Sponsor: Novartis Vaccines and Diagnostics

Investigational Product: Monovalent H5N1 (Surface Antigen Adjuvanted with MF59C.1)

Indication: Prophylaxis: Influenza

Protocol Number: V87_17

Protocol Title: A Phase 2, Randomized, Controlled, Double-blind, Multi-center, Study to Evaluate Safety and Immunogenicity of Two Doses, Administered Three Weeks Apart, of Two Monovalent H5N1 (Surface Antigen Adjuvanted with MF59C.1) Influenza Vaccines Containing 3.75 μg or 7.5 μg of H5N1 Influenza Antigen, in Non-elderly Adult and Elderly Subjects

Phase of Development: Phase 2

Study Period:

Date of first enrolment: 23 SEP 09

Date of last visit: 23 DEC 09

Methodology:

This was a Phase 2, randomized, controlled, double-blind, multicenter study.

Randomization was stratified by center and age group. Enrolled subjects had blood drawn for serology and were randomized at a 1:1 ratio to receive two intramuscular (IM) injections of either the monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75μg H5N1 antigen dose or the same vaccine containing a 7.5μg antigen dose.

Reactogenicity was assessed for the first week following each vaccination (day 1 to 7 and day 22 to 28).

Number of Subjects (planned and analyzed):

Approximately 770 subjects were planned for enrolment in this study. In total, 772 subjects were enrolled in this study.

Study Centers:

Six study centers in Poland and six study centers in Turkey.

Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:

NCT 00914771

PMID 23362618

Objectives:

Primary objectives

- To demonstrate the non-inferiority of antibody responses of two 0.5 mL intramuscular (IM) injections administered 3 weeks apart of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose to a pandemic vaccine containing a 7.5µg H5N1antigen dose in terms of post-immunization geometric mean titers (GMT) at day 43 as determined by single radial hemolysis (SRH) in non-elderly adult and elderly subjects combined.

Co-Primary:
Once non-inferiority was shown as determined by SRH, subsequently non-inferiority was assessed as determined by haemagglutination inhibition (HI) test in a stepwise procedure, thus non-inferiority would be concluded if either non-inferiority would be shown for SRH only or if it would be shown for both SRH and HI.

- To demonstrate the non-inferiority of antibody responses of two 0.5 mL IM injections administered 3 weeks apart of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose to a pandemic vaccine containing a 7.5µg H5N1antigen dose in terms of post-immunization geometric mean titers (GMT) at day 43 as determined by HI in non-elderly adult and elderly subjects combined.

Secondary objectives

- To evaluate the immunogenicity of two 0.5 mL IM injections of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose and a pandemic vaccine containing a 7.5µg H5N1antigen dose according to Committee for Medicinal Products for Human Use (CHMP) criteria in terms of seroprotection, seroconversion and geometric mean ratio (CPMP/BWP/214/96) as determined by SRH in non-elderly adult and elderly subjects separately, for all post-vaccination blood sampling days.
- To evaluate the immunogenicity of two 0.5 mL IM injections of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose and a pandemic vaccine containing a 7.5µg H5N1antigen dose according to CHMP criteria in terms of seroprotection, seroconversion and geometric mean ratio (CPMP/BWP/214/96) as determined by HI in non-elderly adult and elderly subjects separately, for all post-vaccination blood sampling days.
- To evaluate the immunogenicity of two 0.5 mL IM injections of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose and a pandemic vaccine containing a 7.5µg H5N1antigen dose according to Center for Biologics Evaluation and Research (CBER) criteria in terms of HI test in non-elderly adult and elderly subjects separately, for all post-vaccination blood sampling days.
- To evaluate the immunogenicity of two 0.5 mL IM injections of a monovalent MF59-adjuvanted H5N1 pandemic vaccine containing 3.75µg H5N1 antigen dose and a pandemic vaccine containing a 7.5µg H5N1antigen dose, as measured by microneutralization (MN) test in non-elderly adult and elderly subjects separately, for all post-vaccination blood sampling days.

Safety

- To evaluate the safety and tolerability of two monovalent MF59-adjuvanted H5N1 pandemic influenza vaccines, containing either 3.75 or 7.5µg of H5N1 antigen in nonelderly adult and elderly subjects.

Test Product, Dose, Mode of Administration, Lot Number:

H5N1 pandemic influenza vaccine containing 3.75µg of the A/H5N1/Vietnam/1203/04 influenza antigen with 0.25 ml of MF59C.1 adjuvant. The test was supplied in prefilled syringes and was administered in the deltoid muscle. Lot number: IAZ53D18H1

Duration of Study:

Expected subject enrollment interval in the study was for approximately 4 weeks and the duration of individual subject's participation was approximately 6 weeks after randomization.

Reference Therapy, Dose, Mode of Administration, Lot Number:

H5N1 pandemic influenza vaccine containing 7.5µg of the A/Vietnam/1194/2004 influenza antigen with 0.25 ml of MF59C.1 adjuvant. The reference vaccines were supplied in prefilled syringes and were administered in the deltoid muscle. Lot number: IA070202.

Statistical Methods:

Statistical Hypothesis

The objective was to show in a stepwise approach the non-inferiority of the 3.75 µg dose group to the 7.5 µg dose group in terms of antibodies on day 43 (i.e. 3 weeks after the 2nd vaccination):

Step 1: for SRH data:

$H_{01}: \mu_{3.75} - \mu_{7.5} \leq -0.176$ vs. $H_{11}: \mu_{3.75} - \mu_{7.5} > -0.176$ (one-sided test)

It is assumed that log-transformed SRH areas are normal distributed $N(\mu_i, \sigma^2)$ with $\mu_{3.75}$ and $\mu_{7.5}$ denoting the unknown mean in the two dose groups and σ^2 the common variance.

Step 2: for HI data:

$H_{02}: \nu_{3.75} - \nu_{7.5} \leq -0.176$ vs. $H_{12}: \nu_{3.75} - \nu_{7.5} > -0.176$ (one-sided test)

It is assumed that log-transformed antibody titers are normal distributed $N(\nu_i, \sigma^2)$ with $\nu_{3.75}$ and $\nu_{7.5}$ denoting the unknown mean in the two dose groups and σ^2 the common variance.

The alternative hypothesis states that the difference in post vaccination (day 43) means of the log10 transformed antibody titers/SRH values between the 3.75 and the 7.5µg dose group is above the non-inferiority margin -0.176. Non-inferiority can be concluded if the lower limit of the 2-sided 95% CI of the difference in post vaccination (day 43) means is above -0.176. This means in terms of GMT ratios that non-inferiority can be concluded if the lower limit of the 2-sided 95% CI of the post vaccination (day 43) GMT ratio is above 0.667.

The null hypotheses was tested in a stepwise approach, first for SRH and then for HI.

Thus non-inferiority can be concluded if either non-inferiority can be shown for SRH only or if it also can be shown for both SRH and HI. The null hypotheses were tested for the total (i.e. non-elderly and elderly) Per Protocol Set (PPS) and not separately for the age groups.

