

**Phase 1/2 Clinical Study with
Baxter's H5N1 Vaccine**

Clinical Update

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**WHO Meeting on Evaluation of Pandemic Influenza
Prototype Vaccines in Clinical Trials
Geneva, February 15 - 16, 2007**

The following information and data has been presented at the
„WHO Meeting on Evaluation of
Pandemic Influenza Prototype Vaccines in Clinical Trials“
in Geneva, February 15 - 16, 2007
and reflects Baxter's then available knowledge.
This presentation may not be downloaded,
copied or used for any other purposes.
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Specific Features

- Cell culture (Vero cells), not embryonated hens' eggs
- Wildtype viruses, not attenuated reverse genetics (RG) reassortants
- Whole virus vaccine, not split or subunit vaccine
- GMP licensed BSL-3 (Biosafety level 3) manufacturing facility

- Monovalent H5N1 candidate vaccines against a clade 1 (A/Vietnam/1203/2004) and a clade 2 (A/Indonesia/05/2005) strain have been developed based on the **whole virus** approach. These candidate vaccine have been demonstrated to be **highly immunogenic** and **protective** in mouse challenge models
- In addition, an effective **cross-protection** has been shown against the **prototype** human isolate Hong Kong 156 of 1997 and representative H5N1 strains of **clade 1** and **clade 2**
- A clear **dose response** can be seen in the challenge experiments
- Protection and **cross-protection** against representatives of H5N1 **clade 1** and **2** viruses in mice is induced by **nanograms** of H5N1 whole virus candidate vaccine preparations; and comparable to other virus (candidate) vaccine preparations
- **Al(OH)₃ adjuvanted** H5N1 Vietnam 1203 candidate vaccine preparations were **less protective** in mice than **non-adjuvanted** candidate vaccines

Study Design

- **Primary Objective:**
To identify the immunogenicity and safety of different doses of adjuvanted and non-adjuvanted mock-up pandemic influenza vaccine.
- **Number of Subjects:**
N= 270, aged 18 to \leq 45 years, healthy volunteers
- **Number of Vaccinations:**
2 vaccinations on day 0 and day 21
- **Dosing Levels:**
3.75 μ g, 7.5 μ g, 15 μ g, and 30 μ g adjuvanted (Al(OH)₃);
7.5 μ g and 15 μ g also non-adjuvanted

Primary Endpoints

Primary Immunogenicity Endpoint:

- Number of subjects with antibody response to the vaccine strain (A/Vietnam/1203/04) associated with protection 21 days after the first and second vaccination defined as either HI titer $\geq 1:40$ or titer measured by MN test $\geq 1:20$.

Primary Safety Endpoint:

- Systemic reactions after the first and second vaccinations.

Baxter's Phase I/II H5N1 Clinical Trial Preliminary Study Results

Baxter

- Baxter's vero cell derived whole virus H5N1 vaccine is **safe** and has an excellent **tolerability** profile.

Validated 7 Day Safety Data *

	3.75 µg adjuv.	7.5 µg adjuv.	7.5 µg	15 µg adjuv.	15 µg	30 µg adjuv.
1. Vaccination						
N =	45	45	45	44	45	48
Fever	1 (2.2%)	2 (4.4%)	0 (0%)	2 (4.5%)	1 (2.2%)	1 (2.1%)
Malaise	6 (13.3%)	5 (11.1%)	2 (4.4%)	6 (13.9%)	4 (8.9%)	3 (6.3%)
Shivering	0 (0%)	4 (8.9%)	3 (6.7%)	4 (9.1%)	1 (2.2%)	0 (0%)
2. Vaccination						
N =	42	42	42	43	43	45
Fever	0 (0%)	1 (2.4%)	2 (4.8%)	0 (0%)	3 (7.0%)	1 (2.2%)
Malaise	2 (4.8%)	3 (7.1%)	2 (4.8%)	1 (2.3%)	5 (11.6%)	4 (8.9%)
Shivering	0 (0%)	2 (4.8%)	2 (4.8%)	1 (2.3%)	3 (7.0%)	0 (0%)

* All AEs independent of causality

Local Reactions

	3.75 µg adjuv.	7.5 µg adjuv.	7.5 µg not adjuv.	15 µg adjuv.	15 µg not adjuv.	30 µg adjuv.
1. Vaccination						
N =	45	45	45	44	45	48
Local Reactions	13 (28.9%)	10 (22.2%)	5 (11.1%)	11 (25%)	9 (20%)	12 (25%)
2. Vaccination						
N =	42	42	42	43	43	45
Local Reactions	7 (16.7%)	5 (11.9%)	6 (14.3%)	8 (18.6%)	7 (16.3%)	6 (13.3%)

* All AEs independent of causality

Baxter's Phase I/II H5N1 Clinical Trial Study Results To Date

Baxter

- Baxter's vero cell derived whole virus H5N1 vaccine is safe and has an **excellent tolerability** profile.
- Vaccine doses as low as 3.75 µg or 7.5 µg are **highly immunogenic**, as shown in the microneutralization (MN) test.
- The **non-adjuvanted** formulation is more immunogenic than the adjuvanted one.

