

Fact Sheet: Malaria-038 Trial of RTS,S

On October 17, 2007, the prestigious medical journal *The Lancet* published the results of a landmark study of a malaria vaccine candidate carried out by researchers from the Manhiça Health Research Center (CISM), GlaxoSmithKline Biologicals (GSK), the PATH Malaria Vaccine Initiative (PATH/MVI), the Barcelona Centre for International Health Research (CRESIB) at the Hospital Clinic of the University of Barcelona, and the Ministry of Health of Mozambique.

The Malaria-038 trial (MAL 038), conducted in Mozambique, showed for the first time that the RTS,S malaria vaccine candidate has a promising safety and tolerability profile in infants, and provides substantial protection against infection and clinical disease. The MAL 038 trial is the first study of any malaria vaccine candidate to establish proof-of-concept that young infants exposed to intense *P. falciparum* transmission can be protected from infection and clinical disease with a malaria vaccine.

The MAL 038 Results

The MAL 038 trial of 214 infants marks the first time that RTS,S has been administered to infants, the group most vulnerable to malaria. The trial showed that RTS,S reduced the risk of infection by 65 percent over three months after the third and final dose and reduced the risk of clinical disease by 35 percent over a six-month period following the first dose. In addition, RTS,S's safety and reactogenicity profile was similar to that of standard EPI vaccines given to infants, including comparable pain and swelling.

The results from MAL 038 are consistent with earlier trials in older children (aged 1-4 years old). However, the immune systems of young infants differ from those of older children. It is therefore encouraging that the vaccine induces the production of antibodies against malaria and hepatitis B, and is efficacious at reducing malaria infection and clinical disease in infants.

These important findings substantially advance the vision that a vaccine will be capable of protecting young African children and infants and thereby contribute to reducing the heavy burden of disease and death caused by malaria. While other Phase II trials are still in progress, this trial is a strong and positive signal in favor of initiating future Phase III trials.

Design of the Malaria-038 Trial

This double-blind, randomized trial enrolled 214 infants. They received either the candidate malaria vaccine, or a licensed hepatitis B vaccine. (*Engerix-B*TM) in doses given at 10, 14 and 18 weeks of age, administered staggered by two weeks with routine EPI vaccines given at 8, 12 and 16 weeks of age.

SAFETY

All infants were observed for an hour after each vaccination, and visited in their homes at least once a day for six days following every dose. After the full course of vaccination, children were visited in their homes at least monthly for the duration of the study. Investigators found RTS,S has a safety and tolerability profile similar to other commonly used childhood vaccines.

EFFICACY METHODOLOGY

The investigators evaluated the immune response induced by the vaccine by measuring antibodies in the blood, and the vaccine's efficacy. Efficacy against infection was measured for three months after the third vaccine dose and efficacy against clinical disease was measured over six months after the first dose. The efficacy was determined according to two methodologies endorsed by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA):

Active detection of infection (ADI), where all children were given a course of antimalarials two weeks before their last dose of vaccine to destroy any malaria parasites. After the final dose, subjects were examined every two weeks, and tested for malaria at the first sign of illness.

Passive case detection. Children were counted as a case if they were brought to a doctor with malaria (confirmed by a blood test).

ETHICAL REVIEW

This trial was reviewed and approved by ethics committees in Mozambique, Spain and the USA and by the FDA. An independent Data Safety Monitoring Board oversaw the trial and protection of the interests of enrolled infants.

Twenty Years of Vaccine Development

RTS,S is the world's most advanced malaria vaccine candidate. It has been in active development since 1987. Early development of the RTS,S antigen was undertaken by GSK Biologicals, the vaccine division of GSK, in close collaboration with the United States Walter Reed Army Institute of Research (WRAIR). The antigen was combined with a GSK proprietary Adjuvant System. In January 2001, GSK Biologicals and the PATH Malaria Vaccine Initiative (PATH/MVI) entered into a collaboration agreement to develop an RTS,S vaccine for infants and children living in malaria endemic regions, in sub-Saharan Africa.

Clinical evaluation of the RTS,S antigen began in 1992. Successful trials were conducted with adult volunteers in the United States, Belgium, and eventually the Gambia. In 2003 researchers set out to demonstrate efficacy of the vaccine in children in a trial with more than 2,000 children in southern Mozambique. Results from this groundbreaking trial, published in 2004 and 2005 in *The Lancet*, showed that RTS,S was effective in reducing clinical malaria by 35 percent and severe malaria—the form of infection that causes severe complications and death—by 49 percent for at least 18 months.

The MAL 038 study is one of several trials that were initiated following the breakthrough findings of 2004. The results of the MAL 038 trial build on the earlier work and help pave the way for Phase III studies, the final phase of clinical development before licensure. Phase II studies evaluating schedule, dosing and an improved formulation of the vaccine are ongoing. If progress continues as anticipated, Phase III will commence in the later half of 2008. Designed to determine the efficacy of the vaccine, the Phase III study could become the largest vaccine clinical trial ever conducted in Africa.

The following table summarizes the phases of development for the RTS,S candidate malaria vaccine.

Development Phase	Purpose	RTS,S Schedule
Research and Pre-clinical Development	Identify relevant antigens and create vaccine concept; pre-clinical evaluation; develop vaccine manufacturing process	From <i>1987</i> to date
Phase I Clinical Trials	Establish safety and measure immune response in malaria-naïve and malaria-exposed populations	From <i>1992</i> to date
Phase II Clinical Trials	Monitor safety and potential side effects; measure immune response; measure preliminary efficacy against infection and clinical disease; and determine optimum dosage, schedule and formulation.	
Phase III Clinical Trials	Continue to monitor safety, potential side effects, and evaluate efficacy on a large-scale	To begin <i>2008</i>
Submission to Regulatory Authorities	Submit vaccine application to regulatory authorities for approval to market	Foreseen <i>2011</i>
Approval	Make vaccine available for use	
Phase IV Clinical Trials	Post-marketing safety monitoring; measure vaccine effectiveness, assess vaccine compliance, conduct health economics studies.	