Sample Size and Power Considerations

The results of the observed standard deviation of the log10-transformed titers and the upper limit of the respective 80% CI seen in a previous trial in adults (V87P1) were used as basis data for sample size estimation:

- The upper 80% CI of the standard deviation (SD) of the log10-transformed HI titers was 0.8
- The upper 80% CI of the SD of the log10-transformed SRH areas was 0.42.

With a sample size of 326 subjects in each group, there was 80% power to reject the hypothesis that the difference in means of the log10-transformed HI titers of the 3.75µg group and the 7.5µg group are equal or less than non-inferiority margin -0.176, assuming no underlying difference and a common SD of 0.8, using a two group t-test with a 0.025 one-sided significance level.

The overall power to reject both hypotheses was 80%.

When taking a 15% dropout rate (including major protocol violations) into account, 770 subjects had to be enrolled in the study, with 385 subjects randomized to each group.

Comparable numbers of subjects per age group were enrolled. Calculations have been done with SAS 9.1 (proc power).

Statistical Analysis Considerations

Non-inferiority testing was done in a stepwise approach first for SRH and then for HI. It was assessed for the total (i.e. non-elderly and elderly) PPS and not separately for the age groups. No adjustment of alpha level was required, because of the stepwise approach of the non-inferiority testing, i.e. a priory ordering of hypotheses. For the non-inferiority testing log10-transformed antibodies were modeled using Analysis of Variance (ANOVA) with a factor for dose group, age group and center.

All other analyses were done separately for each age group.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Healthy males and females aged 18 years and above on the day of enrollment, who had given informed consent and who have not had influenza vaccine or documented suspected influenza disease within the past 6 months.

Those with immunosuppressive conditions, including chronic use of oral or systemic steroids, were not included. Female subjects of reproductive potential who had used birth control measures for at least 2 months before study participation were included.

Criteria for Evaluation:

Immunogenicity endpoints (Criteria for Assessing Immunogenicity Objectives)

The measures of immunogenicity versus A/H5N1 strains, collected for all evaluable subjects include:

Primary Immunogenicity Endpoints:

- Day 43 post vaccination ratio of GMTs for the 2 different vaccine groups (3.75µg / 7.5µg) including two-sided 95% confidence intervals as measured by HI and SRH in the adult and elderly population combined.

Secondary Immunogenicity Endpoints (separately for adults and elderly):

- Geometric mean titers/area (GMTs/GMAs) on each blood sampling days as determined by HI and SRH, and the applicable geometric mean ratios.
- Percentage of subjects achieving seroconversion[1] or significant increase[2] in antibody titer on each post-vaccination blood sampling days, as measured by HI and SRH.
- Percentage of subjects achieving an HI titer $\geq$ 40/ SRH area $\geq$ 25mm² on each blood sampling days.

In the interpretation of HI and SRH immunogenicity results, CHMP criteria (CPMP/BWP/214/96) were taken in consideration.

Immunogenicity, as determined by HI or SRH, was assessed according to age appropriate CHMP criteria (CPMP/BWP/214/96).

For adults between 18 and 60 years of age:

- Percentage of subjects achieving seroconversion[1] or significant increase[2] in HI antibody / SRH areas > 40%
- Mean geometric increase > 2.5

  Percentage of subjects achieving an HI antibody titer ≥ 40 or SRH area ≥ 25mm^2 should be > 70%.

For elderly adults over 60 years of age:

- Percentage of subjects achieving seroconversion or significant increase in HI antibody / SRH areas > 30%
- Mean geometric increase > 2.0
- Percentage of subjects achieving an HI antibody titer ≥ 40 or SRH area ≥ 25mm^2 should be > 60%.

Immunogenicity, as determined by HI, was also considered according to criteria stated in the CBER guidance for industry (Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines) of May 2007.

For adults 18 to 65 years of age:

- The lower limit of the two-sided 95% confidence interval (CI) for the percentage of subjects achieving seroconversion[3] for HI antibody meets or exceeds 40%
- The lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥ 40 meets or exceeds 70%.

For adults over 65 years of age:

- The lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion[3] for HI antibody meets or exceeds 30%
- The lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥ 40 meets or exceeds 60%.

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[1] Seroconversion was defined as negative pre-vaccination serum / post-vaccination titer ≥40 for HI (area ≥25 mm^2 for SRH).

[2] Significant increase in antibody titer was defined as at least a four-fold increase from non-negative pre vaccination serum (≥ 10) for HI or a 50% increase in area for SRH.

[3] Seroconversion according to CBER was defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer > 1:40 or a pre-vaccination HI titer > 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer.

However, the study was not powered to meet all CBER criteria in the single vaccination groups.

- Percentage of subjects with MN titers ≥ 40, ≥ 80, ≥ 160 on each blood sampling day
- Percentage of subjects achieving at least a four-fold rise in MN antibody titer on each blood sampling day.

Safety Endpoints (Criteria for Assessing Safety Objectives)

The measures of safety (safety endpoints) included descriptions of solicited and unsolicited reactions.

Solicited local reactions included ecchymosis, erythema, induration, swelling and pain at injection site; solicited systemic reactions included headache, arthralgia, chills, fatigue, malaise, myalgia, nausea, sweating and fever as measured by axillary temperature for day 1 through 7 and day 22 to 28 of the study.

All adverse events (AEs) were collected during days 1 to 43 (visit 3). All AEs necessitating a physician's visit or consultation and/or onset of new chronic disease and/or leading to premature study discontinuation and all serious adverse events (SAEs) were collected throughout the entire trial and data was reconciled at day 43 (visit 3).

Results:

Table 1: Overview of Subject Populations as Treated by CHMP Age Groups

	Number of Subjects (%)			
	18-60 YOA		≥ 61 YOA	
	H5N1_3.75	H5N1_7.5	H5N1_3.75	H5N1_7.5
	N=191	N=194	N=166	N=171
Population				
Enrolled	191 (100%)	194 (100%)	166 (100%)	171 (100%)
Per Protocol Set (SRH)	157 (82%)	153 (79%)	124 (75%)	121 (71%)
Per Protocol Set (HI)	155 (81%)	151 (78%)	124 (75%)	121 (71%)
Safety Set	180 (94%)	186 (96%)	159 (96%)	162 (95%)
Safety Set After 2nd Vaccination	176 (92%)	180 (93%)	143 (86%)	149 (87%)
Safety Set Post Injection	180 (94%)	184 (95%)	152 (92%)	155 (91%)
Safety Set Post-injection After 2nd Vaccination	176 (92%)	180 (93%)	138 (83%)	146 (85%)

