

Fact sheet: RTS,S/AS malaria vaccine candidate

The RTS,S/AS 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 with a partially effective profile, is a necessary component of a comprehensive malaria control program and could potentially save hundreds of thousands of lives a year. RTS,S/AS is the most clinically advanced malaria vaccine candidate in the world, and the first to demonstrate in clinical trials that it can protect young children and infants living in malaria-endemic areas against infection and clinical disease caused by *Plasmodium (P.) falciparum*, the most deadly species of the malaria parasite.

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

The RTS,S/AS vaccine candidate is a recombinant protein that fuses a part of the *P. falciparum* circumsporozoite protein with the hepatitis B virus 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.

RTS,S/AS results to date

Clinical evaluation of RTS,S/AS began in adults in the United States and Belgium in 1992. Results of a trial conducted in more than 2,000 children and initiated 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/AS was effective for at least 18 months in reducing clinical malaria by 35 percent and severe malaria by 49 percent^{1,2}.

Data published in October 2007, showed that RTS,S/AS reduced infection by 65 percent over three months of follow-up, after a full vaccination course in infants, the group most vulnerable to malaria³. The vaccine candidate 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 the standard Expanded Program on Immunization (EPI)vaccines commonly given to infants, including comparable pain and swelling. The trial was the first to establish proof-of-concept of efficacy in infants of any malaria vaccine candidate.

Most recently, the results of two distinct studies conducted in Africa were published online in the prestigious *New England Journal of Medicine* on December 8, 2008^{4,5}. Together, these studies substantiate the ongoing efforts for the launch of large-scale Phase III trials of RTS,S/AS01 in its target populations of infants and children.

¹ Alonso PL, Sacarlal J, Aponte JJ, et al. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomized controlled trial. *Lancet* 2004 Oct 16-22;364(9443):1411-20

² Alonso PL, Sacarlal J, Aponte JJ, et al. Duration of protection with RTS,S/AS02A malaria vaccine in prevention of *Plasmodium falciparum* disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *Lancet* 2005 Dec 10;366(9502):2012-8

³ Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet* 2007 Nov 3;370(9598):1543-51. Epub 2007 Oct 18.

⁴ Bejon P, Lusingu J, Olotu A, et al. Efficacy of RTS,S/AS01E: clinical malaria in 5 to 17 month old children. *N Engl J Med* 2008;359:24:2521-2532

⁵ Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* 2008;359; 24::2533-44.

Next steps in advancing RTS,S/AS

Based on the successful trials to date, GSK, MVI, and leading national research institutions are continuing clinical trials in infants and young children, the most vulnerable groups and those who would benefit most from an effective malaria vaccine. In collaboration with Africa-based research institutions, a series of clinical trials are ongoing in Mozambique, Tanzania, Gabon, Ghana, and Kenya.

A large-scale Phase III multi-center efficacy trial in both infants and in young children—the last stage of development before licensure—is expected to launch by early 2009, pending regulatory approval. This Phase III study is designed to further determine efficacy and confirm safety of the vaccine in the target population, and could become the largest malaria vaccine trial ever conducted.

If all goes well, the RTS,S/AS vaccine candidate could be submitted to regulatory authorities in 2011. The partners are committed to work 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/AS is licensed, GSK and MVI will work to ensure this breakthrough vaccine reaches the children and infants who most need it.

Steps in Malaria Vaccine Development

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

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

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

Phase III Clinical Trials: Continue to monitor safety, potential side effects, and fully 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 IV Clinical Trials: Post-marketing 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 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. Founded in 1977, PATH is an international, nonprofit organization that creates sustainable, culturally relevant solutions, enabling 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), one of the world's leading vaccine manufacturers, is headquartered in Rixensart,

Belgium, where the majority of GlaxoSmithKline's activities in the field of vaccine research, development and production are conducted. GSK Bio employs more than 1,600 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 2007, 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.