Immunogenicity – Seroprotection

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Vietnam/1203/2004**

Number of subjects with antibody response associated with protection (titer \geq 1:20), 21 days after 1st/2nd vaccination measured by MN titer

Day	Study Group					
	3.75 μ g adjuvanted	7.5 μ g adjuvanted	7.5 μ g	15 μ g adjuvanted	15 μ g	30 μ g adjuvanted
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
0	0/42 (0%)	3/42 (7.1%)	0/42 (0%)	1/43 (2.3%)	0/43 (0%)	0/46 (0%)
21	9/42 (21.4%)	11/42 (26.2%)	17/42 (40.5%)	7/43 (16.3%)	17/43 (39.5%)	5/46 (10.9%)
42	29/42 (69.0%)	25/39 (64.1%)	32/42 (76.2%)	25/41 (61.0%)	29/41 (70.7%)	29/44 (65.9%)

CHMP Criteria
(for seasonal vaccines)

> 70%

Immunogenicity – GMT Increase

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Vietnam/1203/2004**

Geometric Mean Titer increase of MN titer measured 21 days after 1st/2nd vaccination as compared to pre-vaccination titer

Day	Study Group					
	3.75 µg adjuvanted	7.5 µg adjuvanted	7.5 µg	15 µg adjuvanted	15 µg	30 µg adjuvanted
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
21	2.0	2.0	3.2	1.9	3.1	2.1
42	4.4	4.0	5.3	3.9	5.7	4.6

CHMP Criteria
(for seasonal vaccines)

> 2.5

Baxter's Phase I/II H5N1 Clinical Trial

- Baxter's vero cell derived whole virus H5N1 vaccine is safe and has an **excellent tolerability** profile.
- Vaccine doses as low as 3.75 µg or 7.5 µg are **highly immunogenic**, as shown in the microneutralization (MN) test.
- The **not adjuvanted** formulation is more immunogenic than the adjuvanted one.
- The vaccine **shows cross-neutralization** against an old prototype strain (Hongkong/156/1997) as well as against a recent clade 2 strain (Indonesia/05/2005).

Immunogenicity – Seroprotection

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Hongkong/156/97**

Number of subjects with antibody response associated with protection (titer \geq 1:20), 21 days after 1st/2nd vaccination measured by MN titer

Day	Study Group		
	3.75 μ g adjuvanted	7.5 μ g adjuvanted	7.5 μ g
	n/N (%)	n/N (%)	n/N (%)
0	0/40 (0%)	3/39 (7.7%)	2/42 (4.8%)
21	9/40 (22.5%)	11/39 (28.2%)	20/42 (47.6%)
42	27/40 (67.5%)	25/39 (64.1%)	32/42 (76.2%)

Immunogenicity – GMT Increase

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Hongkong/156/97**

Geometric Mean Titer increase of MN titer measured 21 days after 1st/2nd vaccination as compared to pre-vaccination titer

Day	Study Group		
	3.75 µg adjuvanted	7.5 µg adjuvanted	7.5 µg
	n/N (%)	n/N (%)	n/N (%)
21	2.3	2.2	3.4
42	6.1	5.2	5.9

Immunogenicity – Seroprotection

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Indonesia/05/2005**

Number of subjects with antibody response associated with protection (titer \geq 1:20), 21 days after 1st/2nd vaccination measured by MN titer

Day	Study Group				
	3.75 μ g adjuvanted	7.5 μ g adjuvanted	7.5 μ g	15 μ g adjuvanted	15 μ g
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
0	1/42 (2.4%)	1/39 (2.6%)	0/42 (0%)	1/40 (2.5%)	0/40 (0%)
21	5/42 (11.9%)	5/39 (12.8%)	10/42 (23.8%)	1/40 (2.5%)	7/40 (17.5%)
42	12/42 (28.6%)	14/39 (35.9%)	19/42 (45.2%)	3/40 (7.5%)	15/40 (37.5%)

Immunogenicity – GMT Increase

(Preliminary Data: not validated yet, not audited yet)

Microneutralization Test: **A/Indonesia/05/2005**

Geometric Mean Titer increase of MN titer measured 21 days after 1st/2nd vaccination as compared to pre-vaccination titer

Day	Study Group				
	3.75 µg adjuvanted	7.5 µg adjuvanted	7.5 µg	15 µg adjuvanted	15 µg
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
21	1.7	1.6	2.2	1.4	2.3
42	2.8	2.7	3.2	2.4	3.7

Baxter's Phase I/II H5N1 Clinical Trial Preliminary Study Results

Baxter

- Baxter's vero cell derived whole virus H5N1 vaccine is safe and has an **excellent tolerability** profile.
- Vaccine doses as low as 3.75 µg or 7.5 µg are **highly immunogenic**, as shown in the microneutralization (MN) test.
- The **not adjuvanted** formulation is more immunogenic than the adjuvanted one.
- The vaccine **shows cross-neutralization** against an old prototype strain (Hongkong/156/1997) as well as against a recent clade 2 strain (Indonesia/05/2005).
- Consistent with published data, there is a high variability of the different HI assay systems **for H5N1**, leading us to question the value of HI results.

NIH/NIAID

The H5N1 A/Vietnam/1203/2004 development program has been carried out in close association with the US NIH/NIAID

CDC

H5N1 wildtype virus strains

NIBSC

H5N1 specific reagents

FDA/CBER

H5N1 specific reagents

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