Vaccines and Related Biological Products Advisory Committee (VRBPAC)
Background Package for September 23, 2004 Meeting

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HIV-1 Recombinant Canarypox-Vectored Vaccine with Recombinant gp 120 B/E

Phase III studies of vaccines intended for the prevention of HIV/AIDS require careful consideration of trial design and study endpoints. The demonstration of efficacy from a HIV vaccine study that might result in licensure by the U.S. Food and Drug Administration should follow a series of formalized steps that include input from FDA Advisory Committees.[1] In this case, the Office of the Surgeon General of the Army submitted to the IND study RV144, a phase III clinical trial of ALVAC vCP1521 plus AIDSVAX B/E for the prevention of HIV infection to be conducted exclusively in Thailand. A decision was made by the National Institutes of Health not to proceed with a phase III trial of a similar vaccine series, ALVAC vCP1452 plus AIDSVAX B/B.[2] Scientific journals have aired the differing opinions surrounding the Thai trial.[3,4,5,6] The purpose of the brief presentations by a representative of FDA and a representative of the sponsor is to inform the VRBPAC of the status of the clinical trial and highlight regulatory concerns, including the decision to allow the Thai trial to proceed.

The World Health Organization in the early 1990s designated Thailand as a target country for the development of a vaccine for primary prevention of HIV. At that time, Thailand experienced an alarming increase in HIV infection rates among injection drug users and commercial sex workers. Recent HIV prevalence data demonstrate that approximately 2% of Thai women receiving antenatal care are infected with HIV.[7] The vast majority of HIV infections in Thailand are characterized as the recombinant CRF01_AE, formerly known as clade E.[8] The predominant strain that circulates in the United States (U.S.) is clade B. Another epidemiological consideration for the U.S. FDA is the number of infections with CRF01_AE HIV among persons residing in the U.S. A survey of newly infected U.S. military personnel between the years 1997 and 2000 identified 28 infections among 520 recent seroconverters as non-subtype B; only 5 were characterized as CRF01_AE and four out of the five originated from Southeast Asia.[9]

The vaccine series of ALVAC-HIV vCP1521 plus AIDSVAX B/E is the second vaccine regimen for the prevention of HIV to enter phase III clinical development. ALVAC-HIV vCP1521 is a canarypox-vectored vaccine manufactured by Aventis-Pasteur, Inc. and AIDSVAX B/E is a recombinant glycoprotein (rpg) 120 subunit protein manufactured by VaxGen, Inc. ALVAC-HIV vCP1521 plus AIDSVAX B/E is intended to match the HIV strain CRF01_AE that circulates in Thailand. A recent publication describes ALVAC-HIV vCP1521 and AIDSVAX B/E as follows[8]:

> *ALVAC-HIV (vCP1521)…is a recombinant canarypox vector vaccine expressing CRF01_AE HIV-1 gp120 (92TH023) linked to the transmembrane-anchoring portion of subtype B gp41 (strain LAI) with a deletion in the immunodominant region and also expressing HIV-1 Gag and protease (strain LAI).*

AIDSVAX B/E…is a bivalent HIV gp120 vaccine containing a B envelope from strain MN and a CRF01_AE envelope from strain A244.

Thus, while both vaccines contain some clade B antigen components, the vaccines were specifically designed to enhance the possibility that they might elicit an immune response that would protect against the CRF01_AE strain. The rationale for the consideration of a prime-boost strategy of a canarypox-vectored vaccine with a protein subunit boost centers upon the theoretical ability to elicit strong humoral and cellular immune responses. Indeed, the initial immunogenicity studies of ALVAC vCP125 and ALVAC vCP205 suggested that the addition of a protein boost might enhance neutralizing antibody responses.[4] In general, the ALVAC-HIV constructs combined with protein subunit boosts have been reported to lack robust immunological responses in healthy volunteers.[3] Nevertheless the correlates of immune protection against HIV remain unknown and the sponsors are proceeding with the ALVAC vCP1521 plus AIDSVAX B/E in study RV144. The following table summarizes the immunological responses from the phase II study RV135:

Table 2: Study RV135, immunological responses to ALVAC vCP1521 plus two doses of AIDSVAX B/E at the same regimen to be used in study RV144[8]:

Vaccine regimen: vCP1521 plus AIDSVAX	N	Neutralizing antibody subtype CRF01_AE strains		Binding Ab gp120 MN		Binding Ab gp120 A244		HIV-spec. CD8+ CTL
		CM244	NPO3	%	GMT [95% CI]	%	GMT [95% CI]	
200?g	50	44%	23%	95%	3744 [2167-6469]	86%	596 [301-1180]	24%
600?g	47	64%	31%	100 %	7730 [4961-12,045]	96%	1691 [918-3114]	24%
Placebo	31	0%	0%	0%		0%		0%

The completed efficacy studies for AIDSVAX B/B and AIDSVAX B/E products, conducted in the U.S. and in Thailand, respectively, were well described in the public domain.[10] No efficacy was demonstrated in the prevention of HIV vaccine when these rgp120 subunit vaccines were administered alone. These study results and preliminary immunogenicity results from AVLAC vCP1521 plus AIDSVAX B/E have led some to question the likelihood that this vaccine will protect against HIV infection.[3,6] This particular vaccine regimen had been administered to several hundred volunteers without significant safety concerns[8], and no important safety issues have been identified among the thousands of healthy volunteers who have received ALVAC-HIV products with or without protein subunit boosts.[11] Therefore, sufficient safety information was available regarding the administration of ALVAC vCP1521 plus AIDSVAX B/E that would not preclude the initiation of study RV-144.

The regulatory challenge generated with this trial is the consideration of approving a vaccine strategy that is designed for the prevention of a specific clade of HIV that does not circulate in the U.S. The FDA approves products that are indicated for use in a U.S. population. There are ongoing discussions between various regulatory agencies and non-governmental organizations on how guidance might be provided for approvals for developing countries.[12] Another regulatory concern is a study result of relatively low efficacy which might, nevertheless, be sufficient to have a beneficial impact in Thailand where widespread use of the vaccine series could slow an HIV epidemic of the CRF01_AE strain. However, a low level of efficacy might not provide substantial individual benefit for a person residing in the U.S. The licensed indication for the use of a vaccine regimen with a relatively low level of efficacy would require a different risk-benefit assessment for the U.S. population than would be required for licensure in Thailand.

In summary, we view study RV144 as a "proof of concept" study that would assess the preliminary efficacy of a canarypox vectored HIV-1 vaccine administered in combination with a rgp120 protein boost. The study was allowed to proceed given the current state of knowledge in HIV vaccine research where a correlate of immune protection has not been elucidated, as well as the apparent safety profile of the vaccine regimen. Furthermore, it is worth mentioning that the study is the first study to be conducted in a young adult population where primarily heterosexual transmission of HIV would occur. The purpose of this VRBPAC presentation is to inform the VRBPAC of the regulatory decision to allow the study to proceed and to inform the VRBPAC of some of the regulatory challenges that might arise based on future results of this clinical trial. ----------

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