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RTS,S: Toward a first landmark on the Malaria Vaccine Technology Roadmap

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ABSTRACT

The Malaria Vaccine Technology Roadmap calls for a 2015 landmark goal of a first-generation malaria vaccine that has protective efficacy against severe disease and death, lasting longer than one year. This review focuses on product development efforts over the last five years of RTS,S, a pre-erythrocytic, recombinant subunit, adjuvanted, candidate malaria vaccine designed with this goal of a first-generation malaria vaccine in mind. RTS,S recently completed a successful pivotal Phase III safety, efficacy and immunogenicity study. Although vaccine efficacy was found to be modest, a substantial number of cases of clinical malaria were averted over a 3–4 years period, particularly in settings of significant disease burden. European regulators have subsequently adopted a positive opinion under the Article 58 procedure for an indication of active immunization of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B. Further evaluations of the benefit, risk, feasibility and cost-effectiveness of RTS,S are now anticipated through policy and financing reviews at the global and national levels.

1. Introduction

RTS,S, a subunit malaria vaccine candidate, has now reached the scientific and regulatory milestone of a positive scientific opinion from European regulators for the prevention of malaria in young children in sub-Saharan Africa and continues to progress toward potentially being the first malaria vaccine deployed against a human parasite. RTS,S is comprised of a liposome-based adjuvant (AS01) and hepatitis B virus surface antigen (HBsAg) virus-like particles incorporating a portion of the *Plasmodium falciparum*-derived circumsporozoite protein (CSP) genetically fused to HBsAg. The indication is for active immunization of children aged 6 weeks up to 17 months against malaria caused by *P. falciparum* and against hepatitis B. If approved by national regulatory authorities and recommended by policy makers in countries of use, development of RTS,S will have taken more than 30 years (see Fig. 1). For a summary of the major milestones achieved during the first two dozen years of RTS,S development, the reader is referred to reviews published in 2010 [1,2]. The present review focuses on product development efforts and the associated scientific literature over the last half decade, particularly the Phase III program, the regulatory and anticipated policy and financing pathways, and the planned post-approval program/Phase IV studies.

But first, a recapitulation of the rationale for development of RTS,S in the context of the Malaria Vaccine Technology Roadmap developed by World Health Organization (WHO) in consultation with the Scientific & Public Health Malaria Community [3,4], is provided.

2. RTS,S and the Malaria Vaccine Technology Roadmap 2015 Landmark Goal

The Malaria Vaccine Technology Roadmap (MVTRM) was originally launched in 2006 and focused on the urgent need for vaccines to alleviate the ongoing severe disease and death due to malaria. As such, the priority for the global malaria vaccine development efforts was on *P. falciparum*, children under 5 years of age, and sub-Saharan Africa and other highly endemic regions. Largely driven by

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CSP, circumsporozoite protein; EMA, European Medicines Agency; GFATM, Global Fund to Fight Aids, Tuberculosis and Malaria; HBsAg, hepatitis B virus surface antigen; ITT, intention-to-treat; JTEG, Joint Technical Expert Group; MPAC, Malaria Policy Advisory Committee; MPL, monophosphoryl lipid A; MVTRM, Malaria Vaccine Technology Roadmap; PAP, post-approval program; SAGE, Strategic Advisory Group of Experts; TSP, Thrombospondin-like type I repeat domain; VE, vaccine efficacy; VIS, Vaccine Investment Strategy; WRAIR, Walter Reed Army Institute of Research; WHO, World Health Organization.

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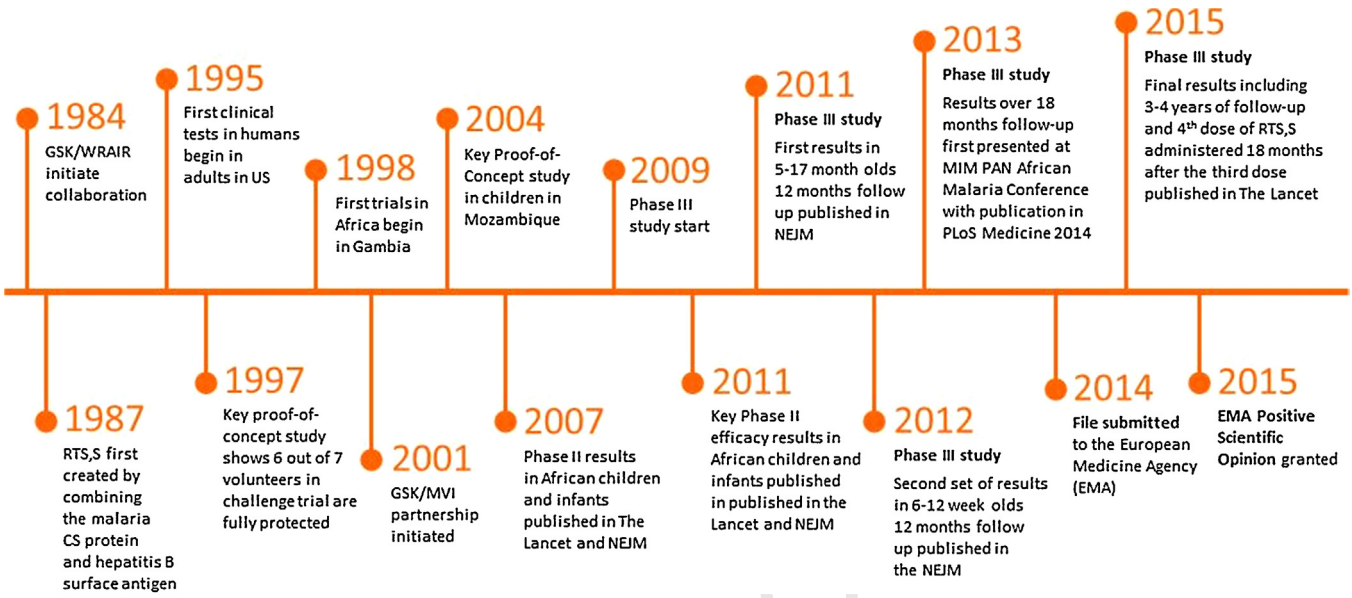

