rate for blood-stage mAbs, and/or infectivity through transmission assays or reduction of community transmission for transmission-blocking mAbs. Therefore, it is important to indicate the primary end-point used to define protective efficacy when reporting study results.

Fig. 1. Clinical evaluation end–points and analytical strategies for mAbs to reduce malaria morbidity and mortality

| Malaria infection | Uncomplicated malaria | Severe malaria | Malaria-related hospitalizations, mortality |

Phase 1–2a
- End-points: infection incidence +/– prevalence, density
- N = 10s

- Exposure: CHMI
- Method: microscopy, molecular assays

Phase 2b
- Primary end-points: clinical malaria (first/only episode) +/– infection
- Secondary end-points: infection, severe malaria
- N = 100s

- Natural exposure
- Methods: microscopy, rapid diagnostic test, molecular assays
- Strategy: active +/– passive case detection

Phase 3
- Primary end-point: clinical malaria (all episodes) +/– infection
- Secondary end-points: infection +/– severe malaria, hospitalizations, mortality
- N = 100s – 10 000s

- Natural exposure
- Methods: microscopy, rapid diagnostic test, molecular assays
- Strategy: passive case detection, all clinical episodes

Phase 4 (post-licensure monitoring, case control)
- End-points: severe malaria, malaria-related hospitalizations and mortality, all-cause mortality

*Safety is evaluated at all stages.

Potential primary and secondary end-points to evaluate mAbs for reducing malaria morbidity and mortality include:

- **Infection**, through CHMI studies[4] or field trials under conditions of natural exposure: Efficacy against new infections may be included as an end-point in Phase 2 trials or measured in additional cohorts in Phase 3 trials that have clinical malaria as the primary end-point *(31)*. Frequent monitoring of secondary infection end-points in sub-cohorts under conditions of natural exposure in Phase 3 studies could help to understand efficacy dynamics and decay and whether clinical trial data are translatable across different transmission settings. For example, assessment of efficacy against new infections could potentially be measured alongside clinical disease end-points using parallel cohorts *(31)*. Standardization of study protocols in terms of the frequency of follow-up and the diagnostic method used to confirm infections (e.g. rapid diagnostic test, microscopy or polymerase chain reaction) will enable better comparability of results from different studies (Annex 1). While data on clinical end-points may be expected in Phase 3 evaluation, use of infection as a primary end-point in Phase 3 could allow for trial efficiencies (e.g. size, duration, cost), but would require early consultation with regulatory authorities on its acceptability for licensure. Developers are strongly encouraged to discuss product-specific evaluation plans and end-points with regulators and WHO.

  In some Phase 2 studies, the use of drug treatment to clear parasites prior to administration of mAbs may be of interest to ensure that any parasites detected in the follow-up period are due to new infections rather than infections that were recrudescent or present at the time of mAb administration. However, use of pre-immunization parasite clearance in Phase 3 studies has implications for product labelling for licensure and use. Treating study subjects prior to mAb administration as a means of pre-immunization parasite clearance in Phase 3 should only be done if the intention is to include this on the label as part of the expected mode of deployment *(32)*.

- **Incidence of all episodes of clinical malaria** should be the primary end-point in Phase 2b and Phase 3 trials. The definition of a clinical malaria episode should include history of fever in the previous 48 hours or measured fever (e.g. axillary temperature of > 37.5°C) at presentation and a parasite density threshold that delivers an acceptable level of sensitivity and specificity *(33)*. This threshold may vary according to the endemicity of malaria in different settings and include, for example, any detectable parasites in low-transmission settings and a minimum parasite density of 5000/μL in moderate- or high-transmission settings. Ensuring that there is a specific case definition will reduce the bias towards the null of vaccine efficacy estimates. The effect on the incidence of first episodes of malaria may also be evaluated in Phase 2 studies, although this is less relevant than the impact on all episodes of malaria to understand the potential public health benefit, which is the preferred approach in Phase 3 evaluations.