CHMP = Committee for Medical Products for Human Use

YOA = Years of Age

SRH = Single Radial Hemolysis

HI = Haemagglutination Inhibition

Table 2: Overview of Subject Populations as Treated by CBER Age Groups

	Number of Subjects (%)			
	18-64 YOA		≥ 65 YOA	
	H5N1_3.75	H5N1_7.5	H5N1_3.75	H5N1_7.5
	N=247	N=247	N=110	N=118
Population				
Enrolled	247 (100%)	247 (100%)	110 (100%)	118 (100%)
Per Protocol Set (SRH)	195 (79%)	190 (77%)	86 (78%)	84 (71%)
Per Protocol Set (HI)	193 (78%)	188 (76%)	86 (78%)	84 (71%)
Safety Set	233 (94%)	234 (95%)	106 (96%)	114 (97%)
Safety Set After 2nd Vaccination	221 (89%)	225 (91%)	98 (89%)	104 (88%)
Safety Set Post Injection	231 (94%)	231 (94%)	101 (92%)	108 (92%)
Safety Set Post-injection After 2nd Vaccination	221 (89%)	225 (91%)	93 (85%)	101 (86%)

CBER = Center for Biological Evaluation and Research
YOA= Years of Age
SRH = Single Radial Hemolysis
HI = Hemagglutination Inhibition

Table 3: Summary of Study Termination, All Subjects

	Number of Subjects (%)	
	H5N1_3.75	H5N1_7.5
Total Number of Subjects Enrolled	357	365
Total Number of Subjects Completed	313 (88%)	325 (89%)
Premature Withdrawal *	44 (12%)	40 (11%)
Withdrawal of Consent	35 (10%)	31(8%)
Lost to Follow-up	9 (3%)	8 (2%)
Inappropriate enrollment	0	1 (< 1%)

* Primary reason for withdrawal

Table 4: Demographic and Other Baseline Characteristics by CHMP Age Groups – Enrolled Set (as Treated)

	18-60 YOA		≥ 61 YOA	
	H5N1_3.75	H5N1_7.5	H5N1_3.75	H5N1_7.5
	N=191	N=194	N=166	N=171
Age (Years)				
Mean ± Std. Dev.	35.1 ± 11.1	36.9 ± 11.3	68.2 ± 5.6	68.7 ±6.1
Sex				
Female	91 (48%)	83 (43%)	88 (53%)	85 (50%)
Male	100 (52%)	111 (57%)	78 (47%)	86 (50%)
Ethnic Origin				
Caucasian	191 (100%)	194 (100%)	166 (100%)	171 (100%)

YOA= Years of Age

Mean ± Std. Dev = Mean ± Standard Deviation

Table 5: Demographic and Other Baseline Characteritic by CBER Age Groups – Enrolled Set (as Treated)

	Number of Subjects (%)			
	18-64 YOA		≥ 65 YOA	
	H5N1_3.75	H5N1_7.5	H5N1_3.75	H5N1_7.5
	N=247	N=247	N=110	N=118
Age (Years)				
Mean ± Std. Dev.	41.3±15.0	42.4±14.5	71.2±4.4	71.5±5.2
Sex				
Female	121 (49%)	110 (45%)	58 (53%)	58 (49%)
Male	126 (51%)	137(55%)	52 (47%)	60 (51%)
Ethnic Origin				
Caucasian	247 (100%)	247 (100%)	110 (100%)	118 (100%)

YOA= Years of Age

Mean ± Std. Dev: Mean ± Standard Deviation

Table 6: Geometric Mean SRH Areas - GMR Calculated Relative to Day 1 and Vaccine Group Ratio – Per Protocol Set (PPS) - Subjects 18 Years and Older

	H5N1_3.75 N=281	H5N1_7.5 N=274	H5N1_3.75 : H5N1_7.5
GMT at Day 1	5.79 (5.25-6.39)	6.02 (5.47-6.63)	0.96 (0.87-1.06)
GMT at Day 22	9.4 (8.12-11)	9.5 (8.24-11)	0.99 (0.86-1.14)
GMR Day 22 to Day 1	1.62 (1.42-1.85)	1.58 (1.38-1.8)	1.03 (0.9-1.17)
GMT at Day 43	24 (21-27) N=280	26 (22-29)	0.94 (0.82-1.07)
GMR Day 43 to Day 1	4.13 (3.53-4.84) N=280	4.24 (3.63-4.95)	0.98 (0.84-1.14)

SRH = Single Radial Hemolysis;
GMT = Geometric mean Titer;
GMR = Geometric Mean Ratio

Table 7: Geometric Mean HI Titers – GMR calculated Relative to Day 1 and Vaccine Group Ratios – PPS –Subjects 18 Years and Older

	H5N1_3.75 N=279	H5N1_7.5 N=272	H5N1_3.75 : H5N1_7.5
Day 1	5.37 (4.93-5.86)	5.68 (5.21-6.18)	0.95 (0.87-1.03)
Day 22	10 (8.22-13)	10 (8.1-13)	1.02 (0.81-1.28)
Day 22 to Day 1	1.93 (1.56-2.38)	1.79 (1.45-2.2)	1.08 (0.88-1.32)
Day 43	42 (30-57)	46 (34-63)	0.9 (0.66-1.22)
Day 43 to Day 1	7.73 (5.66-11)	8.13 (5.99-11)	0.95 (0.7-1.29)

HI = Haemagglutination Inhibition;
GMR = Geometric Mean Ratio

Table 8: Geometric Mean SRH Areas - GMR Calculated Relative to Day 1 and Vaccine Group Ratios, by CHMP Age Groups - PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=124	H5N1_7.5 N=121
Day 1	5.35 (4.85-5.91)	5.32 (4.81-5.87)	6.17 (5.24-7.25)	6.84 (5.82-8.04)
Day 22	9.67 (8.23-11)	9.17 (7.8-11)	8.68 (6.93-11)	9.47 (7.57-12)
Day 22 to Day 1	1.81 (1.54-2.12)	1.72 (1.47-2.03)	1.41 (1.17-1.7)	1.38 (1.15-1.67)
Day 43	34 (30-39)	30 (26-35)	18 (14-22) N=123	24 (19-29)
Day 43 to Day 1	6.36 (5.35-7.55)	5.66 (4.76-6.72)	2.92 (2.28-3.74) N=123	3.47 (2.71-4.43)

YOA = Years of Age;
SRH = Single Radial Hemolysis;
GMR = Geometric Mean Ratio
CHMP = Committee for Medical Products for Human Use

Table 9: Geometric Mean HI Titers - GMR Calculated Relative to Day 1 and Vaccine Group Ratios, by CHMP Age Groups - PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=155	H5N1_7.5 N=151	H5N1_3.75 N=124	H5N1_7.5 N=121
Day 1	5.19 (4.85-5.56)	5.32 (4.96-5.7)	5.6 (4.77-6.58)	6.15 (5.24-7.22)
Day 22	10 (7.82-13)	8.69 (6.73-11)	9.13 (6.39-13)	10 (7.22-15)
Day 22 to Day 1	1.94 (1.53-2.48)	1.63 (1.28-2.08)	1.63 (1.19-2.23)	1.67 (1.22-2.29)
Day 43	64 (44-93)	55 (38-80)	33 (21-51)	47 (30-74)
Day 43 to Day 1	12 (8.46-18)	10 (7.15-15)	5.83 (3.78-9)	7.69 (4.99-12)

