

Fact sheet: Phase 3 trial of RTS,S

The launch of the Phase 3 trial of GlaxoSmithKline's (GSK) malaria vaccine candidate, RTS,S, marks an important milestone after more than 20 years of research and development. Launched in May 2009, the Phase 3 trial will include 11 sites in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania. Together, the 11 sites will enroll up to 16,000 children and infants, making this the largest malaria vaccine trial to date.

RTS,S is the world's most clinically advanced malaria vaccine candidate—a result of a groundbreaking partnership between leading African research institutions, their Northern academic partners, the PATH Malaria Vaccine Initiative (MVI) and GSK Biologicals, with grant monies from the Bill & Melinda Gates Foundation to MVI. Results of clinical studies to date have shown that RTS,S has a promising safety and tolerability profile and reduced the risk of clinical episodes of malaria in young children by 53 percent over an eight-month follow-up period, and decreased by 65 percent the risk of infection in infants over a six-month follow-up period. Findings published in December 2008 indicate that RTS,S can be safely administered to infants in conjunction with traditional childhood vaccines. Recently, a study demonstrated that the vaccine is capable of inducing long-term protection against malaria for up to 45 months of follow-up after initial vaccination.

One of the final stages of testing before regulatory file submission, the Phase 3 trial is designed to confirm safety and further determine the efficacy of the vaccine in infants and children. Under current plans, the RTS,S vaccine candidate would be submitted to regulatory authorities in 2012 based on efficacy in children 5 to 17 months of age. Additional safety and immunogenicity data from the infant population will be submitted soon thereafter, followed by efficacy data for infants once available. Depending on the final clinical profile of the vaccine and the timetable of the regulatory review process, the first vaccine introduction could take place over the next three to five years.

African researchers leading an historic effort

Behind this scientific milestone is a public-private partnership spanning three continents, with African institutions at the forefront. Top Africa-based research centers are conducting the Phase 3 trial, with support from GSK Biologicals and MVI.

This monumental research effort will help build lasting capacity for future scientific research endeavors. Sites were selected for their track record of conducting world-class research, fostering strong community relations and a commitment to meeting the

RTS,S Phase 3 sites and affiliated partners

Burkina Faso – Nanoro

Institut de Recherche en Science de la Santé
(IRSS) / Centre Muraz

Gabon – Lambaréné

Albert Schweitzer Hospital, Medical Research Unit
+ University of Tübingen

Ghana – Agogo (Kumasi)

Kumasi Centre for Collaborative Research
Kwame Nkrumah University of Science and Technology,
School of Medical Sciences
+ Bernhard Nocht Institute
+ Komfo Anokye Teaching Hospital

Ghana – Kintampo

Kintampo Health Research Centre, Ghana Health Service
+ London School of Hygiene and Tropical Medicine

Kenya – Kilifi

Kenya Medical Research Institute
Wellcome Trust
+ University of Oxford
+ London School of Hygiene and Tropical Medicine

Kenya – Kombewa (Kisumu)

Kenya Medical Research Institute
+ Walter Reed Army Institute of Research

Kenya – Siaya (Kisumu)

Kenya Medical Research Institute
+ Centers for Disease Control and Prevention

Malawi – Lilongwe

University of North Carolina Project

Mozambique – Manhica

Centro de Investigação em Saúde de Manhiça
+ Barcelona International Health Research Centre,
+ University of Barcelona

Tanzania – Bagamoyo

Ifakara Health Institute
+ Swiss Tropical Institute
+ National Institute for Medical Research, Tanzania

Tanzania – Korogwe

National Institute for Medical Research, Tanzania
Kilimanjaro Christian Medical Centre
+ London School of Hygiene and Tropical Medicine
+ University of Copenhagen

+ Indicates an affiliated partner

most rigorous ethical and regulatory standards. The sites coordinate their efforts and share information through a formal structure, the Clinical Trial Partnership Committee, which includes sites' Northern academic partners, MVI and GSK, with support from the Malaria Clinical Trials Alliance.

Located in seven countries across sub-Saharan Africa, the trial sites represent diverse malaria transmission settings, from year-round occurrence to a more limited seasonal threat.

