Development and clinical evaluation of an avian influenza A(H5N1) vaccine at IVAC, Vietnam

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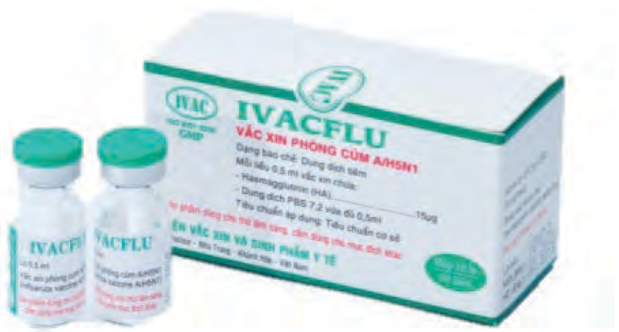
PATH
A catalyst for global health

Presentation Outline

1. Overview of PATH support
2. Phase 1 clinical trial of IVAC influenza A/H5N1 vaccine
   i. Trial design
   ii. Trial outcomes and discussion
   iii. Conclusions



Overview of PATH support for influenza vaccine development in Vietnam

MOH

- Support the development of policy, regulations, and guidelines for development

VABIOTECH

- Assist with research and development of cell-based influenza vaccine

IVAC

- Provide support for IVAC to produce WHO-GMP influenza vaccines to enable supply for domestic needs and export in future

Research Institutions: Pasteur Institute Ho Chi Minh City, National Institute of Hygiene and Epidemiology

- Provide technical support for conduct of GCP standard clinical trials of influenza vaccines

Phase 1 clinical trial of IVAC influenza A/ H5N1 vaccine

Trial Objectives

Primary objective:

To evaluate the safety profile of two intramuscular doses of the inactivated A/H5N1 whole virion, aluminum adsorbed influenza vaccine (IVACFLU-A/H5N1) in healthy adults.

Secondary objective:

To evaluate the immunogenicity of inactivated A/H5N1 whole virion, aluminum adsorbed influenza vaccine (IVACFLU-A/H5N1) at two different dose levels in healthy adults.

Study Design

- **Study design:** Phase 1, double-blind, randomized, placebo-controlled trial
- **Study population:** 76 healthy male and female adults, 18 to 30 years of age *(**32** high dose: 15 mcg HA/0.5 ml; **32** low dose: 7.5 mcg HA/0.5 ml; and **12** placebo: PBS).*
- **Vaccination schedule:** 2 injections, 21 days apart
- **Study methodology:** Evaluation of safety and immunogenicity
- **Field monitoring:** IVAC, PATH
- **Data management and analysis:** Quintiles

Study Design Scheme[1]

S1 (105 healthy adults, 18-30 years of age); Sign ICF-A;
Physical exam; Blood testing (biochemical, hematological), Urine testing (biochemical)