YOA = Years of Age;
HI = Hemagglutination Inhibition;
GMR = Geometric Mean Ratio
CHMP = Committee for Medical Products for Human Use

Table 10: Percentage of Subjects with Seroconversion or Significant Increase in SRH Areas, by CHMP Age Groups – PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=124	H5N1_7.5 N=121
Seroconversion Visit 2 (Day 22)	23 (26%) (17-36) N=90	18 (21%) (13-31) N=86	12 (17%) (9-28) N=70	8 (13%) (6-23) N=64
Significant Increase Visit 2 (Day 22)	13 (19%) (11-31) N=67	16 (24%) (14-36) N=67	8 (15%) (7-27) N=54	13 (23%) (13-36) N=57
Seroconversion or Significant Increase Visit 2 (Day 22)	36 (23%) (17-30)	34 (22%) (16-30)	20 (16%) (10-24)	21 (17%) (11-25)
Seroconversion Visit 3 (Day 43)	73 (81%) (71-89) N=90	62 (72%) (61-81) N=86	31 (44%) (32-57) N=70	41 (64%) (51-76) N=64
Significant Increase Visit 3 (Day 43)	50 (75%) (63-84) N=67	54 (81%) (69-89) N=67	32 (60%) (46-74) N=53	40 (70%) (57-82) N=57
Seroconversion or Significant Increase Visit 3 (Day 43)	123 (78%) (71-85)	116 (76%) (68-82)	63 (51%) (42-60) N=123	81 (67%) (58-75)

YOA = Years of Age;

SRH = Single Radial Hemolysis

CHMP = Committee for Medical Products for Human Use

Table 11: Number and Percentage of Subjects with Seroconversion or Significant Increase in HI Titers, by CHMP Age Groups – PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=155	H5N1_7.5 N=151	H5N1_3.75 N=124	H5N1_7.5 N=121
Seroconversion Visit 2 (Day 22)	32 (21%) (15-29) N=151	25 (17%) (11-24) N=146	19 (16%) (10-24) N=116	19 (18%) (11-26) N=108
Significant Increase Visit 2 (Day 22)	2 (50%) (7-93) N=4	2 (40%) (5-85) N=5	2 (25%) (3-65) N=8	4 (31%) (9-61) N=13
Seroconversion or Significant Increase Visit 2 (Day 22)	34 (22%) (16-29)	27 (18%) (12-25)	21 (17%) (11-25)	23 (19%) (12-27)
Seroconversion Visit 3 (Day 43)	96 (64%) (55-71) N=151	92 (63%) (55-71) N=146	62 (53%) (44-63) N=116	67 (62%) (52-71) N=108
Significant Increase Visit 3 (Day 43)	4 (100%) (40-100) N=4	3 (60%) (15-95) N=5	4 (50%) (16-84) N=8	7 (54%) (25-81) N=13
Seroconversion or Significant Increase Visit 3 (Day 43)	100 (65%) (56-72)	95 (63%) (55-71)	66 (53%) (44-62)	74 (61%) (52-70)

YOA = Years of Age;

HI = Haemagglutination Inhibition

CHMP = Committee for Medical Products for Human Use

Table 12: Percentage of Subjects with Seroconversion or Significant Increase in HI Titers, by CBER Age Groups – PPS

	Adults 18-64 YOA		Elderly ≥ 65 YOA	
	H5N1_3.75 N=193	H5N1_7.5 N=188	H5N1_3.75 N=86	H5N1_7.5 N=84
Seroconversion Visit 2 (Day 22)	32 (17%) (12-23) N=186	30 (17%) (12-23) N=178	19 (23%) (15-34) N=81	14 (18%) (10-29) N=76
Significant Increase Visit 2 (Day 22)	3 (43%) (10-82) N=7	3 (30%) (7-65) N=10	1 (20%) (1-72) N=5	3 (38%) (9-76) N=8
Seroconversion or Significant Increase Visit 2 (Day 22)	35 (18%) (13-24)	33 (18%) (12-24)	20 (23%) (15-34)	17 (20%) (12-30)
Seroconversion Visit 3 (Day 43)	114 (61%) (54-68) N=186	111 (62%) (55-69) N=178	44 (54%) (43-65) N=81	48 (63%) (51-74) N=76
Significant Increase Visit 3 (Day 43)	5 (71%) (29-96) N=7	7 (70%) (35-93) N=10	3 (60%) (15-95) N=5	3 (38%) (9-76) N=8
Seroconversion or Significant Increase Visit 3 (Day 43)	119 (62%) (54-69)	118 (63%) (55-70)	47 (55%) (44-65)	51 (61%) (49-71)

YOA = Years of Age;

HI = Haemagglutination Inhibition

CBER = Center for Biologics Evaluation and Research

Table 13: Percentage of Subjects with SRH Areas ≥ 25 mm^2, by CHMP Age Groups - PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=124	H5N1_7.5 N=121
Day 1	4 (3%) (1-6)	2 (1%) (0-5)	5 (4%) (1-9)	9 (7%) (3-14)
Day 22	38 (24%) (18-32)	34 (22%) (16-30)	26 (21%) (14-29)	30 (25%) (17-33)
Day 43	120 (76%) (69-83)	108 (71%) (63-78)	64 (52%) (43-61) N=123	84 (69%) (60-77)

YOA = Years of Age;
SRH = Single Radial Hemolysis
CHMP = Committee for Medical Products for Human Use

Table 14: Percentage of Subjects with HI Titers ≥ 1:40, by CHMP Age Groups - PPS

	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=155	H5N1_7.5 N=151	H5N1_3.75 N=124	H5N1_7.5 N=121
Day 1	2 (1%) (0-5)	3 (2%) (0-6)	4 (3%) (1-8)	7 (6%) (2-12)
Day 22	36 (23%) (17-31)	29 (19%) (13-26)	25 (20%) (13-28)	30 (25%) (17-33)
Day 43	100 (65%) (56-72)	96 (64%) (55-71)	69 (56%) (46-65)	78 (64%) (55-73)

YOA = Years of Age;
HI = Haemagglutination Inhibition
CHMP = Committee for Medical Products for Human Use

Table 15: Percentage of Subjects with HI Titers ≥ 1:40, by CBER Age Groups - PPS

	Adults 18-64 YOA		Elderly ≥ 65 YOA	
	H5N1_3.75 N=193	H5N1_7.5 N=188	H5N1_3.75 N=86	H5N1_7.5 N=84
Day 1	3 (2%) (0-4)	5 (3%) (1-6)	3 (3%) (1-10)	5 (6%) (2-13)
Day 22	38 (20%) (14-26)	38 (20%) (15-27)	23 (27%) (18-37)	21 (25%) (16-36)
Day 43	120 (62%) (55-69)	119 (63%) (56-70)	49 (57%) (46-68)	55 (65%) (54-76)

YOA = Years of Age;
HI = Haemagglutination Inhibition
CBER = Center for Biologics Evaluation and Research

Table 16: Geometric Mean MN Titers and Vaccine Group Ratios, by CHMP Age Groups - PPS