Fig. 1. The timeline for development of RTS,S through 2015 spans 30 years. The effort by GlaxoSmithKline (GSK) can be traced back to a collaboration with Walter Reed Army Institute of Research (WRAIR) initiated in 1984. GSK and the PATH Malaria Vaccine Initiative (MVI) partnership was initiated in 2001. Proof-of-concept (PoC) was established in 2004 and the pivotal Phase III trial was initiated in 2009 (reviewed in [1]) and completed in 2014 [34]. GSK submitted a regulatory application to the European Medicines Agency (EMA) for review under the Article 58 procedure in 2014 [39]. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in July 2015 [6].

the progress of early clinical development of RTS,S, the MVTRM set the following landmark goal: "By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50 percent against severe disease and death and lasts longer than one year" [3].

The shared vision and strategic goals of the MVTRM were expanded in 2013 to include development of vaccines against *Plasmodium vivax* and development of malaria vaccines that reduce transmission of the parasite [4]. This expansion was driven by marked changes in malaria epidemiology associated with the scale-up of malaria control measures and the resultant reductions in malaria parasite transmission, a shift in peak age of clinical malaria to older age groups, and a decline in malaria-related deaths, coupled with substantial changes in the malaria research agenda. As the focus of the RTS,S development program was on the pediatric indication to prevent clinical malaria, the contribution of RTS,S to the strategic goal of developing vaccines that interrupt malaria parasite transmission (also known as VIMTs) has been largely unexplored to date, other than some recent preliminary findings that suggest that serum from RTS,S-vaccinated individuals does not inhibit sporogony in mosquitoes [5]. That said, the original 2015 landmark, which captures the goal of a first-generation malaria vaccine, remains unchanged in the updated MVTRM [4]. In that regard, on 23 July 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in accordance with the European Medicines Agency (EMA) Article 58 procedure, recommending the granting of a marketing authorization for RTS,S for an indication of active immunization of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B [6].

3. Circumsporozoite protein and RTS,S

The sporozoite plays a central role in the parasite life cycle, from the maturing *Plasmodium* oocyst in the midgut of the definitive host to initial infection of the intermediate host. In the case of *P. falciparum*, sporozoites are transmitted to the intermediate human host through the bites of the definitive female *Anopheles* mosquito hosts having parasite-infected salivary glands. Only a fraction of the sporozoites in the mosquito salivary glands are injected into the circulation and ultimately infect hepatocytes in susceptible humans. Because the parasite endures a significant numerical bottleneck as it is transmitted between hosts, it is thought the parasite is most vulnerable to immune attack as it cycles between the definitive and intermediate hosts [7]. That protective immunity able to block transmission of the parasite as it passes through these numerical bottlenecks is never acquired [8], despite repeated infections, provides an opportunity to induce novel immune responses through active immunization [9].

The circumsporozoite protein (CSP), which is the major surface protein of *Plasmodium* ssp. sporozoites, forms a dense coat on the parasite's surface and has been proposed to contribute to several critical roles as the parasites develops within the female mosquito and infects the mammalian host [10]. Although the primary amino acid sequences of CSPs differ between *Plasmodium* ssp., the basic architectures are similar (Fig. 2): a N-terminus that encodes a signal peptide sequence, binds heparin sulfate proteoglycans (Region I), and contains a conserved five amino acid (KLKQP) proteolytic cleavage site sequence and Pexel motifs [11]; a middle third that consists of tandem, species-specific amino acid repeats that are immunodominant B-cell epitopes recognized by the neutralizing antibodies [12] and contributes to sporozoite development in the mosquito [13]; and a C-terminus that contains a thrombospondin-like type I repeat domain (TSP) with cell adhesion properties (Region II), a canonical glycosylphosphatidylinositol (GPI) anchor addition sequence, and three known T cell epitopes—a highly variable $CD4^+$ T-cell epitope before the TSP, a highly variable $CD8^+$ T-cell epitope within the TSP, and a "promiscuous" $CD4^+$ T-cell epitope whose structure is conserved among all parasite isolates [14].

RTS,S contains 189 amino acids from CSP (NF54 199-387aa), including the last 18 NANP repeats and the C-terminus exclusive of the GPI anchor addition sequence. Approximately 25% of the Hepatitis B virus surface antigen (HBsAg) monomers in RTS,S particles are genetically fused to the truncated CSP and serve as protein carriers. Despite self-assembly into HBsAg virus-like particles, non-adjuvant RTS,S is weakly immunogenic and requires an adjuvant

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