  The case detection system has an important bearing on the interpretation of efficacy. Either active case detection (ACD) or passive case detection (PCD) may be used. In Phase 2b efficacy studies with a modest number of subjects, the use of ACD, which includes regular home visits by study staff, may be appropriate. PCD will generally be preferred for Phase 3 trials in

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4   These have been widely used in early screening of disease-reducing vaccines (see *Appendix 1. Controlled human malaria infection trials (30)*).

order to measure the public health impact of reducing the malaria burden in health facilities *(32)*. The results of study end-points detected through PCD systems will be impacted by factors such as distance of trial participants from the health facility, treatment-seeking behaviour, differences in clinical characteristics of cases and the approach to diagnosis. Clear descriptions of any PCD systems used in a trial, including potential limitations or variations at study sites, should be well documented. Important differences in PCD systems between studies or sites may confound the comparison of results between locations. Potential confounding factors related to ACD systems used in trials, such as the frequency of follow-up visits, should also be clearly described.

- **Severe malaria, malaria-related hospitalization and mortality, and all-cause mortality:** Although these end-points are of greatest relevance to public health, they are less common than uncomplicated disease and require considerably larger sample sizes to measure with precision in Phase 3 trials. These end-points may be more amenable to evaluation in Phase 4 studies.

4.2 Trial design considerations

The following section describes overall considerations for the design of trials to evaluate the safety and efficacy of malaria mAbs. However, product developers will need to consult with relevant regulatory agencies and WHO departments regarding product-specific clinical development plans and requirements for licensure and/or WHO recommendation.

4.2.1 Efficacy and duration of protection

To best evaluate the potential public health impact of a malaria mAb candidate, target efficacy and duration of efficacy should both be documented. Standardizing follow-up periods and frequency of monitoring to determine duration of efficacy will also enable better comparability across studies. Trials conducted in perennial transmission settings will be better able to assess the duration of protection than trials conducted in intensely seasonal transmission settings. This is an important parameter to define, even for products intended for seasonal administration, as the required duration of protection will vary between settings.

Maintenance of protection for the entire malaria risk period with a single dose is preferred over repeat administration, but the optimal dose regimen will be informed by clinical trial data and early-stage evidence of duration of protection. If repeat dosing is required (annually or within a single transmission season), data should be generated to examine the possibility of reduced efficacy with subsequent administration, e.g. due to the development of anti-drug antibodies (ADAs).

4.2.2 Comparator arms

Interventions used in malaria control programmes are continuously evolving. SMC is the recommended standard of care in children under 5 years of age in areas of highly seasonal transmission in the Sahel subregion of Africa. Following the recommendation for wide-scale use of the RTS,S/AS01 malaria vaccine, trials may need to consider the use of this first-generation vaccine in the country where trials are planned. The choice of comparator and trial designs considered appropriate will depend on the context in which a mAb candidate is intended for use, the view of local ethical committees, the needs of regulators to support licensure and the opinion of public health stakeholders involved in decision-making for implementation.

Consideration of comparator arms may also be important in cost-effectiveness evaluations to guide programmatic decision-making following licensure.

Studies should be conducted across settings with a range of transmission intensities and seasonal variation. Data on efficacy should be obtained from a representative selection of areas in which the product may ultimately be deployed. The sponsor may choose to perform separate studies in different geographical areas or to conduct one large multi-centre study. If the latter approach is adopted, a predefined stratification of enrolment by area should be used to support secondary analyses of efficacy by transmission pattern *(32)*.

4.2.3 Post-licensure and Phase 4 studies

In addition to monitoring safety in routine use, post-licensure studies can provide critical additional data, for example, on the generalizability of efficacy or effectiveness results in transmission settings that differ from those in which the candidate was trialled. Several end-points, including severe malaria, malaria-related hospitalization and inpatient mortality, and all-cause mortality, while relevant to understanding the broader public health impact of mAbs, may not be feasible in Phase 3 trials, but could be evaluated in post-licensure studies.

The potential for rebound, a period of increased malaria risk after time-limited protection from malaria due to an intervention relative to individuals of the same age group and population who did not receive the intervention, may need to be considered during clinical trials and post-licensure studies. Longer periods of follow-up (more than one year) following policy recommendation, using the same end-points in the intervention and rebound periods, can enable the measurement of relative risk over time and cumulative net impact *(34)*.

4.2.4 Studies in additional target populations

For evaluation in younger, more vulnerable age groups, safety and efficacy in adults or older children should first be demonstrated in Phase 1 and 2 studies. Subsequent age de-escalation studies can be conducted to ensure that the product is equally safe and efficacious in younger children, followed by Phase 3 studies in the target age group.

To evaluate the safety of mAbs during pregnancy and lactation, studies should follow staged evaluation designs similar to those recommended for vaccines. Options may include first conducting studies in women of childbearing age with specific follow-up in women who become pregnant in the months immediately following immunization with mAbs. For trials evaluating immunization during pregnancy, regulatory authorities may generally recommend starting trials in women in their third trimester *(35,36)*.