76 subjects were selected into S2/D0

Block randomization

Sentinel cohort of 19 subjects

S2/D0

- High dose: **8**
- Low dose: **8**
- Placebo: **3**

Remain group of 57 subjects

S2/D0

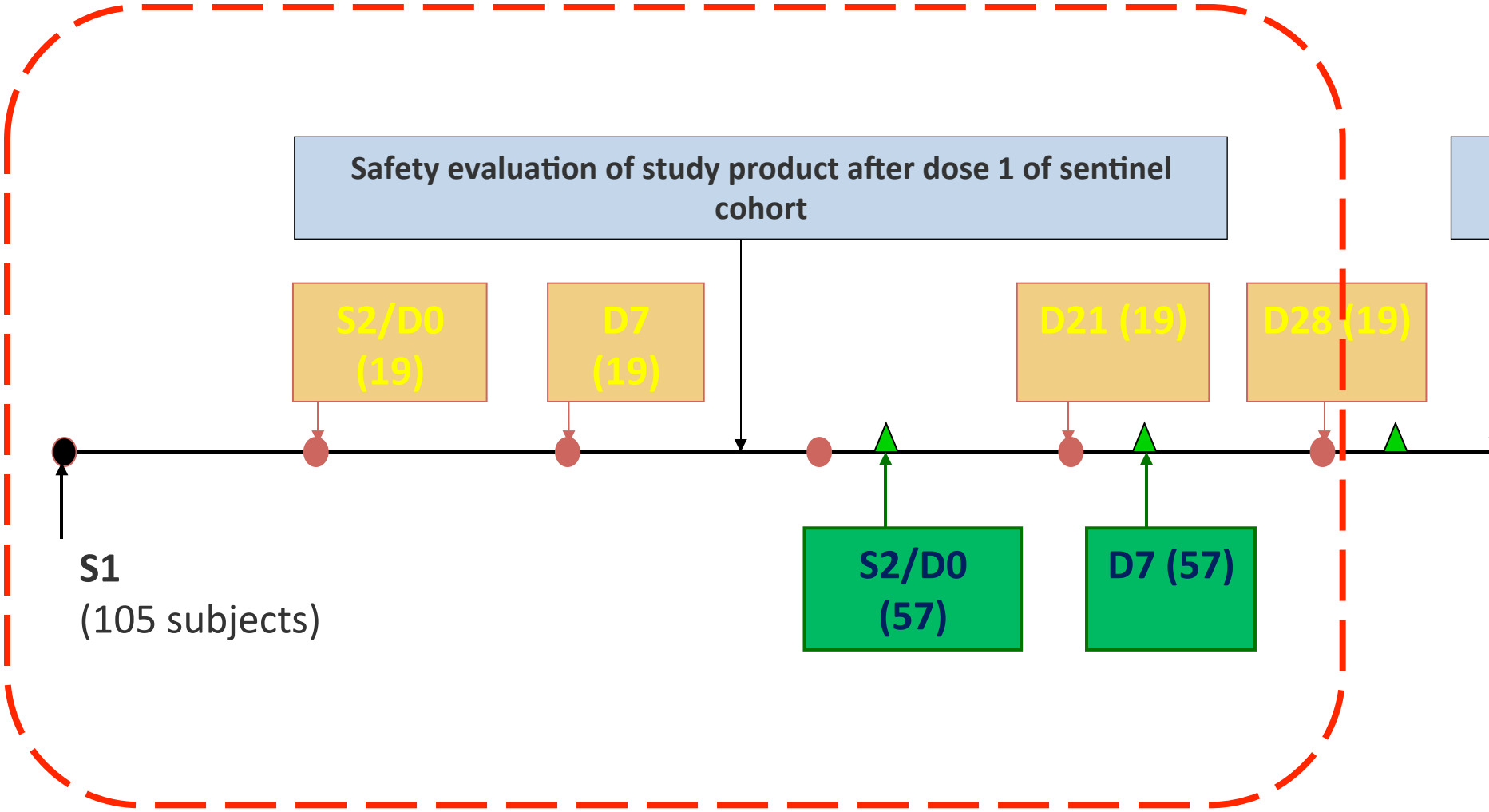
- High dose: **24**
- Low dose: **24**
- Placebo: **9**