Structure and design of Phase 3

To develop a safe and effective vaccine for those most vulnerable to malaria, researchers will enroll two groups of participants: children aged 5 to 17 months, and infants aged 6 to 12 weeks. The Phase 3 trial is a double-blind study, in which participants will initially receive three doses of either RTS,S or a "control vaccine." After a year and a half, participants will receive a fourth dose of the vaccine to evaluate the impact of a "booster" dose.

All 6-12 week old infants in the trial will also receive a standard, licensed vaccine that protects against five common childhood illnesses and is recommended by the World Health Organization (WHO). The combination vaccine will be administered alongside the study vaccinations. By delivering these vaccines together, researchers hope to confirm that RTS,S can be administered together with commonly used childhood vaccines.

The RTS,S development partners have placed the utmost emphasis on the health and safety of the study participants. The Phase 3 trial will be conducted according to the highest international standards for safety, ethics, and clinical practices. The trial has been designed in consultation with appropriate regulatory authorities and the WHO. An independent data monitoring committee will also oversee the trial to ensure the ongoing safety of the study participants.

More than 20 years of progress

The RTS,S vaccine candidate was invented in 1987 by scientists working in GSK Biologicals' laboratories. Today, RTS,S is the most clinically advanced malaria vaccine candidate in the world. RTS,S aims to trigger the immune system to defend against the *Plasmodium falciparum* malaria parasite when it enters the human host's bloodstream and/or when the parasite infects liver cells. This prevents the parasite from maturing and multiplying in the liver, reentering the bloodstream and infecting red blood cells, where the host would begin to show symptoms of disease.

Protocol of the Phase 3 study

The multi-center, double-blind, controlled trial will enroll up to 16,000 participants; at least 6,000 in each of two age groups: children, aged 5 to 17 months and infants, 6 to 12 weeks old.

Participants will initially receive three doses of either RTS,S formulated with GSK's AS01E Adjuvant System or a control vaccine (on a 0, 1, 2 month schedule). After a year and a half they will receive a fourth dose of either RTS,S or another control vaccine (at month 20) to assess whether a "booster" dose may enhance the protective effect of RTS,S. Neither the volunteers nor the investigators will know which vaccine is being administered in order to ensure there is no bias when interpreting the results.

Two age groups: Study participants will be enrolled from two different age groups, each of which has three "arms." The first group, children aged 5 to 17 months, will be randomly selected to receive: (a) four doses of RTS,S (three plus one booster), (b) three doses of RTS,S and one of meningitis C vaccine, or (c) three doses of rabies vaccine and one of meningitis C.

The second group, infants aged 6 to 12 weeks, will also be randomly assigned to one of three study "arms" which will receive either: (a) four doses of RTS,S (three plus one booster), (b) three doses of RTS,S and one of meningitis C, or (c) four doses of meningitis C. All infants—regardless of which study arm they are assigned to—will receive the first three doses at the same time as a licensed DTPw/HepB/Hib vaccine as recommended by the WHO's Expanded Program on Immunization schedule.

Endpoints: To measure the vaccine's efficacy, researchers will follow participants for at least two and a half years, and monitor cases of clinical malaria disease. Clinical malaria is a highly relevant public health outcome for a vaccine and is characterized by a fever and the presence of parasites in the blood. Researchers will also monitor the incidence of severe malaria and other clinically relevant endpoints.

To stimulate an immune response to the malaria parasite, the RTS,S antigen fuses a critical circumsporozoite protein—the surface protein that helps the parasite invade human liver cells—with a protein found in GSK Biologicals' hepatitis B vaccine. The addition of GSK's proprietary Adjuvant Systems strengthens the immune response even further.

Early development and clinical testing of the vaccine was part of an ongoing collaboration between GSK and the United States Walter Reed Army Institute of Research. RTS,S was initially tested in healthy adults in the United States and Belgium before the first study in Africa was conducted in adults living in The Gambia in 1998. In January 2001, GSK and MVI, with grant monies from the Bill & Melinda Gates Foundation to MVI, entered into a public-private partnership to develop an RTS,S-based vaccine for infants and children living in malaria endemic regions in sub-Saharan Africa.

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 Bio), 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.