

RTS,S Malaria Vaccine Clinical Trials

The RTS,S Malaria Vaccine Candidate

Malaria kills more than one million people a year worldwide and sickens millions more, most of them children living in sub-Saharan Africa. The international community urgently needs a safe and effective vaccine to control the disease. A vaccine, even a partially effective one, is a necessary component of a comprehensive malaria program and could potentially save hundreds of thousands of lives a year. RTS,S is the world's most advanced malaria vaccine candidate and the first to demonstrate in clinical trials that it can protect young children living in malaria-endemic areas against infection and clinical disease caused by *Plasmodium (P.) falciparum*, the most deadly form of the malaria parasite.

The RTS,S malaria vaccine candidate was created in 1987. Its early development was undertaken by GlaxoSmithKline (GSK) Biologicals, the vaccine division of GSK, in close collaboration with the Walter Reed Army Institute of Research (WRAIR). In January 2001, GSK and the PATH Malaria Vaccine Initiative (MVI)—with support from the Bill & Melinda Gates Foundation—entered into an agreement to develop the vaccine for infants and young children, with a geographic focus on sub-Saharan Africa.

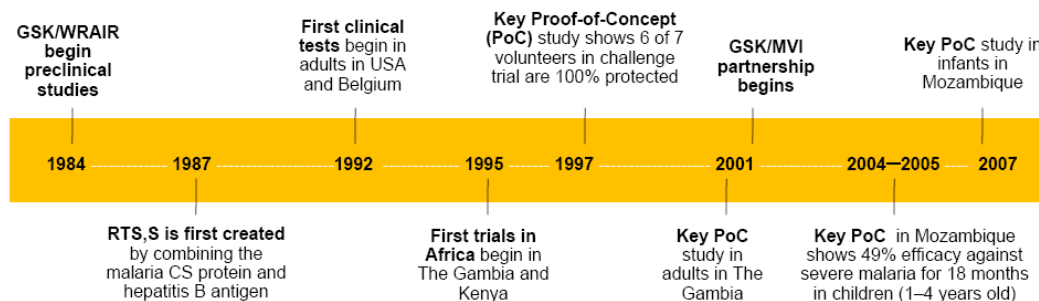
The RTS,S vaccine candidate is a recombinant protein that fuses a part of the *P. falciparum* circumsporozoite (CS) protein with the hepatitis B surface antigen. Combined with a proprietary GSK adjuvant system, RTS,S induces the production of antibodies and T cells that are believed to diminish the capacity of the malaria parasite to infect, survive, and develop in the human liver. In addition to inducing partial protection against malaria, the RTS,S vaccine candidate is also designed to protect against hepatitis B, a severe form of hepatitis and an important etiological factor in end-stage liver disease and liver cancer.

RTS,S Results to Date

Clinical evaluation of RTS,S began in adults in the United States and Belgium in 1992. Results of a trial of more than 2,000 children, started in 2003 in southern Mozambique, demonstrated the feasibility of administering a malaria vaccine in children. Findings from this trial, published in 2004 and 2005 in the medical journal *The Lancet*, showed that RTS,S was effective for at least 18 months in reducing clinical malaria by 35 percent and severe malaria by 49 percent, thus establishing RTS,S as the most advanced malaria vaccine candidate. Recent data, published on October 17, 2007, showed that RTS,S reduced infection by 65 percent over three months of follow-up, after a full vaccination course in infants—the group most vulnerable to malaria. The vaccine also reduced the risk of clinical malaria by 35.5 percent over a six-month period following the first dose. Importantly, it also displayed a promising safety and tolerability profile, similar to standard Expanded Program of Immunization vaccines commonly given to infants,

including comparable pain and swelling. The trial is the first proof-of-concept in infants of any malaria vaccine candidate, and substantially advances the vision that a vaccine could contribute to reducing the intolerable burden of disease and death caused by malaria.

RTS,S Key Milestones



Next Steps in Advancing RTS,S

Based on the successful 2004 Mozambique trial, GSK, MVI and leading local research institutions are conducting additional clinical trials in infants and young children. Researchers are exploring ways to maximize the vaccine candidate's potential by testing different formulations, dosing, and schedules. In collaboration with Africa-based research institutions, a series of clinical trials are ongoing in Mozambique, Tanzania, Gabon, Ghana, and Kenya, with other sites under consideration.

If the Phase 2 trials are successful, a large-scale Phase 3 trial—the last stage of development before licensure—will be launched in the second half of 2008. The Phase 3 studies are designed to fully determine the efficacy of the vaccine and could become the largest clinical trial ever conducted for a vaccine in Africa.

If all goes well, the RTS,S vaccine could be submitted to regulatory authorities in 2011. The partners are committed to working with governments and supranational organizations to determine demand and to develop policies and systems for financing the procurement of a prospective malaria vaccine and the implementation of vaccination programs. Once RTS,S is licensed, GSK and MVI will work to ensure this revolutionary vaccine candidate reaches the children who most need it.

Steps in Malaria Vaccine Candidate Development

Research and Preclinical Development: Identify relevant antigens and create vaccine concept; conduct pre-clinical evaluation; develop vaccine manufacturing process.

Phase 1 Clinical Trials: Establish the safety and measure immune response in malaria-naïve and malaria-exposed populations.

Phase 2 Clinical Trials: Monitor safety and potential side effects; measure immune response; measure preliminary efficacy against infection and clinical disease; and determine optimum dosage and schedule.

Phase 3 Clinical Trials: Continue to monitor safety, potential side effects, and evaluate efficacy on a large scale.

Submission to Regulatory Authorities: Submit vaccine application to regulatory authorities for approval to market.

Introduction: Make vaccine available for use.

Phase 4 Clinical Trials: Conduct postmarketing safety monitoring; measure duration of protection and assess vaccine compliance.

The PATH Malaria Vaccine Initiative (MVI) is a global program established at PATH through an initial grant of \$50 million from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. MVI's vision is a world free from malaria. For more information, please visit www.malariavaccine.org. **PATH** is an international, nonprofit organization that creates sustainable, culturally relevant solutions that enable communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act. PATH's work improves global health and well-being. For more information, please visit www.path.org.

GlaxoSmithKline Biologicals (GSK Bio), one of the world's leading vaccine manufacturers, is headquartered in Rixensaart, Belgium, where the majority of GlaxoSmithKline's activities in the field of vaccine research, development and production are conducted. GSK Bio employs more than 1,500 scientists, who are devoted to discovering new vaccines and developing more cost-effective and convenient combination products to prevent infections that cause serious medical problems worldwide. In 2006, GSK Bio distributed more than 1.1 billion doses of vaccines to 169 countries in both the developed and the developing world, an average of more than 3 million doses per day. GlaxoSmithKline—one of the world's leading research-based pharmaceutical and healthcare companies—is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information please visit www.gsk.com.