Summary: 32 high dose; 32 low dose; 12 placebo

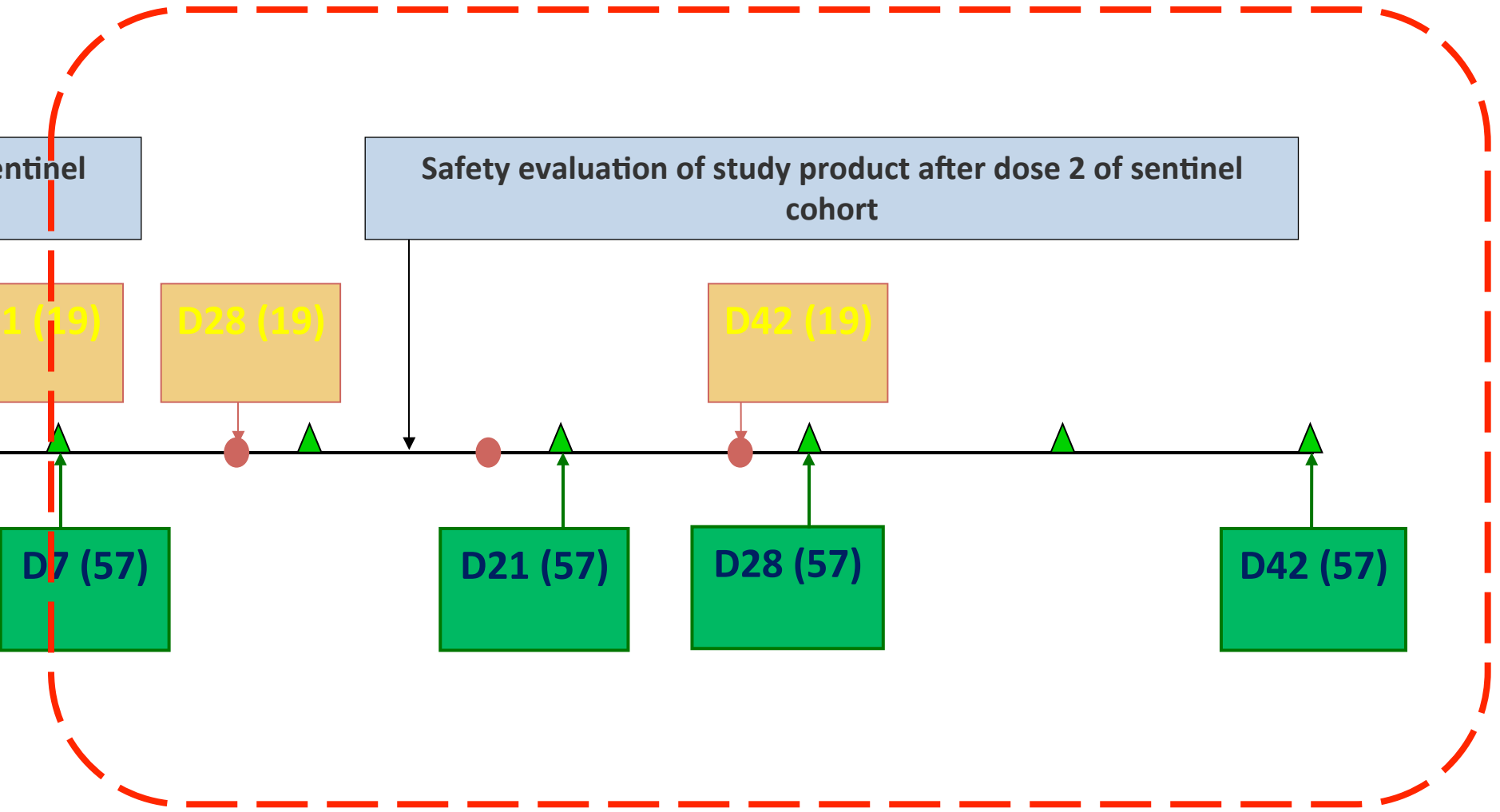
High dose: 15 mcg HA/0.5 ml; low dose: 7.5 mcg HA/0.5 ml; placebo: PBS

Vaccination of the remaining cohort was carried out after the safety data for the post-dose 1 and the post-dose 2 from the sentinel cohort was reviewed by the SMC.

Study Activities Scheme(1)



Study Activities Scheme(2)



Primary Outcome Measures
(Safety)

- Immediate reactions occurring within 60 minutes of administration of any dose.
- Adverse events (reactogenicity) commonly solicited local and systemic reactions occurring greater than 60 minutes through 7 days after administration of any dose.
- All other adverse events (including unsolicited events) following any dose, including clinical findings and abnormal laboratory findings on days 7 and 28.
- All serious adverse events (SAEs) occurring within 3 weeks of receipt of any dose.

Secondary Endpoints (Immunogenicity)

- Proportion of subjects achieving **HAI/MNT titer ≥ 1:40** after each dose.
- Proportion of subjects achieving **a four-fold rise in HAI/MNT** between doses or from baseline to post-injection 2.
- **GMT** of HAI/MNT after each dose.
- **Geometric mean titer ratio** of HAI/MNT antibody between doses or from baseline to post-injection 2 .

