

Read Ahead for FDA/VRBPAC Meeting 23 September 2004

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Introduction

The U.S. Army's Office of the Surgeon General is the sponsor of several INDs with the U.S. Food and Drug Administration (FDA). IND # 8795 is the application for a combination of candidate HIV vaccines: ALVAC-HIV vCP1521 (Aventis Pasteur) and AIDSVAX[®] B/E gp120 (VaxGen). A phase III trial of this vaccine combination has begun in collaboration with the Ministry of Public Health of Thailand. The purpose of this document is to provide information to the members of the Vaccine and Related Biologic Products Advisory Committee of the U.S. FDA in association with the trial update scheduled for September 23, 2004. The associated research which provided the foundation for this trial has been recently summarized (Brown and Nitayaphan, *Milit Med* 169:588, 2004; attached). An earlier phase I/II trial was conducted under this IND and the clinical study report was filed with the FDA in September 2003.

Background

Joint HIV Vaccine Development

The U.S. Army Medical Research and Materiel Command (MRMC), through the Walter Reed Army Institute of Research and its subsidiary laboratory in Bangkok [the Armed Forces Research Institute for Medical Sciences (AFRIMS)], has collaborated with Thai scientific and public health leaders to jointly develop and evaluate candidate HIV vaccines. This collaboration began in the early 1990s and includes the Royal Thai Army Medical Department, Mahidol University and Chiang Mai University and AFRIMS, forming the Thai AIDS Vaccine Evaluation Group (TAVEG). Industry partners from VaxGen, Chiron Vaccines and Aventis Pasteur (AvP) joined the collaboration and each developed candidate HIV vaccines with components derived from the predominant strain (>85% of isolates) of HIV in Thailand, subtype E (CRF01_A/E). Gp120 Env subunit HIV vaccines to T cell line adapted subtype B strains, developed for use in the United States, were included in bivalent B/E vaccines, in an attempt to mirror the dual subtype epidemiology of HIV in Thailand, where between 5 and 15% of infections may be due to subtype B HIV infection. Four vaccine candidates resulted from these efforts and were assessed in phase I/II trials carried out by the TAVEG. [The VaxGen candidate was assessed as a single vaccine thru phase II and III trials by the Bangkok Vaccine Evaluation Group (BVEG).] These clinical trials have placed Thailand at its leadership position in HIV vaccine evaluation among the less industrialized countries of the world, and led to AFRIMS becoming the U.S. Department of Defense's lead platform for HIV vaccine evaluation and testing.

A strategic plan has been followed which, in the absence of knowledge of the mechanism of protective immunity or empirically derived correlates of protection, has elected to optimize the likelihood of success by utilizing vaccine combinations to stimulate the humoral and cellular arms of the immune system. The joint testing and evaluation of candidate vaccines in Thailand has progressed through phase I and II trials of monomeric gp120 candidates alone to live vectored vaccines combined with a number of soluble envelope proteins. In this unusual situation of testing and evaluation of a candidate vaccine combinations with individual products produced by different manufacturers, the INDs are held by U.S. Army's Office of the Surgeon General. Following are the candidate vaccines that have been tested in these phase I/II trials in Thailand by the TAVEG. The first generation vaccines (1 & 2) were designed to induce humoral immunity alone; the second generation vaccine combinations (3a, 3b & 4) were designed to induce both humoral and cellular immunity.

	<u>Vaccine</u>	<u>Manufacturer</u>
1.	Monomeric gp120 protein (B)	Chiron
2.	Monomeric gp120 protein (E)	Chiron
3a.	ALVAC-HIV (vCP1521) + gp120 protein (B/E)	Aventis Pasteur + Chiron
3b.	ALVAC-HIV (vCP1521) + oligo gp160 protein (E)	Aventis Pasteur
4.	ALVAC-HIV (vCP1521) + AIDSVAX [®] B/E gp120	Aventis Pasteur + VaxGen
Note: Studies 3a and 3b ("RV132") were carried out under IND #8590; study 4 ("RV135") was carried out under IND #8795.		

The phase I/II trials carried out by the TAVEG were performed at four academic centers [Chiang Mai University, Mahidol University (2 sites) and Phramongkutklo Army Medical Center], involving about 700 volunteers. Volunteers were HIV-negative Thai adults, selected to be at low risk of HIV infection. All candidate vaccines were found to be safe and well-tolerated, and no HIV infections occurred to volunteers during the course of these trials.