4.3 Safety considerations

The safety and reactogenicity of mAb candidates should be comparable to the safety and reactogenicity of malaria vaccines or drugs administered for disease prevention in the same age groups in the settings intended for use.

If repeat administration of mAbs per individual is expected, either during a single transmission season or annually, the possibility of ADAs *(37–39)* that may interfere with efficacy or lead to adverse reactions should be evaluated. ADA studies should have a follow-up period that is long enough to monitor the effect of repeat doses, which may vary according to the intended dose schedule. Studies should be designed to evaluate the total number of repeat doses envisioned in the lifetime of an individual, potentially as part of post-licensure monitoring.

The safe co-administration of mAbs with routine interventions, including vaccines and malaria drugs used for treatment or chemoprevention, should also be evaluated in the settings where they are intended for use. Non-interference between malaria vaccines and mAbs that target the same antigen should also be evaluated. While passive immunization with mAbs may present a low risk of interaction with vaccines, early immunological studies are needed to rule out potential safety concerns.

Another potential safety consideration, which has been a concern with SARS-CoV-2 therapeutic mAbs, is the emergence of pathogen mutations arising in immunocompromised patients that are able to escape neutralizing antibodies *(40)*. It may be of interest to monitor the effect of selection pressures introduced by the use of malaria mAbs that may lead to immunologically important mutations; further discussion is needed on the most suitable study designs for evaluating and monitoring these risks.

4.4 Modelling and simulation to inform target mAb product characteristics

Mathematical and statistical modelling may help to provide a rational basis for the specification of product characteristics and testing and deployment considerations. For example, data from early clinical development of mAb candidates are useful for modelling pharmacokinetic and pharmacodynamic profiles, accounting for factors such as mode of action, initial efficacy, antibody half-life and efficacy decay rate *(41)*. The use of malaria transmission models with sufficient detail to capture mAb properties, diverse settings and populations, and the entire malaria transmission cycle could enable early investigation of the potential public health benefit of mAbs. Modelling can support considerations and decisions related to clinical trial testing and implementation, such as target age range, population coverage, extrapolation of adult efficacy data to children, seasonal malaria patterns and deployment timing with the transmission season given product characteristics. Such analysis can help to understand the trade-offs between product characteristics and implementation strategies and will be useful for translating clinical trial evidence, optimizing trial design, estimating potential public health impact and prioritizing deployment strategies. In addition, this analysis can help to inform the likely dose range needed to achieve the level and duration of protection required to reduce target levels of clinical incidence and/or other outcomes of interest (i.e. incidence of infection, severe malaria, hospitalization or death) *(42)*.

5. PRODUCTION AND MANUFACTURING

In addition to ensuring safety and demonstrating efficacy, product developers should address manufacturing considerations early in development so that production of licensed products can be scaled to cover the target population in need without significant delay. Several factors are key to low-cost, rapid mAb development and manufacturing.

A mAb candidate should ideally be selected for or engineered to be easily expressed and have low viscosity. This involves substantial upfront biophysical characterization and in silico analysis to determine product suitability for manufacturing and formulation, which can result in a differential cost of development even for candidates with similar potency. Factors that affect manufacturing and formulation include the ability to engineer a product to remove potential hurdles, such as unwanted post-translational modifications or characteristics that affect formulation stability (e.g. propensity for aggregation, conformational stability, colloidal stability, protein–protein interactions, non-specific binding, etc.).

Potency, dose and volume also affect the manufacturing process and final cost of goods. High dose volumes can make subcutaneous or intramuscular administration unfeasible, particularly in young children and infants (43), and less suitable for wide-scale use in LMICs. Intravenous administration may potentially be feasible in special populations, such as pregnant women receiving mAbs in antenatal clinics or as PDMC in children admitted to hospital with severe anaemia. However, data supporting the feasibility and acceptability of intravenous administration for these target populations in LMICs would likely be needed during evidence review for policy recommendation. At the same time, high-concentration formulations can result in increased viscosity and aggregation, presenting processing challenges, such as the filtration required to concentrate the product or lower recovery and excessive loss of the final product (44). mAbs also need to be sufficiently stable and soluble at the concentrations required to achieve efficacy at volumes that can be administered feasibly in the target population. Therefore, formulation studies should be closely linked to downstream manufacturing considerations.

