

DMID H1N1 Clinical Trials

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Monovalent H1N1 Vaccine Safety Oversight

Conclusion and Take Home Message

- ❑ There have been no SAEs associated with the vaccine by the PIs or the Medical Monitors
- ❑ The Safety Monitoring Committee has not recommended a modification or halting of any trial
- ❑ The observed pattern of reactogenicity and adverse events is comparable with seasonal influenza vaccination

Monovalent H1N1 Vaccine Immunogenicity

Conclusion and Take Home Message

- ❑ H1N1 Monovalent can be given with, before or after TIV without impacting either vaccine's immunogenicity
- ❑ A single 15 mcg dose of H1N1 vaccine will elicit robust immune responses in:
 - ❑ Pregnant Women
 - ❑ Children 10 -18 years of age
 - ❑ Adults between 18 and 65
 - ❑ Adults over 65
- ❑ Children less than 10 did not have robust responses
 - ❑ CDC recommends two dose for children 6 months to 9 years

NIAID trials “Policy Focus”

■ Help inform policy, “gap” areas

- accelerate availability of 1 vs. 2 dose data in different populations
- administration with seasonal influenza vaccine
- use of different adjuvanted products
- mixing stockpiled vaccines and adjuvant

■ Data not intended to support licensure

■ Complimentary to company planned trials

■ Safety in General and Special populations

- young infants
- pregnant women
- immunocompromised

NIAID H1N1 Vaccine Trials

Policy Focus: Stable Chronic Medical Condition

- No change in prescription medication, dose, or frequency of medication in the last 3 months and health outcomes of the specific disease are considered to be within acceptable limits in the last 6 months. Any change that is due to change of health care provider, insurance company etc, or that is done for financial reasons, as long as in the same class of medication will not be considered a violation of this inclusion criterion. Any change in prescription medication due to **improvement** of a disease outcome will not be considered a violation of this inclusion criterion.

NIAID H1N1 Vaccine Trials

■ First 3 protocols:

- ❑ 1 vs. 2 doses of unadjuvanted CSL vaccine in healthy adults: enrollment complete ~ 400
- ❑ 1 vs. 2 doses of unadjuvanted SP vaccine in healthy adults: enrollment complete ~ 400
- ❑ co- vs. sequential administration of TIV and H1N1 vaccine in adults: enrollment complete ~ 800

■ Next 2 protocols

- ❑ 1 vs. 2 doses of unadjuvanted SP vaccine in healthy children: enrollment complete ~ 600
- ❑ co- vs. sequential administration of TIV and H1N1 vaccine in children: enrollment complete ~ 600

DMID 09-0043

Adult, One Dose, Two Dose, CSL

Study Groups	Stratum	Day 0	Day 21
Group 1, n=200	Age 18-64, n=100	CSL H1N1 Vaccine 15 mcg	CSL H1N1 Vaccine 15 mcg
	Age \geq 65, n=100		
Group 2, n=200	Age 18-64, n=100	CSL H1N1 Vaccine 30 mcg	CSL H1N1 Vaccine 30 mcg
	Age \geq 65, n=100		

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0043

Adult, One Dose, Two Dose, CSL

- Enrolled between 7 Aug and 21 Aug
- Demographics: F 54%, M 46%
- Age: <65 Median: 45.5
- Age: >65 Median: 71.5
- Age Overall Median: 64.7 (Min 18.1, Max 92)

DMID 09-0053

Adult, One Dose Two Dose, Sanofi

Study Groups	Stratum	Day 0	Day 21
Group 1, n=200	Age 18-64, n=100	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg
	Age \geq 65, n=100		
Group 2, n=200	Age 18-64, n=100	Sanofi Pasteur H1N1 Vaccine 30 mcg	Sanofi Pasteur H1N1 Vaccine 30 mcg
	Age \geq 65, n=100		