		A/H5N1/Indonesia/5/05			A/H5N1/Turkey/1/05			A/H5N1/Vietnam/1194/04		
		H5N1_3.75	H5N1_7.5	H5N1_3.75 : H5N1_7.5	H5N1_3.75	H5N1_7.5	H5N1_3.75 : H5N1_7.5	H5N1_3.75	H5N1_7.5	H5N1_3.75 : H5N1_7.5
		N=157	**N=153**		**N=157**	**N=153**		**N=157**	**N=153**	
Adults 18-60 YOA	Day 1	5.02 (4.89-5.17)	5.15 (5.01-5.3)	0.97 (0.94-1.01)	4.97 (4.82-5.13)	5.1 (4.94-5.26)	0.98 (0.94-1.01)	5 (4.84-5.17)	5.12 (4.95-5.29)	0.98 (0.94-1.01)
	Day 22							8.87 (7.6-10)	6.82 (5.84-7.95)	1.3 (1.1-1.15)
	Day 22 to day 1									
	Day 43	11 (8.81-13)	10 (8.58-13)	1.03 (0.82-1.28)	12 (10-15)	11 (8.86-13)	1.15 (0.93-1.42)	45 (36-56)	32 (25-39)	1.43 (1.12-1.83)
	Day 43 to day 1	2.14 (1.75-2.62)	2.03 (1.66-2.49)	1.05 (0.84-1.32)	2.48 (2.06-2.98)	2.11 (1.75-2.54)	1.18 (0.96-1.45)	9.04 (7.24-11)	6.17 (4.94-7.7)	1.46 (1.14-1.88)
		N=124	**N=121**		**N=124**	**N=121**		**N=124**	**N=121**	
Elderly ≥ 61 YOA	Day 1	5.1 (4.92-5.29)	5.05 (4.87-5.23)	1.01 (0.97-1.05)	4.98 (4.7-5.28)	5.18 (4.88-5.49)	0.96 (0.91-1.02)	5.09 (4.74-5.46)	5.34 (4.98-5.73)	0.95 (0.89-1.02)
	Day 22							7.41 (5.94-9.25)	7 (5.62-8.73)	1.06 (0.84-1.33)
	Day 22 to day 1							1.46 (1.19-1.78)	1.31 (1.07-1.6)	1.11 (0.9-1.37)
	Day 43	8.24 (6.77-10)	8.41 (6.92-10)	0.98 (0.8-1.2)	8.4 (6.79-10)	10 (8.33-13)	0.82 (0.65-1.02)	19 (15-26)	24 (18-31)	0.82 (0.61-1.09)
	Day 43 to day 1	1.61 (1.33-1.96)	1.67 (1.37-2.02)	0.97 (0.79-1.19)	1.69 (10.37-2.07)	1.99 (1.62-2.44)	0.85 (0.69-1.05)	3.8 (2.9-4.98)	4.42 (3.38-5.79)	0.86 (0.65-1.14)

YOA = Years of Age;
MN = Microneutralization
CHMP = Committee for Medical Products for Human Use

Table 17: Percentage of Subjects with MN Titers ≥ 1:40, by CHMP Age Groups - PPS

	Adults 18-60 YOA					
	A/H5N1/Indonesia/5/05		A/H5N1/Turkey/1/05		A/H5N1/Vietnam/1194/04	
	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=157	H5N1_7.5 N=153
Day 1	0 (0%) (0-2)	0 (0%) (0-2)	0 (0%) (0-2)	0 (0%) (0-2)	0 (0%) (0-2)	0 (1%) (0.017-4)
Day 22					11 (7%) (4-12)	4 (3%) (1-7)
Day 43	24 (15%) (10-22)	18 (12%) (7-18)	21 (13%) (8-20)	15 (10%) (6-16)	84 (54%) (45-61)	66 (43%) (35-51)
	Elderly ≥ 61 YOA					
	A/H5N1/Indonesia/5/05		A/H5N1/Turkey/1/05		A/H5N1/Vietnam/1194/04	
	H5N1_3.75 N=124	H5N1_7.5 N=121	H5N1_3.75 N=124	H5N1_7.5 N=121	H5N1_3.75 N=124	H5N1_7.5 N=121
Day 1	0 (0%) (0-3)	0 (0%) (0-3)	0 (0%) (0-3)	1 (1%) (0.021-5)	0 (0%) (0-3)	2 (2%) (0-6)
Day 22					10 (8%) (4-14)	10 (8%) (4-15)
Day 43	6 (5%) (2-10)	12 (10%) (5-17)	9 (7%) (3-13)	11 (9%) (5-16)	40 (32%) (24-41)	46 (38%) (29-47)

YOA = Years of Age;
MN = Microneutralization
CHMP = Committee for Medical Products for Human Use

Table 18: Percentage of Subjects with at Least 4-fold Increase From Baseline in MN Titers, by CHMP Age Groups - PPS

	Adults 18-60 YOA					
	A/H5N1/Indonesia/5/05		A/H5N1/Turkey/1/05		A/H5N1/Vietnam/1194/04	
	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=157	H5N1_7.5 N=153	H5N1_3.75 N=157	H5N1_7.5 N=153
4-Fold Increase Day 22 to Day 1					31 (20%) (14-27)	11 (7%) (4-12)
4-Fold Increase Day 43 to Day 1	43 (27%) (21-35)	43 (28%) (21-36)	53 (34%) (26-42)	43 (28%) (21-36)	123 (78%) (71-85)	100 (65%) (57-73)
4-Fold Increase Day 43 to Day 22					98 (62%) (54-70)	84 (55%) (47-63)
	Elderly ≥ 61 YOA					
	A/H5N1/Indonesia/5/05		A/H5N1/Turkey/1/05		A/H5N1/Vietnam/1194/04	
	H5N1_3.75 N=124	H5N1_7.5 N=121	H5N1_3.75 N=124	H5N1_7.5 N=121	H5N1_3.75 N=124	H5N1_7.5 N=121
4-Fold Increase Day 22 to Day 1					18 (15%) (9-22)	13 (11%) (6-18)
4-Fold Increase Day 43 to Day 1	19 (15%) (9-23)	22 (18%) (12-26)	23 (19%) (12-27)	29 (24%) (17-33)	65 (52%) (43-61)	70 (58%) (49-67)
4-Fold Increase Day 43 to Day 22					44 (35%) (27-45)	53 (44%) (35-53)

YOA = Years of Age;

MN = Microneutralization

CHMP = Committee for Medical Products for Human Use

Table 19: Summary of Subjects With at Least One Reactogenicity Sign by Vaccination, by CHMP Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