If a product's indication includes a large target population and/or repeat administration requiring high volumes, the scale and speed of manufacturing processes needed may make it difficult to meet demand at a cost suitable for LMICs. Traditionally, commercial mAbs are produced in mammalian Chinese hamster ovary (CHO) cell lines engineered to produce large quantities of antibodies (1–5 g/L), grown in large bioreactors, then purified and formulated through batch production (16). While CHO cells can produce fully functional proteins that are well tolerated in humans, they require long production times at high cost.

Therefore, a variety of antibody-expression systems and delivery platforms have been considered to accelerate clinical development, increase yields and reduce the production costs of mAbs. Alternative production hosts such as yeast, *Escherichia coli* and plants have been proposed, which may enable more rapid production (29,43).

Innovations are being explored to improve the efficiency and cost of large-scale mAb production. These include integrated continuous biomanufacturing platforms and/or single-use automated operations that can be used in tandem and require lower capital investment to construct (16,45). Modular and transportable facility units are also being developed, which could enable small-footprint in-country production in

LMICs. However, most of these technologies have yet to be tested or used for quality-controlled local production in LMIC settings. Ensuring adequate production to meet the supply needed for a large target population will require multiple manufacturers and could benefit from long-term investment in manufacturing in malaria-endemic countries to provide affordable mAbs at scale, facilitating global access.

WHO is preparing guidance on the manufacturing and quality control of mAbs and mAb fragments, as well as regulatory considerations for the preclinical and clinical evaluation of mAbs for infectious diseases. Once available, these guidance documents will be accessible at: www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/guidelines-for-biologicals.

6. WHO PREQUALIFICATION

WHO prequalification enables procurement through United Nations agencies and other global mechanisms and provides international assurance of quality, safety, efficacy and suitability for LMIC programmes. WHO encourages developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development, and to discuss product and regulatory requirements with the WHO Prequalification Team early in the process. Regulatory pathways impact eligibility for prequalification. Readers are encouraged to refer to the WHO Coordinated Scientific Advice Procedure, which ensures that consolidated advice is provided on clinical development strategies from all relevant WHO departments *(46)*.

The WHO Prequalification Team – Medicines will review and prequalify generic biosimilar mAbs through a "full assessment", if the product is not approved by a stringent regulatory authority, and through an "abridged assessment", if the product is already approved by a stringent regulatory authority. In some cases, the WHO Prequalification Team – Medicines will also undertake an "abridged assessment" for originator products that have been approved by a stringent regulatory authority. Specific requirements for the prequalification of mAbs are outlined in *Pilot prequalification of biotherapeutic products (3)*. WHO launched a pilot project to prequalify select biosimilars, which resulted in WHO prequalification of the first mAb in late 2019, a trastuzumab biosimilar for the treatment of breast cancer *(47)*. Recognizing that regulatory assessment of mAbs can be challenging for many countries, WHO has published guidance documents on the regulatory considerations for biotherapeutics and on mAbs as similar biotherapeutic products *(48)*. However, additional guidance on the prequalification of preventive mAbs has not been issued at the time of writing. It is also important to note that, at the time of this publication, no malaria mAbs have been approved by a stringent regulatory authority, so the pilot project outlined for biosimilars would not be applicable.

7. PPCs FOR mAbs TO REDUCE MALARIA MORBIDITY AND MORTALITY IN CHILDREN

Parameters	Preferred product characteristics	Notes
Indication for use	Reduction of morbidity and mortality in children due to *P. falciparum* infection	See "Section 2.1. Priority use case scenario: reduction of morbidity and mortality in children".
Target population	Infants and children in the age groups that contribute substantially to the disease burden	In most settings, this will be children aged 5 years and under, but may include children over 5 years in some settings.
Safety	Safety, tolerability and reactogenicity comparable to other vaccines or drugs administered for disease prevention in the same age groups in the settings intended for use If more than one dose of mAbs is to be given, the impact of ADAs should be evaluated *(49)*.	See "Section 4.3. Safety considerations".

| **Efficacy and duration** | At least 80% preventive efficacy against clinical disease at 3–4 months' follow-up

In Phase 3 trials, all episodes of clinical malaria detected through PCD should be the primary trial end-point. Efficacy against infection may be suitable as a primary end-point in Phase 2 studies, or measured in Phase 3 alongside clinical disease end-points in parallel cohorts.