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0053

Adult, One Dose Two Dose, Sanofi

- Enrolled between 7 Aug and 18 Aug
- Demographics: F 53%, M 47%
- Age: <65 Median: 45.6
- Age: >65 Median: 72.6
- Age Overall Median: 65 (Min 18.3, Max 88)

DMID 09-0039

Adult, H1N1 and TIV Co administration

Study Groups	Stratum	Day 0	Day 21	Day 42
Group 1, n=200	Age 18-64 yrs, n=100	Sanofi Pasteur H1N1 Vaccine 15 mcg + placebo	Sanofi Pasteur H1N1 Vaccine 15 mcg + placebo	TIV
	Age ≥65 yrs, n=100			
Group 2, n=200	Age 18-64 yrs, n=100	Sanofi Pasteur H1N1 Vaccine 15 mcg + TIV	Sanofi Pasteur H1N1 Vaccine 15 mcg + placebo	Placebo
	Age ≥65 yrs, n=100			
Group 3, n=200	Age 18-64 yrs, n=100	Sanofi Pasteur H1N1 Vaccine 15 mcg + placebo	Sanofi Pasteur H1N1 Vaccine 15 mcg + TIV	Placebo
	Age ≥65 yrs, n=100			
Group 4, n=200	Age 18-64 yrs, n=100	TIV + placebo	Sanofi Pasteur H1N1 Vaccine 15 mcg + placebo	Sanofi Pasteur H1N1 Vaccine 15 mcg
	Age ≥65 yrs, n=100			

d, or QA'd:

Data is Preliminary

DMID 09-0039

Adult, H1N1 and TIV Co administration

- Enrolled between 7 Aug and 28 Aug
- Demographics: F 55%, M 45%
- Age: <65 Median: 48.4
- Age: >65 Median: 70.4
- Age Overall Median: 64.3 (Min 18.2, Max 92)

NIAID H1N1 Vaccine Trials

■ First 3 protocols:

- ❑ 1 vs. 2 doses of unadjuvanted CSL vaccine in healthy adults: enrollment complete ~ 400
- ❑ 1 vs. 2 doses of unadjuvanted SP vaccine in healthy adults: enrollment complete ~ 400
- ❑ co- vs. sequential administration of TIV and H1N1 vaccine in adults: enrollment complete ~ 800

■ Next 2 protocols

- ❑ 1 vs. 2 doses of unadjuvanted SP vaccine in healthy children: enrollment complete ~ 600
- ❑ co- vs. sequential administration of TIV and H1N1 vaccine in children: enrollment complete ~ 600

DMID 09-0054

Peds One Dose, Two Dose, Sanofi

Study Group	Stratum	Day 0	Day 21
Group 1, n=300	Age \geq 6 months – <36 months, n=100	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg
	Age \geq 36 months – 9 years, n=100		
	Age 10 years – 17 years, n=100		
Group 2, n=300	Age \geq 6 months – <36 months, n=100	Sanofi Pasteur H1N1 Vaccine 30 mcg	Sanofi Pasteur H1N1 Vaccine 30 mcg
	Age \geq 36 months – 9 years, n=100		
	Age 10 years – 17 years, n=100		

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0054

Peds One Dose, Two Dose, Sanofi

- Enrolled between 19 Aug and 9 Sept
- Demographics: F 46%, M 54%
- Age: 6m to < 36 mo Median: 1.7 y
- Age: 36 mo to 9 years Median: 6.7 y
- Age: 10 to 17 years Median: 14 y
- Age Overall Median: 6.8 (Min 0.5, Max 17.9)

