



Adjuvant – H5N1 Vaccine Antigen “Mix-N-Match” Study

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Pandemic Influenza Prototype Vaccines in Clinical Trials
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U.S. H5N1 Vaccine Stockpiles 2007

H5N1 Vaccine Strain	Clade	2004	2005	2006	2007	Totals
A/VTN/1203/04	1	0.45	7.05	0.91		8.41
A/Indo/05/05	2.1			6.44	2.25	8.69
A/BHG/QL/1A/05*	2.2				6.42	6.42
A/Anhui/1/05	2.3				2.51	2.51
Totals (90 ug/dose)		0.45 M	7.05 M	7.35 M	11.18 M	26.03 M
Totals w/adjuvants 7.5 ug/dose		5.4 M	84.6 M	88.2 M	134.2 M	312 M

^ doses represented as 90 ug HA/dose antigen alone

* A/Bar-headed Goose/Quinghai Lake/1A/05



Pandemic Influenza Vaccine Strategic Goal/Specific Aim

- **STRATEGIC GOAL:** Expand the supply of influenza vaccines available during a pandemic by the optimization of antigen content using adjuvants
- **SPECIFIC AIM:** Determine whether stockpiled H5N1 vaccine antigens manufactured by one company can be used safely and effectively with adjuvants from other manufacturers during an influenza pandemic under Emergency Usage Authorization.



Mix-N-Match Plan: Products

- Conduct a series of laboratory, animal, and clinical studies
 - Physicochemical analyses (GSK, Novartis)
 - Murine immunogenicity studies (CRO)
 - Rabbit toxicology studies (CRO)
 - Ferret challenge studies (CDC)
 - Phase I clinical study: dosage-ranging study for safety, immunogenicity, & cross-reactivity (NIH)
 - Phase 2 clinical study: single dosage study (NIH)

Adjuvant	H5N1 A/Indonesia/05/2005
ASO3 GSK	sanofi pasteur
MF59 Novartis	sanofi pasteur



Physiochemical Studies

Step 1: Physicochemical Analysis of Adjuvant/Antigen Mixture

- Determine compatibility of adjuvant and antigen combinations
- pH, buffer, ionic strength, detergents, excipients
- Liquid adjuvant manufacturers will conduct studies on mixtures of blinded antigens with adjuvants as admixtures to determine effects on adjuvant properties (size, shape, micelle formation kinetics)
- Adjuvant manufacturers will receive H5N1 vaccine antigens, mix, and analyze
- Joint team will evaluate data and inform what combinations are compatible for subsequent animal studies



Animal Immunogenicity Studies

Step 2a: Murine Immunogenicity Studies with H5N1 vaccine with Adjuvants

- Healthy adult mice housed at CRO are immunized i.m. as admixture with two doses (1 ug HA/dose) of an antigen/liquid adjuvant mixture
- Animals are bled at day 0, 21, and 42 days post-immunization
- Antibody titers (HI & MN) are determined by CRO
- Joint team will evaluate data and inform what combinations are immunogenic and to what extent for subsequent Phase 1 clinical studies



Rabbit Toxicology Studies

Step 2b: Rabbit Toxicology Studies with H5N1 vaccine with Adjuvants

- Toxicology plans for each antigen/adjuvant combination in concert with IND held by NIH
- Healthy adult rabbits housed at CRO are immunized i.m. as admixture of two doses at highest antigen dosage (15 ug HA/dose) of an antigen/liquid adjuvant mixture or antigen alone i.m.
- Animals are bled at day 0, 21, and 42 days post-immunization
- Antibody titers (HI & MN) are determined by CRO
- Immunized animals are observed daily and sacrificed at 56 days p.i. for organ/tissue pathology by CRO
- Joint team will evaluate data and inform what combinations are well-tolerated and immunogenic and to what extent for subsequent Phase 1 clinical studies



FDA/VRBPAC Meeting

Step 3a: VRBPAC meeting

- Briefing of VRBPAC on the results of pre-clinical studies & clinical plan
- HHS/BARDA will coordinate & lead presentations
- Provides public disclosure & discussion of study plans



ASPR

Phase 1 & 2 Clinical Studies

Steps 3b & 5a: Phase 1 & 2 dose-ranging clinical studies for safety, immunogenicity, and cross-reactivity

- (See Dr. Linda Lambert's presentation)



Ferret Challenge Protection Studies

Step 5b: Ferret Challenge Protection Studies with H5N1 vaccine with Adjuvants and H5N1 Viruses for cross-immunogenicity and cross-protection.

- Healthy adult ferrets housed in CDC colony are immunized with one dose (TBD ug HA) of an antigen/adjuvant mixture
- At 21 days post-immunization, ferrets are challenged with TCID50 dose of H5N1 virus (A/Vietnam/1203/2004 or A/Indonesia/05/2005)
- Challenged animals are monitored for viral pathology, antibody titers (HI & MN) and virus shedding
- Evaluate data as supplement to Phase 1 clinical studies



Data Review

Step 6: Data Review to Inform Policy

- Retrieve data from clinical sites to central database manager (NIH)
- Distribution & analysis of data sets to USG and industry (only on their products)
- Study results, conclusions, & recommendations presented to policy makers
- Publication – possibly a single conjoint public document with blinded data products
- Data marketing – no marketing of data results by agreement among vaccine manufacturers
- Cross-reference agreements – companies may enter into agreements to provide their data and/or product to one another