The combination of ALVAC-HIV (vCP1521) and AIDSVAX B/E gp120 was chosen for advancement to phase III evaluation based on a combination of the safety and immunogenicity data of the vaccine candidates in humans, and considerations related to manufacturing and supply of product necessary to support the study. This vaccine combination was evaluated in a phase II trial in Thailand (protocol RV135) with results presented to the U.S. FDA as part of the “End of Phase II” package in Q3 2002. The results of that trial are published (Nitayaphan, *J Infect Dis* 190:702, 2004; attached); a separate analysis of the relationship of CTL response to HLA class I type from both phase I/II trials with ALVAC-HIV (vCP1521) is also published (Paris, *Tissue Antigens* 64:251, 2004; attached).

Summary of Phase II Clinical Trial Results

ALVAC-HIV vCP1521 plus AIDSVAX B/E gp120 were tested in study RV135 (Nitayaphan, *J Infect Dis* 190:702, 2004) which evaluated this combination with two doses of AIDSVAX B/E, 200 and 600 µg (two antigens combined). Both vaccines are given as IM injections; ALVAC at 0, 1, 3 and 6 months, AIDSVAX at 3 and 6 months. Both vaccines were found to be safe and well tolerated. The trial demonstrated that the higher dose of ‘boosting’ vaccine induced stronger immune responses. Thus, the combination advanced to phase III evaluation utilized the higher dose of AIDSVAX B/E.

Of 133 volunteers enrolled in RV135, 122 completed the trial. There were no serious vaccine-related adverse events, nor were there any intercurrent HIV infections. Lymphoproliferative responses to gp120 E were detected in 31% of vaccine recipients after two doses of ALVAC (pre-protein boost) and in 63% of vaccine recipients after the full course of immunization. HIV-specific CD8 CTL responses were detected in 24% of vaccinees and 0% of placebo recipients. Antibody responses increased in frequency and magnitude in association with the dose level of AIDSVAX B/E. Binding and neutralizing antibodies to the MN strain were induced in 100% and 98%, respectively, of the volunteers receiving 600 µg of AIDSVAX B/E, and such antibodies to E strains were induced in 96% and 71%, respectively, of these volunteers. Antibody-dependent cellular cytotoxicity was detected against gp120 in 86% of these vaccinees and 0% of placebo recipients.

The relationship to HLA type was explored in 187 volunteers who received ALVAC-HIV vCP1521 in either of the two phase I/II trials (RV132 + RV135). Precursor cytolytic CD8 T-cell responses were detected in 21% of these vaccine recipients, and while there was a positive association with HLA-B44 (odds ratio of 7.6),

there were no statistically significant negative associations. Thus, although larger studies will be required, there appear to be no HLA-based limitations to the use of ALVAC-HIV vCP1521.

Rationale for Advancement to Phase III Testing

The U.S. Army MRMCM has elected to move forward with a vaccine combination that stimulates both the humoral and cellular arms of the immune system. The collaborative effort in Thailand follows the hypothesis that vaccine antigens should match the HIV subtypes circulating in the region, and the candidate vaccines under assessment utilize subtype E envelope antigens and B Gag/Pol antigens. Volunteer safety is a prime concern. Although approximately 200 persons had previously received the specific vCP1521 ALVAC-HIV construct, both ALVAC-HIV and AIDSVAX have well documented safety profiles. ALVAC-HIV has been tested in numerous variations in approximately 2500 persons and with a variety of subtype B sequences. AIDSVAX B/E was recently tested and found safe in more than 2500 Thai adults. Based on these factors, criteria for progressing to phase III evaluation were that the subtype E candidate vaccines demonstrate safety and an immunogenicity profiles similar to subtype B (vCP205) ALVAC-HIV and AIDSVAX candidate vaccines.

Following review of the phase II trial results, the U.S. and Thai governments, along with vaccine manufacturers, agreed to proceed to phase III testing. For nearly two years prior to initiation, information pertaining to RV144 was publicly presented. Eleven governmental and academic scientific, ethical and regulatory review bodies in Thailand and the United States, as well as the World Health Organization and the Joint U.N. Programme on HIV/AIDS (WHO-UNAIDS) reviewed and endorsed this clinical trial. The Category B-End of Phase 2 Meeting with the U.S. FDA was held November 8, 2002.

Trial Management

This multi-national collaboration includes a large number of partners. Sponsorship is shared by the U.S. Army's Office of the Surgeon General (IND holder) and the Division of AIDS of the National Institute of Allergy and Infectious Diseases. The investigator team is led by Dr. Supachai Rerks-Ngarm of the Department of Disease Control, Thai Ministry of Public Health, in collaboration with the Royal Thai Army Medical Department and the Faculty of Tropical Medicine, Mahidol University; Aventis Pasteur and VaxGen are industry partners. These relationships are formalized through an Interagency Agreement [U.S. Army Medical Research and Materiel Command (USAMRMC) and NIAID], Cooperative Research and Development Agreements (USAMRMC and each of the two companies), a Cooperative Agreement (USAMRMC and the Henry M. Jackson Foundation); and contracts (the Jackson Foundation and the investigator institutions).