DMID 09-0047

Peds: H1N1 and TIV Co administration

Study Groups	Stratum	Day 0	Day 21	Day 42
Group 1, n=150	Age \geq 6 months – <36 months, n=50	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg	TIV
	Age \geq 36 months – 9 years, n=50			
	Age 10 years – 17 years, n=50			
Group 2, n=150	Age \geq 6 months – <36 months, n=50	Sanofi Pasteur H1N1 Vaccine 15 mcg + TIV	Sanofi Pasteur H1N1 Vaccine 15 mcg	
	Age \geq 36 months – 9 years, n=50			
	Age 10 years – 17 years, n=50			
Group 3, n=150	Age \geq 6 months – <36 months, n=50	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg + TIV	
	Age \geq 36 months – 9 years, n=50			
	Age 10 years – 17 years, n=50			
Group 4, n=150	Age \geq 6 months – <36 months n=50	TIV	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg
	Age \geq 36 months – 9 years, n=50			
	Age 10 years – 17 years, n=50			

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0047

Peds: H1N1 and TIV Co administration

- Enrolled between 20 Aug and 21 Sept
- Demographics: F 48%, M 52%
- Age: 6m to < 36 mo Median: 2.2 y
- Age: 36 mo to 9 years Median: 6.2 y
- Age: 10 to 17 years Median: 14 y
- Age Overall Median: 7.3 (Min 1.1, Max 17.9)

NIAID H1N1 Vaccine Trials

■ Monovalent H1N1 in Pregnant Women

- ❑ Sanofi Pasteur, unadjuvanted, 1 dose, 2 dose 21 days apart
- ❑ 2nd and 3rd trimester women
- ❑ Enrollment ~120

DMID 09-0056

Pregnant Women, One Dose, Two Dose

Study Group	Day 0	Day 21
Group 1 N= 60	Sanofi Pasteur H1N1 Vaccine 15 mcg	Sanofi Pasteur H1N1 Vaccine 15 mcg
Group 2 N=60	Sanofi Pasteur H1N1 Vaccine 30 mcg	Sanofi Pasteur H1N1 Vaccine 30 mcg

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0056

Pregnant Women, One Dose, Two Dose

- Enrolled between 9 Sept and 15 Oct
- Demographics: F 100%, M 0%
- Age: Median: 31.9 (Min 18.9, Max 39.4)

NIAID H1N1 Vaccine Trials

- **Mixing and Matching Adjuvant and Antigen from different companies:**

- **Presently Enrolling**

- vaccines: sanofi pasteur H1N1 vaccine
- adjuvant: GSK's AS03
- mixed prior to administration
- protocol: 3.75 μ g +AS03, 7.5 μ g and 15 μ g +/- AS03
- 2 doses, 21 days apart

DMID 09-0058 Mix and Match

Study Groups	Stratum	Day 0	Day 21
Group 1, n=150	Age 18-64, n=100	Sanofi Pasteur H1N1 vaccine 3.75 mcg plus GSK AS03 adjuvant	Sanofi Pasteur H1N1 vaccine 3.75 mcg plus GSK AS03 adjuvant
	Age \geq 65, n=50		
Group 2, n=150	Age 18-64, n=100	Sanofi Pasteur H1N1 vaccine 7.5 mcg plus GSK AS03 adjuvant	Sanofi Pasteur H1N1 vaccine 7.5 mcg plus GSK AS03 adjuvant
	Age \geq 65, n=50		
Group 3, n=150	Age 18-64, n=100	Sanofi Pasteur H1N1 vaccine 15 mcg plus GSK AS03 adjuvant	Sanofi Pasteur H1N1 vaccine 15 mcg plus GSK AS03 adjuvant
	Age \geq 65, n=50		
Group 4, n=150	Age 18-64, n=100	Sanofi Pasteur H1N1 vaccine 7.5 mcg unadjuvanted	Sanofi Pasteur H1N1 vaccine 7.5 mcg unadjuvanted
	Age \geq 65, n=50		
Group 5, n=150	Age 18-64, n=100	Sanofi Pasteur H1N1 vaccine 15 mcg unadjuvanted	Sanofi Pasteur H1N1 vaccine 15 mcg unadjuvanted
	Age \geq 65, n=50		