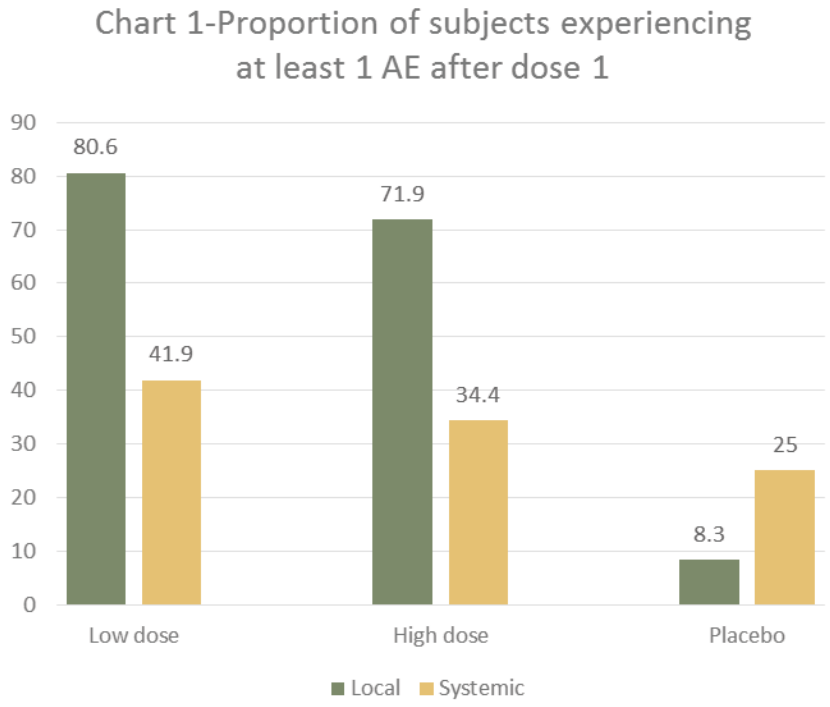
HAI = Hemagglutination Inhibition

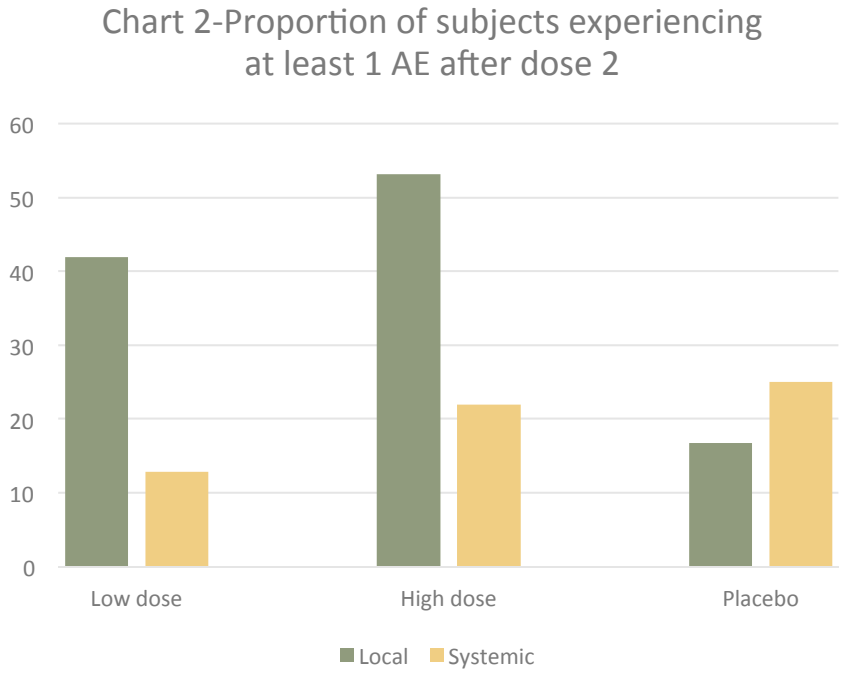
MNT = Microneutralization

Results of Safety Evaluation

(Primary Objective)

Proportion (%) of Subjects Experiencing at Least One AE After Dose 1 and Dose 2





During the course of the trial, **no recorded SAE occurred** within 3 weeks after administration of any dose.

Summary of Local Reactions from 60 Minutes Through 7 Days After Vaccination of Both Dose 1 and 2

Symptoms	Low dose (n=31) No of subjects (%)	High dose (n=32) No of subjects (%)	Both doses (n = 63) No of subjects (%)	Placebo (n=12) No of subjects (%)
Number of subjects experiencing at least one local reaction after injection:				
- No of subjects (%) - [95% CI]	25 (80.6) [62.5-92.5]	24 (75.0) [56.6-88.5]	49 (77.8) [65.5-87.3]	3(25.5) [5.5 – 57.2]
Redness at injection site	0 (0)	0 (0)	0 (0)	0 (0)
Swelling at injection site	0 (0)	0 (0)	0 (0)	0 (0)
Hardness at injection site	0 (0)	0 (0)	0 (0)	0 (0)
Pain at injection site	**21 (67.0)**	**23 (71.9)**	**44 (69.8)**	3 (25.0)
Tenderness at injection site	**18 (58.1)**	**16 (50.0)**	**34 (54.0)**	1 (8.3)

Summary of Systemic Reactions from 60 Minutes Through 7 Days After Vaccination of Both Dose 1 and 2