Trial-specific committees have been established for oversight, including a Requirements and Obligations Committee within the sponsor agencies and a Pharmacovigilance Committee with representatives of all the collaborative partners.

These committees meet regularly by teleconference and information is shared among members by utilizing a secure website. The sponsor has also established a Data and Safety Monitoring Board (DSMB), chaired by Dr. Walter Dowdle, with five of its 10 members being designees of the National AIDS Commission of Thailand. The DSMB plans to have meetings to monitor volunteer safety every six months and as needed, and to have a single interim efficacy assessment about two thirds of the way through the trial. The following paragraphs summarize the trial protocol.

Phase III Trial: Protocol (RV144) Summary

TITLE: A Phase III Trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX⁷ B/E) Boosting in HIV-uninfected Thai Adults

IND (# 8795) Holder: Office of The Surgeon General, U.S. Army Medical Department

OBJECTIVES:

Primary Objective:

To determine whether immunizations with an integrated combination of ALVAC-HIV (vCP1521) boosted by AIDSVAX⁷ gp120 B/E prevent HIV infection in healthy Thai volunteers.

Secondary Objectives:

- ?? To determine whether immunization with this vaccine combination results in reduced HIV viral load among those acquiring HIV-1 infection, comparing vaccine recipients to placebo recipients.
- ?? To determine whether immunization with this vaccine combination results in an increased CD4 count among those acquiring HIV-1 infection, comparing vaccine recipients to placebo recipients.
- ?? To confirm the safety of this vaccine combination in Thai volunteers.
- ?? To evaluate whether participation in this HIV vaccine trial is associated with behavior change that may increase the risk of HIV infection.

SUBJECTS: 16,000 HIV-uninfected Thai subjects, male or female, aged 20 through 30 years (inclusive), available for 3.5 years of participation. Subjects who are 18 or 19 years of age and married will also be eligible for enrollment. [Assumptions employed for sample size calculations utilized results of HIV incidence and follow-up rates determined in cohort studies carried out in the study area (Brown and Nitayaphan, Milit Med 169:588-93, 2004).]

STUDY SITES: Ministry of Public Health (MOPH) facilities in Chon Buri and Rayong Provinces, Thailand, to include health centers, hospitals, and Rayong STD Clinic.

PRODUCT DESCRIPTIONS:

ALVAC-HIV (vCP1521), produced by Aventis Pasteur (Marcy L'Etoile, France), is a recombinant canarypox vector vaccine that has been genetically engineered to express subtype E HIV-1: gp120 (subtype E) linked to the transmembrane anchoring portion of gp41 (subtype B), and HIV-1 gag and protease (subtype B). ALVAC-HIV (vCP1521) is formulated at a dose of $>10^6$ CCID₅₀. The diluent supplied for reconstitution of ALVAC-HIV (vCP1521) consists of sterile 0.4% NaCl.

ALVAC Placebo (Aventis Pasteur) is supplied as a sterile, lyophilized product that consists of a mixture of virus stabilizer, and freeze drying medium. The diluent supplied for reconstitution of ALVAC Placebo consists of sterile 0.4% NaCl.

AIDSVAX² B/E, produced by VaxGen, Inc. (Brisbane, CA), is a bivalent HIV gp120 envelope glycoprotein vaccine containing a subtype E envelope from the HIV-1 strain A244 and a subtype B envelope from the HIV-1 strain MN. The recombinant gp120s are produced in genetically engineered Chinese hamster ovary (CHO) cell lines. The envelope glycoproteins are coformulated and administered at a combined dose of 600 µg (300 µg of each antigen). AIDSVAX² B/E is formulated with 600 µg of alum adjuvant.

AIDSVAX Placebo (VaxGen, Inc.) is 600 µg alum adjuvant.

ROUTE OF ADMINISTRATION: Intramuscular into the deltoid muscle.

ALVAC-HIV or ALVAC Placebo (1 mL) into left deltoid

AIDSVAX² B/E or AIDSVAX Placebo (1 mL) into right deltoid.

SCHEDULE OF IMMUNIZATION:

Group	Subjects	Weeks			
		0	4	12	24
I	8,000	ALVAC Placebo	ALVAC Placebo	ALVAC Placebo + AIDSVAX Placebo	ALVAC Placebo + AIDSVAX Placebo
II	8,000	ALVAC-HIV	ALVAC-HIV	ALVAC-HIV + AIDSVAX ² B/E	ALVAC-HIV + AIDSVAX ² B/E

STUDY ENDPOINTS:

Primary Endpoint

The primary endpoint of the trial is acquisition of HIV infection as determined by repeatedly reactive EIA, positive Western blot and positive HIV nucleic acid testing (from two different blood collections).