Data is not monitored, or QA'd:
Data is Preliminary

DMID 09-0058 Mix and Match

- Enrolling: Started 24 Sept
- Demographics: F 53%, M 47%
- Age: < 65 Median: 42.3 y
- Age: >65 Median: 71.6 y
- Age Overall Median: 52 (Min 18.6, Max 91.3)

- 0 AESIs

Monovalent H1N1 Vaccine Safety Oversight

❑ Safety Monitoring Committee

❑ Charges

- ❑ Reviews all protocols prior to implementation for safety consideration
- ❑ Reviews all adverse events, serious adverse events, subject withdrawals, subject terminations, protocols deviations
- ❑ After analysis of safety, determines if a study should proceed, be modified or be stopped.

Monovalent H1N1 Vaccine Safety Oversight

- ❑ One Safety Monitoring Committee for all DMID H1N1 Trials
 - ❑ 5 Members
 - ❑ All with infectious disease expertise
 - ❑ Additional Expertise: HIV, OB-GYN, Internal Medicine, Pediatrics, Biostatistics
 - ❑ 2 Special Safety Consultants
 - ❑ These bring 2 added expertise:
 - ❑ Large Clinical Trial Pharmacovigilance
 - ❑ Adjuvant
- ❑ Over 40 Independent Safety Monitors:
 - ❑ local, independent, medical evaluators

Monovalent H1N1 Vaccine Safety Oversight

Safety Monitoring Committee

Organization

- Scheduled Meeting Monthly: (4)
- Daily Access to web based safety data summaries
- Data Review and Summaries as requested (2)
- Ad Hoc Review of Events: Electronic (~15)
- Ad Hoc Review of Events: Conference Call (3)

NIAID H1N1 Vaccine Trials

Halting Rules for Trials

- **Halting Rules:** Further enrollment and vaccinations will be halted for SMC review/recommendation if any of the following are reported:
 - Any death occurring within the 8 days following administration of study vaccine (Day 0-7) that was not the result of trauma or accident.
 - Systemic anaphylaxis within 24 hours of administration
 - Two or more subjects urticaria within 72 hours
 - Ulceration, abscess, or necrosis at the injection site
 - Vaccine-related SAE.
 - Acute weakness of limbs and or cranial nerve innervated muscles

NIAID H1N1 Vaccine Trials

Rules for Withdrawal of Subjects

- Subsequent vaccinations will not be administered to a subject if:
 - Solicited or unsolicited severe adverse events that occur without a clear, alternative cause.
 - A new medical condition for which continued participation, that poses a risk to the subject.
 - Presence of signs or symptoms that could confound or confuse assessment of vaccine reactogenicity.
 - Subject no longer meets inclusion/exclusion criteria.
 - Subject withdrawal of consent/ Loss to follow-up / Termination of the study.
 - PI discretion

NIAID H1N1 Vaccine Trials

Over View: Safety

- Overall Enrollment ~ 3600
- Number of Vaccinations ~ 7800
- 8 Trials in Progress
- Safety follow up continues in all trials
- There have been < 30 SAEs
- Severe local and severe systemic reactions have been approximately 1% in the unadjuvanted studies
- Studies have met halting rules three times that the SMC felt the need to meet. Each review has lead to no modification of the protocol, the informed consent, or safety follow up.

NIAID H1N1 Vaccine Trials

Over View: Reactogenicity

- Highest Rate of Reactogenicity
- After any vaccination in any group in unadjuvanted protocol
- So vaccination could be 15 mcg, 30 mcg or Seasonal Influenza

	Moderate/ Severe		
• Elevated Temperature	1.9	/	0.2
• Feverishness	3.5	/	0.8
• Malaise	6.3	/	0
• Myalgia	3.3	/	0.5
• Headache	4.8	/	0.3
• Nausea	3.5	/	0.5
• Pain	3.7	/	0
• Tenderness	4.1	/	0.2
• Swelling	0.8	/	0

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Any Questions?