Symptoms	Low dose (n=31) No of subjects(%)	High dose (n=32) No of subjects(%)	Both doses (n = 63) No of subjects(%)	Placebo (n=12) No of subjects(%)
Number of subjects experiencing at least one systemic reaction after injection:				
- No of subjects (%) - [95% CI]	13 (41.9) [24.5 – 60.9]	14 (43.8) [26.4 – 62.3]	27 (42.9) [30.5-56.0]	4 (33.3) [9.9 – 65.1]
Chills	1 (3.2)	3 (9.4)	4 (6.3)	0 (0.0)
Cough	3 (9.7)	2 (6.3)	5 (7.9)	2 (16.7)
Ear pain	0 (0.0)	1 (3.1)	1 (1.6)	0 (0.0)
Fatigue/malaise	3 (9.7)	5 (15.6)	8 (12.7)	2 (16.7)
Fever (Measured)	0 (0.0)	3 (9.4)	3 (4.8)	0 (0.0)
Feverishness	5 (16.1)	3 (9.4)	8 (12.7)	0 (0.0)
Headache	2 (6.5)	8 (25.0)	10 (15.9)	3 (25.0)
Hoarseness of voice	0 (0.0)	2 (6.3)	2 (3.2)	1 (8.3)
Nasal congestion	1 (3.2)	2 (6.3)	3 (4.8)	0 (0.0)

Summary of Unsolicited AEs After Dose 1 and Dose 2

Symptoms	Low dose (n=31) Frequency (%)	High dose (n=32) Frequency (%)	Placebo (n = 12) Frequency (%)
Number of subjects having at least one unsolicited AE	12 (38.7) [21.8 – 57.8]	12 (37.5) [21.1 – 56.3]	4 (33.3) [9.9 – 65.1]

Severity of all unsolicited AEs was minor except one case of a broken clavicle which occurred due to a transportation accident. All unsolicited AEs were evaluated as unrelated to the study drug.

Discussion on Safety

- No subjects in either the placebo or vaccine cohorts experienced any AEs (based on vital signs, local, and systemic reactions) within 60 minutes after each dose administration.

- The frequencies of solicited local and systemic AEs occurring from 60 minutes through 7 days after any dose were similar to those of licensed H5N1 vaccines.

Discussion on Safety

- Some subjects had out-of-normal range hematology and chemistry values that were noted in this Phase 1 trial, including some out-of-range values at baseline and some discrepancies between day 0 and day 28 that were demonstrated in both the placebo cohort and vaccine cohorts. These abnormal test values were assessed to be of non-clinical significance, and those with abnormal laboratory values on day 42 were monitored until laboratory values came back to normal or stabilized.
- No deaths or other SAE cases occurred in this trial.

Results of Immunogenicity Evaluation

(Secondary Objective)

Results of HAI and MNT Assays at Baseline (minimum dilution threshold ≥ 1/10 was selected)

Study Cohort	Type of Assay	
	HAI	MNT
Placebo	0/12 (0%)	0/12 (0%)
Low dose	0/31 (0%)	0/31 (0%)
High dose	0/32 (0%)	0/32 (0%)

Proportion of Subjects With HAI Titer ≥ 1:40 After Each Dose

Cohort	Post-injection 1 Proportion % (95% CI)	Post-injection 2 Proportion % (95% CI)
Placebo (n=12)	0 (0.0 – 26.5)	0 (0.0 – 26.5)
Low dose (n=31)	22.6 (9.6 – 41.1)	41.9 (24.6 – 60.9)
High dose (n=32)	28.1 (13.8 – 46.8)	56.3 (37.7 – 73.6)

GMT of HAI After Each Dose

Cohort	Baseline GMT (95% CI)	Post-injection 1 GMT (95% CI)	Post-injection 2 GMT (95% CI)
Placebo (n=12)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Low dose (n=31)	5.0 (5.0 – 5.0)	12.8 (8.0 – 20.6)	24.5 (15.5 – 38.6)
High dose (n=32)	5.0 (5.0 – 5.0)	11.9 (8.2 – 17.3)	27.1 (20.0 – 36.7)

GMT Ratio of HAI Antibody Between Doses or From Baseline to Post-Injection 2

Cohort	GMT Ratio of HAI between doses (95% CI)	GMT ratio of HAI from Baseline to post-injection 2 (95% CI)
Placebo (n=12)	1 (1.0 – 1.0)	1 (1.0 – 1.0)
Low dose (n=31)	1.9 (1.5 – 2.5)	4.9 (3.1 – 7.7)
High dose (n=32)	2.3 (1.7 – 3.0)	5.4 (4.0 – 7.3)

Proportion of Subjects *Achieving a Four-fold* Rise in HAI Titer Between Doses or from Baseline to Post-injection 2