Secondary Endpoints

The secondary endpoints of the trial are the following:

- ?? Plasma viral load in volunteers developing HIV infection during the trial.
- ?? CD4 T cell count in volunteers developing HIV infection during the trial.
- ?? Safety assessment of this vaccine combination in Thai volunteers
- ?? Change in HIV risk behaviors associated with participation in the vaccine trial.

OVERALL STUDY DESIGN :

This is a community-based, randomized (vaccine : placebo = 1:1), multicenter, double-blind, placebo-controlled clinical trial. Screening of potential volunteers, including HIV testing and counseling, is carried out under a separate protocol entitled “Screening and evaluation of potential volunteers for a trial in Thailand of a candidate preventive HIV vaccine” (RV148). Eligible volunteers are being enrolled over approximately two years. Vaccinations for each individual occur over a 24-week period (at 0, 4, 12, 24 weeks). Women are tested for pregnancy at each vaccination visit and volunteers testing positive are not vaccinated. Blood is collected for plasma (for diagnostics and HIV-specific antibodies) at 0, 24 and 26 weeks, and every 6 months during the follow-up phase. The blood collection at 0, 6, 12 and 42 months is also used for cryopreservation and archiving of PBMCs (for HIV-specific cellular immune responses). At week 24 and at each six-month follow-up visit, volunteers have HIV testing, preceded by pretest counseling and followed (approximately 2-3 weeks later) by post-test counseling. Assessment of HIV risk behavior is performed at baseline, week 26 and at each 6-month follow-up visit. Education on risk behavior reduction is given at each vaccination visit and at each post-test counseling visit. Volunteers diagnosed with an HIV infection based on the testing of blood collected at two separate time points are counseled, referred to the specialized clinics for HIV care and management in accordance with the National Guidelines of the Thai Ministry of Public Health, and monitored with HIV viral load and CD4 cell quantitation.

Implementation and Oversight of Phase III Trial

Screening of potential volunteers began in September 2003 with the first volunteers enrolled and vaccinated in the trial (RV144) in October 2003. Screening and vaccination sites began enrollment in a phased and rolling manner to allow optimal attention to performance of trial procedures and logistics. After completion of the initial phase-in stages of the trial, a meeting of all collaborators was held in February 2004, chaired by Dr. Vallop Thaineua, the Permanent Secretary of the Ministry of Public Health, and attended by senior representatives of the sponsor, investigator and manufacturer organizations. At that time it was agreed by all partners to move forward with full implementation of the trial across all sites in the two provinces (47 screening sites and 8 vaccination sites).

The investigator team includes more than 500 staff in Thailand, among whom more than 100 are dedicated fulltime to this trial. The majority of staff are from the health care facilities in the study area. In addition, full-time research teams from Mahidol University work in each of the eight vaccination sites. Vaccine is stored centrally prior to distribution to vaccination sites in a secure section of the Ministry of Public Health's regional facility for EPI vaccines. Blood specimens are processed and stored in a dedicated central laboratory in Chon Buri Province from which aliquots for diagnostic testing are shipped to the AFRIMS laboratory in Bangkok which is accredited by the College of American Pathologists. Data from clinical report forms are forwarded from each vaccination site to the Data Management Unit at Mahidol University via a dedicated DataFax system. Oversight of the data management is provided by the Walter Reed Army Institute of Research and independent statistical analysis is performed by the EMMES Corporation.

As of 15 August 2004, more than 7,500 volunteers have been screened as potential volunteers for the trial, and more than 4500 have been enrolled and begun the vaccination series. At the current rate of enrollment into the trial, completion of enrollment is projected to be in the fourth quarter of 2005. The trial's Data and Safety Monitoring Board held its organizational meeting by teleconference in January 2004 and a full face-to-face meeting in Thailand in July 2004. Subsequent to the July review, the DSMB informed the sponsors and investigator team that the trial should continue.

Attachments

Article describing phase I/II trial and results (Nitayaphan S, Pitisuttithum P, Karnasuta,C, et al. J Infect Dis 190:702-6, 2004).

Article describing analysis of relationship between CTL response and HLA type (Paris R, Bejrachandra S, Karnasuta C, et al. Tissue Antigens 64:251-6, 2004).

Article summarizing associated research in Thailand (Brown AE and Nitayaphan S. Milit Med 169:588-93, 2004).