		Number (%) of Subjects With Solicited Reactions			
		Injection: 1		Injection: 2	
		H5N1_3.75 N=180	H5N1_7.5 N=184	H5N1_3.75 N=176	H5N1_7.5 N=180
Adults 18-60 YOA	Any	118(66)	120(65)	91(52)	90(50)
	Local	97(54)	105(57)	72(41)	75(42)
	Systemic	83(46)	64(35)	59(34)	50(28)
	Other	15(8)	14(8)	14(8)	13(7)
		N=152	**N=155**	**N=138**	**N=146**
Elderly ≥ 61 YOA	Any	65(43)	61(39)	55(40)	55(38)
	Local	46(30)	45(29)	38(28)	35(24)
	Systemic	44(29)	37(24)	41(30)	40(27)
	Other	7(5)	10(6)	10(7)	12(8)

YOA=Years of Age

CHMP = Committee for Medical Products for Human Use

Table 20: Summary of Subjects With at Least One Reactogenicity Sign by Vaccination, by CBER Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

		Number (%) of Subjects With Solicited Reactions			
		Injection: 1		Injection: 2	
		H5N1_3.75 N=231	H5N1_7.5 N=231	H5N1_3.75 N=221	H5N1_7.5 N=225
Adults 18-64 YOA	Any	146 (63)	129 (56)	113 (51)	110 (49)
	Local	116 (50)	112 (48)	88 (40)	87 (39)
	Systemic	102 (44)	72 (31)	73 (33)	67 (30)
	Other	18 (8)	16 (7)	16 (7)	18 (8)
		N=101	**N=108**	**N=93**	**N=101**
Elderly ≥ 65 YOA	Any	37 (37)	52 (48)	33 (35)	35 (35)
	Local	27 (27)	28 (35)	22 (24)	23 (23)
	Systemic	25 (25)	29 (27)	27 (29)	23 (23)
	Other	4 (4)	8 (7)	8 (9)	7 (7)

YOA=Years of Age
CBER = Center for Biologics Evaluation and Research

Table 21: Summary of Local Reactions by Vaccination, by CHMP Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

			Number (%) of Subjects With Injection Site Reactions			
			Injection: 1		Injection: 2	
			H5N1_3.75 N=180	H5N1_7.5 N=184	H5N1_3.75 N=176	H5N1_7.5 N=180
Adults 18-60 YOA	Ecchymosis (mm)	Any	1(1)	0	0	1(1)
		> 100 mm	0	0	0	0
	Ecchymosis PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Erythema (mm)	Any	4(2)	7(4)	6(3)	7(4)
		> 100 mm	0	0	0	0
	Erythema PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Induration (mm)	Any	7(4)	6(3)	5(3)	7(4)
		> 100 mm	0	0	0	0
	Induration PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Swelling (mm)	Any	2(1)	2(1)	5(3)	5(3)
		> 100 mm	0	0	0	0
	Swelling PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Pain	Any	96(53)	104(57)	70(40)	73(41)
		Severe	2(1)	4(2)	4(2)	3(2)
		Plt	0	0	0	0
			N=151	**N=155**	**N=138**	**N=146**
Elderly ≥ 61 YOA	Ecchymosis (mm)	Any	1(1)	0	2(1)	1(1)
		> 100 mm	0	0	0	0
	Ecchymosis PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Erythema (mm)	Any	3(2)	1(1)	2(1)	3(2)
		> 100 mm	0	0	0	0
	Erythema PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Induration (mm)	Any	6(4)	3(2)	3(2)	2(1)
		> 100 mm	0	0	0	0
	Induration PLT	Yes	0	0	0	0
		Nd	0	0	0	0

			Number (%) of Subjects With Injection Site Reactions			
	Swelling (mm)	Any	6(4)	0	3(2)	2(1)
		> 100 mm	0	0	0	0
	Swelling PLT	Yes	0	0	0	0
		Nd	0	0	0	0
	Pain	Any	46(30)	45(29)	36(26)	31(21)
		Severe	1(1)	1(1)	3(2)	0
		Plt	0	0	0	0

YOA=Years of Age

Note: The numbers (N) in the header is the total number of subjects with documented reactions.

PLT Potential Life Threatening

CHMP = Committee for Medical Products for Human Use

Table 22: Summary of Local Reactions by Vaccination, by CBER Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

			Number (%) of Subjects With Injection Site Reactions			
			Injection: 1		Injection: 2	
			H5N1_3.75 N=230	H5N1_7.5 N=231	H5N1_3.75 N=221	H5N1_7.5 N=225
Adults 18-64 YOA	Ecchymosis (mm)	Any	2 (1%)	0	1 (<1%)	1 (<1%)
		> 100 mm	0	0	0	0
	Erythema (mm)	Any	4 (2%)	7 (3%)	6 (3%)	8 (4%)
		> 100 mm	0	0	0	0
	Induration (mm)	Any	10 (4%)	6 (3%)	6 (3%)	7 (3%)
		> 100 mm	0	0	0	0
	Swelling (mm)	Any	5 (2%)	2 (1%)	6 (3%)	6 (3%)
		> 100 mm	0	0	0	0
	Pain	Any	115 (50%)	111 (48%)	86 (39%)	83 (37%)
		Severe	2 (1%)	4 (2%)	6 (3%)	3 (1%)
		Plt	0	0	0	0
			N=101	**N=108**	**N=93**	**N=101**
Elderly ≥ 65 YOA	Ecchymosis (mm)	Any	0	0	1 (1%)	1 (1%)
		> 100 mm	0	0	0	0
	Erythema (mm)	Any	3 (3%)	1 (1%)	2 (2%)	2 (2%)
		> 100 mm	0	0	0	0
	Induration (mm)	Any	3 (3%)	3 (3%)	2 (2%)	2 (2%)
		> 100 mm	0	0	0	0

			Number (%) of Subjects With Injection Site Reactions			
	Swelling (mm)	Any	3 (3%)	0	2 (2%)	1 (1%)
		> 100 mm	0	0	0	0
	Pain	Any	27 (27%)	38 (35%)	20 (22%)	21 (21%)
		Severe	1 (1%)	1 (1%)	1 (1%)	0
		Plt	0	0	0	0

YOA= Years of Age

Note: The numbers (N) in the header is the total number of subjects with documented reactions.

PLT Potential Life Threatening

CBER = Center for Biologics Evaluation and Research

Table 23: Summary of Systemic and Other Reactions by Vaccination, by CHMP Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

			Number (%) of Subjects With Injection Site Reactions			
			Injection: 1		Injection: 2	
			H5N1_3.75 N=180	H5N1_7.5 N=184	H5N1_3.75 N=176	H5N1_7.5 N=180
Adults 18-60 YOA	Headache	Any	40 (22%)	35 (19%)	29 (16%)	23 (13%)
		Severe	4 (2%)	3 (2%)	5 (3%)	5 (3%)
		Plt	0	0	0	0
	Arthralgia	Any	20 (11%)	11 (6%)	15 (9%)	15 (8%)
		Severe	2 (1%)	1 (1%)	3 (2%)	1 (1%)
		Plt	0	0	0	0
	Chills	Any	19 (11%)	12 (7%)	10 (6%)	9 (5%)
		Severe	1 (1%)	1 (1%)	1 (1%)	2 (1%)
		Plt	0	0	0	0
	Fatigue	Any	52 (29%)	28 (15%)	38 (22%)	36 (20%)
		Severe	3 (2%)	1 (1%)	3 (2%)	2 (1%)
		Plt	0	0	0	0
	Malaise	Any	34 (19%)	30 (16%)	31 (18%)	28 (16%)
		Severe	2 (1%)	2 (1%)	5 (3%)	4 (2%)
		Plt	0	0	0	0
	Myalgia	Any	36 (20%)	31 (17%)	35 (20%)	25 (14%)
		Severe	1 (1%)	1 (1%)	6 (3%)	1 (1%)
		Plt	0	0	0	0