Efficacy should be maintained with repeat dosing (i.e. no significant reduction in protective efficacy due to ADAs). | Preferred duration against clinical disease is a minimum of 3–4 months (demonstrated in at least a moderate-transmission setting), but duration up to six months is highly desirable if needed to cover the period of malaria risk, depending on the settings intended for use.

mAbs with lower efficacy and a longer duration may have useful public health impact. Total efficacy can be measured as the preventive efficacy over the time of malaria risk (or the area under the efficacy–time curve during the risk period).

Choice of comparator will depend on the locally relevant standard of care (which may include malaria vaccines, SMC or both) at the time of clinical evaluation.

ACD is useful for measuring infection end-points, while PCD of clinical malaria is preferred in Phase 3 trials in order to better understand the public health impact on burden reduction in health facilities. Frequent monitoring of secondary infection end-points in sub-cohorts under conditions of natural exposure in Phase 3 studies can also help to understand efficacy dynamics and decay and translation of clinical trial data across a diversity of transmission settings.

Use of pre-immunization parasite clearance in Phase 3 studies has implications for product labelling for licensure and use. Treating study subjects prior to mAb administration as a means of pre-immunization parasite clearance in Phase 3 should only be used if the intention is to include this on the label as part of the expected mode of deployment.

Assessment of more severe end-points, including severe malaria, malaria-related hospitalization and inpatient mortality, and all-cause mortality, may be difficult to measure with precision in Phase 3 trials due to the large sample sizes required and are more suitable for evaluation in post-licensure or Phase 4 studies.

See:

"Section 4.1. End-points, case definitions and analytical strategies in late-stage clinical development"; and

"Section 4.2. Trial design considerations". |

Dose regimen and schedule	A single-dose regimen is highly preferred, but additional doses may be acceptable if needed to maintain protection for the duration of the malaria risk period. As noted above, the impact of repeat administration on efficacy and safety should be assessed. The dosing schedule should be feasible to implement by malaria control programmes in the settings intended for use. Fixed dosing, based on weight categories, is preferred.	mAbs requiring more than one dose to protect throughout the malaria season may be considered, based on local cost-effectiveness analyses and programmatic suitability. See "Section 4.2.1. Efficacy and duration of protection".
Co-administration	Safe co-administration with routine interventions in children, including childhood vaccines, and malaria drugs used for treatment or chemoprevention in the settings intended for use. Non-interference between malaria mAbs and vaccines sharing the same target antigen that may be co-administered.ª	Potential interference with any licensed malaria vaccines or drugs will need to be evaluated. Choice of vaccines for co-administration studies should be driven by the vaccines in use in the target population, such as those delivered through routine childhood immunization programmes. Relevant co-administration studies are typically included in pre-licensure clinical development plans. If necessary, further co-administration studies could be performed in parallel or following completion of Phase 3 efficacy studies. The principles of the design of these studies are discussed in *WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (51)*. See "Section 4.3. Safety considerations".
Formulation/ presentation	Malaria mAbs should meet WHO-defined criteria for programmatic suitability regarding formulation, presentation, packaging and disposal *(52)*.	
Route of administration	Intramuscular or subcutaneous dose is preferred, using standard volumes for injection.	A 0.5 mL dose is preferable for young infants, but up to and including 1.0 mL in infants and young children < 5 years is considered suitable *(53)*. Larger dose volumes should be supported by studies evaluating safety and tolerability in the target child population.

Product stability and storage	mAbs should be stable in refrigerated conditions (2°C to 8°C) for 24 months *(54)*. A single-vial product or pre-filled syringe is preferred. WHO-defined recommendations on presentation, packaging, thermostability, storage volume and disposal should be met, where applicable to mAbs *(52)*.	Specific requirements for prequalification of mAbs are outlined in the *Pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products (3)*. However, final guidance on prequalification of preventive mAbs has not yet been issued at this time.
Registration, WHO prequalification and programmatic suitability	Must be licensed and approved by national regulatory authorities in countries of use. WHO-defined criteria for prequalification and programmatic suitability, and recommendations on presentation, packaging, thermostability, storage, volume and disposal should be met, where applicable to mAbs.	Specific requirements for prequalification of mAbs are outlined in the *Pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products (3)*. However, final guidance on prequalification of preventive mAbs has not yet been issued at this time. The WHO Prequalification Team – Medicines can undertake an "abridged assessment" of originator mAb products that have been approved by a stringent regulatory authority. Prequalification by WHO will facilitate approval and ability to purchase products for LMICs. See "Section 6. WHO Prequalification".
Access and affordability	Dose, regimen, cost of goods and health system delivery costs should enable affordable supply and delivery and should not be a barrier to access in LMIC settings.	Analyses of the cost-effectiveness and acceptability from an LMIC perspective should be conducted. Price considerations should also take into account the ability of those LMICs that are not eligible for external funding (e.g. through Gavi, the Vaccine Alliance, and the Global Fund to Fight AIDS, Tuberculosis and Malaria) to pay. See "Section 5. Production and manufacturing".