Cohort	Proportion achieving a four-fold rise of HAI between doses Proportion % (95% CI)	Proportion achieving a four-fold rise of HAI from baseline to post-injection 2 Proportion % (95% CI)
Placebo (n=12)	0 (0.0 – 26.5)	0 (0.0 – 26.5)
Low dose (n=31)	29.0 (14.2 – 48.0)	67.7 (48.6 – 83.3)
High dose (n=32)	34.4 (18.6 – 53.2)	71.9 (53.25 – 86.3)

GMT of Neutralizing Antibody After Each Dose

Cohort	Baseline	Post-injection 1	Post-injection 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Placebo (n=12)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Low dose (n=31)	5.0 (5.0 – 5.0)	9.4 (6.0 – 14.6)	21.9 (14.0 – 34.4)
High dose (n=32)	5.0 (5.0 – 5.0)	9.4 (6.5 – 13.5)	23.3 (16.5 – 32.8)

GMT Ratio of MNT Between Doses or from Baseline to Post-Injection 2

Cohort	GMT ratio of MNT between doses Ratio (95% CI)	GMT ratio of MNT from baseline to post-injection 2 Ratio (95% CI)
Placebo (n=12)	1.0 (1.0 – 1.0)	1.0 (1.0 – 1.0)
Low dose (n=31)	1.9 (1.2 – 2.9)	4.4 (2.8 – 6.9)
High dose (n=32)	1.9 (1.3 – 2.7)	4.7 (3.3 – 6.6)

Proportion of Subjects *Achieving a Four-fold Rise* in MNT Between Doses or from Baseline to Post-Injection 2

Cohort	Proportion achieving a four-fold rise of MNT between doses Proportion % (95% CI)	Proportion achieving a four-fold rise of MNT from baseline to post-injection 2 Proportion % (95% CI)
Placebo (n=12)	0.0 (0.0 – 26.5)	0.0 (0.0 – 26.5)
Low dose (n=31)	35.5 (19.2 – 54.6)	61.3 (42.2 – 78.2)
High dose (n=32)	40.6 (23.7 – 59.4)	71.9 (53.3 – 86.3)

Discussion of Immunogenicity

Dose 7.5 mcg/0.5ml and 15 mcg/0.5ml

- **For low dose of 7.5 mcg/0.5 ml**, with the seroconversion proportion in at least 40% of subjects (**67.7%**; 95% CI: 48.6% – 83.3%); however, the upper bound of 95%CI of the HAI antibody titer is less than 70% (41.9%, 95% CI: 24.6% – **60.9%**). This vaccine does not meet the per protocol criteria; as a result, the dose of 7.5 mcg HA/0.5 ml is not recommended in the next phases of clinical trials.
- **For high dose of 15 mcg HA/0.5 ml**, with the seroconversion proportion in at least 40% of subjects (71.9%; 95% CI: 53.3% – 86.3%); and with the upper range of 95%CI of the percentage of subjects with HAI antibody titer ≥ 1:40 not less than 70% (56.3%; 95% CI: 37.7% – 73.6%). This vaccine meets the per protocol criteria; so this dose is recommended to be tested in the next trial phases.
- **Consideration for adding 30 mcg HA/0.5 ml dose** to test in the next phase of clinical trials: In order to get obtain evidence of the immunogenicity and safety of a higher vaccine dose, and to have more choices in selecting the appropriate dose for the license application.

Final Conclusions

Phase 1 double-blind, randomization and placebo-controlled clinical trial conducted in 75 healthy adult subjects (32 high dose, 31 low dose, 12 placebo) had the following results:

- **Local and systemic reactions** as well as other solicited AEs of IVACFLU-A/H5N1 vaccine with doses of 7.5 mcg/0.5 ml and 15 mcg/0.5 ml were similar to those of A/H5N1 vaccines licensed in the world, and there were no SAEs occurring in study subjects.
- **15 mcg/0.5 ml dose of IVACFLU-A/H5N1 vaccine** was initially **immunogenic** based on the results of HAI and MNT assays which are commonly used for assessing the immunogenicity of influenza vaccines.

Acknowledgments

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- Study was implemented in collaboration with the research team at Pasteur Institute Ho Chi Minh City; Long An's provincial People's Committee, provincial Health Department, provincial Preventive Medicine Center; Ben Luc's district People's Committee, District Health Center; and Commune Health Centers of Long Hiep, Phuoc Loi, Tan Buu, Thanh Duc, and Nhat Chanh of Ben Luc district.