			Number (%) of Subjects With Injection Site Reactions			
	Sweating	Any	21 (12%)	14 (8%)	17 (10%)	16 (9%)
		Severe	2 (1%)	3 (2%)	3 (2%)	1 (1%)
		Plt	0	0	0	0
	Nausea	Any	10 (6%)	10 (5%)	6 (3%)	11 (6%)
		Severe	0	0	1 (1%)	1 (1%)
		Plt	0	0	0	0
	Fever (≥ 38C)	Yes	2 (1%)	2 (1%)	2 (1%)	2 (1%)
	Other					
	Axillary Body Temperature	<38.0 C	178 (99%)	182 (99%)	174 (99%)	178 (99%)
		> 40.0 C	0	0	0	0
	Stayed home due to Reaction	Yes	1 (1%)	2 (1%)	4 (2%)	4 (2%)
	Analgesic Antipiretics Used	Yes	15 (8%)	12 (7%)	12 (7%)	11 (6%)
			N=151	**N=155**	**N=138**	**N=146**
Elderly ≥ 61 YOA	Headache	Any	20 (13%)	17 (11%)	20 (14%)	17 (12%)
		Severe	2 (1%)	1 (1%)	4 (3%)	1 (1%)
		Plt	0	0	0	0
	Arthralgia	Any	14 (9%)	9 (6%)	15 (11%)	5 (3%)
		Severe	2 (1%)	0	6 (4%)	0
		Plt	0	0	0	0
	Chills	Any	10 (7%)	5 (3%)	14 (10%)	5 (3%)
		Severe	2 (1%)	0	2 (1%)	2 (1%)
		Plt	0	0	0	0
	Fatigue	Any	23 (15%)	19 (12%)	24 (17%)	22 (15%)
		Severe	3 (2%)	1 (1%)	3 (2%)	1 (1%)
		Plt	0	0	0	0
	Malaise	Any	22 (14%)	18 (12%)	27 (20%)	17 (12%)
		Severe	3 (2%)	0	3 (2%)	1 (1%)
		Plt	0	0	0	0
	Myalgia	Any	18 (12%)	20 (13%)	24 (18%)	9 (6%)
		Severe	2 (1%)	0	7 (5%)	0
		Plt	0	0	0	0
	Sweating	Any	11 (7%)	4 (3%)	12 (9%)	7 (5%)
		Severe	2 (1%)	1 (1%)	1 (1%)	1 (1%)
		Plt	0	0	0	0
	Nausea	Any	6 (4%)	2 (1%)	5 (4%)	5 (3%)
		Severe	0	0	0	0
		Plt	0	0	0	0

		Number (%) of Subjects With Injection Site Reactions			
Fever (≥ 38°C)	Yes	3 (2%)	1 (1%)	2 (1%)	1 (1%)
Other					
Axillary Body Temperature	<38.0 C	149 (98%)	154 (99%)	136 (99%)	145 (99%)
	> 40.0 C	0	0	0	0
Stayed Home due to Reaction	Yes	5 (3%)	3 (2%)	6 (4%)	4 (3%)
Analgesic Antipyretic Used	Yes	5 (3%)	7 (5%)	7 (5%)	9 (6%)

YOA=Years of Age

Note: The numbers (N) in the header is the total number of subjects with documented reactions

PLT Potential Life Threatening

CHMP = Committee for Medical Products for Human Use

Table 24: Summary of Systemic and Other Reactions by Vaccination, by CBER Age Groups – (Day 1 to 7, Day 22 to 28) - Safety Set

			Number (%) of Subjects With Injection Site Reactions			
			Injection: 1		Injection: 2	
			H5N1_3.75 N=230	H5N1_7.5 N=231	H5N1_3.75 N=221	H5N1_7.5 N=225
Adults 18-60 YOA	Headache	Any	50 (22%)	40 (17%)	37 (17%)	30 (13%)
		Severe	5 (2%)	3 (1%)	7 (3%)	5 (2%)
		Plt	0	0	0	0
	Arthralgia	Any	25 (11%)	12 (5%)	18 (8%)	17 (8%)
		Severe	3 (1%)	1 (<1%)	5 (2%)	1 (<1%)
		Plt	0	0	0	0
	Chills	Any	22 (10%)	14 (6%)	13 (6%)	11 (5%)
		Severe	2 (1%)	1 (<1%)	2 (1%)	2 (1%)
		Plt	0	0	0	0
	Fatigue	Any	60 (26%)	33 (14%)	46 (21%)	45 (20%)
		Severe	4 (2%)	1 (<1%)	4 (2%)	3 (1%)
		Plt	0	0	0	0
	Malaise	Any	45 (19%)	35 (15%)	39 (18%)	35 (16%)
		Severe	3 (1%)	2 (1%)	6 (3%)	4 (2%)
		Plt	0	0	0	0
	Myalgia	Any	46 (20%)	35 (15%)	44 (20%)	29 (13%)
		Severe	2 (1%)	0	9 (4%)	1 (<1%)
		Plt	0	0	0	0
	Sweating	Any	26 (11%)	15 (6%)	22 (10%)	17 (8%)
		Severe	3 (1%)	0	3 (1%)	1 (<1%)
		Plt	0	0	0	0
	Nausea	Any	13 (6%)	10 (4%)	9 (4%)	13 (6%)
		Severe	0	0	1 (<1%)	1 (<1%)
		Plt		0	0	0
	Fever (≥ 38°C)	Yes	4 (2%)	2 (1%)	4 (2%)	2 (1%)
	Other					
	Axillary Body Temperature	<38.0 C	227 (98%)	229 (99%)	217 (98%)	223 (99%)
		> 40.0 C	0	0	0	0
	Stayed Home due to Reaction	Yes	4 (2%)	3 (1%)	5 (2%)	6 (3%)
	Analgesic Antipiretics Used	Yes	17 (7%)	13 (6%)	14 (6%)	14 (6%)
			N=101	**N=108**	**N=93**	**N=101**