a   Studies on mAb–vaccine interaction are generally not required by regulatory authorities to support licensure. The potential risk of interference would be determined by the mAbs' mechanism of action. To date, non-malaria mAb–vaccine interaction studies have been limited to mAbs directed against human immune mediators to assess whether the mAbs would alter the immune system and affect the response to vaccinations (e.g. secukinumab, dupilumab) (50).

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ANNEX. CLINICAL DEVELOPMENT DATA STANDARDIZATION TEMPLATES

Standardization of trial data collection can enable comparisons between studies. Tables A1.1 and A1.2 illustrate key variables to measure at harmonized follow-up time points to reflect the dynamics of efficacy. These data can aid the interpretation of results across different CHMI studies and field trials.

Table A1.1 Example data template for CHMI studies

mAb candidate[a]	Dose regimen[b]	Challenge & inoculation schedule[c,d]	Challenge strain	Study population			Infection end-point			Vaccinated		Controls		Efficacy (incl. primary end-point)[h]
				Location	Exposure	Age range & sex	Measure-ment[e]	Assay[f]	Follow-up	Number protected, PMR, or infectivity[g]	Number not protected	Number protected, PMR, or infectivity[g]	Number not protected	
			Pf7G8	USA	Malaria naive	18–65 yrs (males)			21 days					

a   Description of candidate should indicate life-cycle stage targeted (pre-erythrocytic; blood stage; sexual, sporogonic or mosquito stage).

b   Dose regimen should include dose and schedule.

c   Challenge and inoculation schedule should specify timing in relation to last mAbs dose.

d   Route of inoculation for malaria challenge should specify intravenous/intramuscular/intradermal sporozoite injection, mosquito bite or blood-stage inoculation.

e   Measurement description should indicate definition of end-point (e.g. slide/polymerase chain reaction positivity, parasite density).

f   Assay (e.g. polymerase chain reaction, microscopy)

g   PMR: parasite multiplication rate (blood-stage mAbs), or infectivity (transmission-blocking mAbs). Number protected should indicate measure of infection used to define protective efficacy. End-points will differ depending on the product type. Pre-erythrocytic mAbs will primarily measure number protected, blood-stage mAbs will measure parasite multiplication rate, and transmission-blocking mAbs will measure infectivity. All should compare immunized and control groups in terms of the respective end-points.

h   Efficacy should indicate the primary end-point used to define protective efficacy. Measure of protective efficacy will vary by product type - e.g. individuals protected (pre-erythrocytic mAbs), reduction in parasite density (blood-stage mAbs), reduction in infectivity (transmission-blocking mAbs).

Table A1.2 Example data template for field trials under conditions of natural exposure

| mAb candidate[a] | Trial registration number | Dose regimen (incl. timing w/ season)[b] | Malaria control measures in place | Study population | | End-point | | | Vaccinated | | | | Controls | | | | Efficacy (incl. primary end-point)[d] |
				Location	Age range & sex	End-point	Method	Follow-up[b]	Sample size	PYAR[c]	Number of events	Incidence rate	Sample size	PYAR[c]	Number of events	Incidence rate	

a   mAb candidate, including life-cycle stage targets (pre-erythrocytic; blood stage; sexual, sporogonic or mosquito stage).

b   Dose regimen should include dose, schedule and timing with malaria transmission season. Timing of mAbs administration schedule with malaria transmission season and duration of follow-up should enable protective efficacy (including number of events by study arm) to be considered in the context of the period of malaria risk.

c   PYAR: person-years at risk

d   Efficacy should indicate primary end-point used to define protective efficacy. Measure of protective efficacy will vary by product type - e.g. individuals protected (pre-erythrocytic mAbs), reduction in parasite density (blood-stage mAbs), validated surrogate end-point or reduction of community transmission (transmission-blocking mAbs).

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