			Number (%) of Subjects With Injection Site Reactions			
Elderly ≥ 61 YOA	Headache	Any	10 (10%)	12 (11%)	12 (13%)	10 (10%)
		Severe	1 (1%)	1 (1%)	2 (2%)	1 (1%)
		Plt	0	0	0	0
	Arthralgia	Any	9 (9%)	8 (7%)	12 (13%)	3 (3%)
		Severe	1 (1%)	0	4 (4%)	0
		Plt	0	0	0	0
	Chills	Any	7 (7%)	3 (3%)	11 (12%)	3 (3%)
		Severe	1 (1%)	0	1 (1%)	2 (2%)
		Plt	0	0	0	0
	Fatigue	Any	15 (15%)	14 (13%)	16 (17%)	13 (13%)
		Severe	2 (2%)	1 (1%)	2 (2%)	0
		Plt	0	0	0	0
	Malaise	Any	11 (11%)	13 (13%)	19 (20%)	10 (10%)
		Severe	2 (2%)	0	2 (2%)	1 (1%)
		Plt	0	0	0	0
	Myalgia	Any	8 (8%)	16 (15%)	15 (16%)	5 (5%)
		Severe	1 (1%)	0	4 (4%)	0
		Plt	0	0	0	0
	Sweating	Any	6 (6%)	3 (3%)	7 (8%)	6 (6%)
		Severe	1 (1%)	1 (1%)	1 (1%)	1 (1%)
		Plt	0	0	0	0
	Nausea	Any	3 (3%)	2 (2%)	2 (2%)	3 (3%)
		Severe	0	0	0	0
		Plt	0	0	0	0
	Fever (≥ 38°C)	Yes	1 (1%)	1 (1%)	0	1 (1%)
	Other					
	Axillary Body Temperature	<38.0 C	100 (99%)	107 (99%)	93 (100%)	100 (99%)
		> 40.0 C	0	0	0	0
	Stayed Home due to Reaction	Yes	2 (2%)	2 (2%)	5 (5%)	2 (2%)
	Analgesic Antipiretics Used	Yes	3 (3%)	6 (6%)	5 (5%)	6 (6%)

YOA=Years of Age

Note: The numbers (N) in the header is the total number of subjects with documented reactions.

PLT Potential Life Threatening

CBER = Center for Biologics Evaluation and Research

Table 25: Overview of Subjects With Unsolicited AEs, by Vaccination, by CHMP Age Groups – (Day 1 to 43) - Safety Set

		Number (%) of Subjects With Adverse Events			
		Injection: 1		Injection: 2	
		H5N1_3.75 N=180	H5N1_7.5 N=186	H5N1_3.75 N=176	H5N1_7.5 N=180
Adults 18-60 YOA	Any AE	25 (14)	18 (10)	15 (9)	17 (9)
	At least possibly related AE	6 (3)	5 (3)	5 (3)	7 (4)
	Any AE leading to discontinuation	0	0	0	0
	Any SAE	0	0	0	1
		N=159	**N=162**	**N=143**	**N=149**
Elderly ≥ 61 YOA	Any AE	19 (12)	24 (15)	18 (13)	14 (9)
	At least possibly related AE	10 (6)	5 (3)	6 (4)	7 (5)
	Any AE leading to discontinuation	0	0	0	0
	Any SAE	1	1	0	0

YOA= Years of Age

AEs = Adverse Events

SAEs = Serious Adverse Events

CHMP = Committee for Medical Products for Human Use

Table 26: Overview of Subjects With Unsolicited AEs, by Vaccination, by CBER Age Groups – (Day 1 to 43) - Safety Set

		Number (%) of Subjects With Adverse Events			
		Injection: 1		Injection: 2	
		H5N1_3.75 N=233	H5N1_7.5 N=234	H5N1_3.75 N=221	H5N1_7.5 N=225
Adults 18-64 YOA	Any AE	34 (15%)	25 (11%)	20 (9%)	21 (9%)
	At least possibly related AE	9 (4%)	6 (3%)	7 (3%)	9 (4%)
	Any AE leading to discontinuation	0	0	0	0
	Any SAE	0	0	0	1 (< 1%)
		N=106	**N=114**	**N=98**	**N=104**
Elderly ≥ 65 YOA	Any AE	10 (9%)	17 (15%)	13 (13%)	10 (10%)
	At least possibly related AE	7 (7%)	4 (4%)	4 (4%)	5 (5%)
	Any AE leading to discontinuation	0	0	0	0
	Any SAE	1 (1%)	1 (1%)	0	0

YOA= Years of Age

AEs = Adverse Events

SAEs = Serious Adverse Events

CBER = Center for Biologics Evaluation and Research

Table 27: Serious Adverse Events After Any Vaccination, by CHMP Age Groups, by Preferred Term Sorted by System Organ Class - – (Day 1 to 43) – Safety Set

	Number (%) of Subjects			
	Adults 18-60 YOA		Elderly ≥ 61 YOA	
	H5N1_3.75 N=180	H5N1_7.5 N=186	H5N1_3.75 N=159	H5N1_7.5 N=162
Nervous System Disorder				
Dystonia	0	1(1%)	0	0
Sciatica	0	0	1(1%)	0
Musculoskeletal., Connective tissue & Bone Disorder				
Intervertebral disc disorder	0	0	1(1%)	0
Gastrointestinal disorder				
Gastrointestinal haemorrhage	0	0	0	1(1%)

YOA= Years of Age

CHMP = Committee for Medical Products for Human Use

Table 28: Serious Adverse Events After Any Vaccination, by CBER Age Groups, by Preferred Term Sorted by System Organ Class - – (Day 1 to 43) – Safety Set

	Number (%) of Subjects			
	Adults 18-64 YOA		Elderly ≥ 65 YOA	
	H5N1_3.75 N=233	H5N1_7.5 N=234	H5N1_3.75 N=106	H5N1_7.5 N=114
Nervous System Disorder				
Dystonia	0	1 (<1%)	0	0
Sciatica	0	0	1 (1%)	0
Musculoskeletal., Connective tissue & Bone Disorder				
Intervertebral disc disorder	0	0	1 (1%)	0
Gastrointestinal disorder				
Gastrointestinal haemorrhage	0	0	0	1 (1%)

YOA= Years of Age

Table 29: Unsolicited AEs Reported by ≥ 5% of Subjects, by CHMP Age Groups, by Preferred Term Sorted by System Organ Class – (Day1 to 43) - Safety Set

None reported.

Table 30: Unsolicited AEs Reported by ≥ 5% of Subjects, by CBER Age Groups, by Preferred Term Sorted by System Organ Class - (Day1 to 43) - Safety Set

None reported.

Conclusion:

The 3.75 μg dose level was found to be non-inferior to the 7.5 μg dose level in terms of the primary endpoint in this study, and in terms of the criteria set forth by the Committee for Medical Products for Human Use (CHMP) and Center for Biological Evaluation and Research (CBER) regulatory documents for vaccine immunological responses. The adult population (18-60 years of age) tended to develop better immune responses with the 3.75 μg dose, and the elderly population (≥ 61 years of age) tended to develop better immune responses with the 7.5 μg doses. Both age groups and dose levels developed cross-reactive antibodies to 2 heterologous H5N1 strains.

The vaccines were well tolerated by subjects, with injection site pain the most commonly reported reaction. The percentage of solicited reactions occurring within 7 days of each vaccination was similar between dose levels, with slightly fewer subjects reporting events after the 2nd vaccination. Unsolicited adverse events (AEs) were few and balanced between groups.

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