Sponsor: Novartis Vaccines and Diagnostics

Investigational Product: Adjuvanted monovalent H1N1 influenza virus vaccine (aH1N1c)

Indication: Prophylaxis of A(H1N1) 2009 Pandemic Influenza

Protocol Number: V110_03

Protocol Title: A Randomized, Single-blind, Dose-Ranging Study to Evaluate Immunogenicity, Safety and Tolerability of Different Formulations of Adjuvanted and Non-Adjuvanted Cell-Derived, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine in Healthy Subjects 18 or More Years of Age

Phase of Development: Phase III

Study Period:

Date of first enrolment: 08 AUG 09

Date of last visit: 11 MAR 11

Methodology:

This was a randomized, single-blind, dose-ranging study. A total of 600 healthy subjects; 360 adults (18-60 years of age) and 240 elderly (≥ 61 years of age) were to be enrolled in this study.

Adults 18-60 were randomized in a 1:1:1 ratio to receive:

- H1N1sw 3.75 µg + half MF59 (Group A)
- H1N1sw 7.5 µg + full MF59 (Group B)
- H1N1sw 15 µg + without MF59 (Group C)

Adults over 60 were randomized in a 1:1 ratio to receive:

- H1N1sw 3.75 µg + half MF59 (Group A)
- H1N1sw 7.5 µg + full MF59 (Group B)

Two doses of vaccine were administered intramuscularly (IM), 3 weeks apart. After approximately 12 months following administration of the first vaccine, subjects received a third (booster) vaccine. The booster was administered using Adjuvanted Trivalent Inactivated Influenza Virus Vaccine (aTIV) vaccine. All vaccinated subjects were analyzed for safety and immunogenicity. Subjects were followed for approximately 6 months after the booster dose for safety assessments. Local and systemic reactions were collected for the first week following each vaccination along with prescription and non-prescription medications administered. All Adverse Events (AEs) and medications associated with AEs were collected for the first 3 weeks after

each vaccination (ie, day 1 to day 43 and day 366 to day 387). Serious adverse events, onset of chronic disease, and AEs that led to withdrawal from the study were collected for the entire study period (day 1 to day 546).

Number of Subjects (planned and analyzed):

The planned and actual enrollment numbers are shown in Table 1 below. Due to fast enrollment at the sites, the actual enrollment, especially in the 18 to 60 years age stratum, exceeded that planned.

Table 1: Planned and Actual Numbers of Subjects Enrolled

	18 to 60 years		Over 60 years	
	Planned	Actual	Planned	Actual
3.75_halfMF59	120	183	120	135
7.5_fullMF59	120	179	120	133
15_noMF59	120	182	-	-

Study Centers:

Seven sites in Germany, three sites in Belgium, and one site in Switzerland.

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

NCT Number: NCT00970177
PMID: 22626675

Objectives:

Primary Objective:

To identify the preferred vaccine formulation (with and without MF59), dosage (of antigen and adjuvant) and schedule (one or two administrations) of the aH1N1c vaccine in healthy adults based on CHMP criteria and pairwise statistical comparisons for immunogenicity, and safety & tolerability.

Secondary Objectives:

- To evaluate immunogenicity against the A/California H1N1sw strain after a booster dose of aTIV vaccine, recommended for the 2010/2011 season, administered 12 months after the primary course with respect to CHMP criteria.
- To evaluate the non-inferiority of the post-vaccination (day 43) hemagglutination inhibition (HI) geometric mean titer (GMT) of the half dose (3.75 µg of HA + half MF59) of aH1N1c vaccine to the corresponding GMTs of the full dose (7.5 µg of HA + full MF59) of aH1N1c vaccine, after two doses administered 3 weeks apart in the pooled adult and elderly population.

Safety Objectives:

To evaluate the safety and tolerability of aH1N1c vaccine for 3 weeks after first and second vaccination.

To evaluate the safety and tolerability of aH1N1c vaccine up to 12 months after the first vaccine.

To evaluate safety (up to 6 months) and tolerability of aTIV vaccine (containing the H1N1sw strain) adjuvanted as booster 12 months after the first dose of aH1N1c vaccine.

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

All three study vaccines were Madin-Darby Canine Kidney (MDCK) cell culture-derived, novel swine origin A/H1N1 (A/California/7/2009) monovalent inactivated subunit influenza virus vaccines. Full (100%) MF59 refers to the adjuvant content of the European licensed seasonal influenza vaccine, aTIV.

Booster was administered using aTIV, as the H1N1 (A/California/7/2009) strain has been included among those recommended for 2010 / 2011 influenza season.

Table 2: Formulation of Vaccines

Group	Vaccine formulation			Volume for Injecti	Lot No	Expiry Date
	Antigen content	MF59 content				
3.75_halfMF5	3.75 µg	4.875 µg	50% (half)	0.25	RE002011	30 SEP
7.5_fullMF59	7.5 µg	9.75 µg	100% (full)	0.5	RE002011	30 SEP
15_noMF59	15	-	0 (no)	0.5	RE001011	29 SEP
aTIV	45	9.75 µg	100% (full)	0.5	104601	May 11

Duration of Study:

Expected duration of the subject's participation was approximately 18 months from study entry to last visit.

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

As all three vaccines as well as the booster contained the novel swine origin A/H1N1 antigen they were all classified as test vaccines.

Statistical Methods:

The per-protocol analysis set (PPS) was used for the immunogenicity endpoints.

There was no statistical null hypothesis associated with the primary immunogenicity objective. For the purpose of analysis, the immunogenicity parameters were grouped into two types:

- Percentages computed from dichotomous variables (ie, seroprotection and seroconversion) and;
- Geometric mean titers (GMTs) and Geometric mean ratios (GMRs).

In the pairwise comparisons, the difference between the two vaccine groups was considered statistically significant in the following cases;

- For the percentages, if the 95% confidence interval (CI) around the differences between the percentages observed in the two vaccine groups did not include 0;
- For GMTs and GMRs, if the 95% CI of the GMT (and/or GMR) ratio between the two vaccine groups did not include 1.

Immunogenicity Variables

HI and Microneutralization (MN) antibody titers were logarithmically transformed for purposes of analyses. It was assumed that the log-transformed values were normally distributed and that the sample sizes in vaccine groups were similar. Immunogenicity results following the booster vaccination were defined as 3 weeks after the booster dose. Missing values were left out of the analyses. For all HI analyses, values below the limit of detection (ie, 10) were reported as < 10.

The response variables as determined by HI were as follows:

1. GMT on day 1, day 22 and day 43 for the primary course, and on day 366 and day 387 for the booster;
2. Day 22/day 1, day 43/day 1, day 43/day 22, day 366/day 1, day 387/day 366 and day 387/day 1, GMR of HI;
3. Percentage of subjects achieving a seroconversion or a significant increase on day 22, day 43, day 366 and day 387 and the percentage of subjects achieving seroconversion or a significant increase on day 387 referring to pre-booster values;
4. Percentage of subjects with an HI titer ≥ 40, on day 1, day 22, day 43, day 366 and day 387.

The response variables as determined by MN were as follows:

1. Geometric mean MN titer (GMT) on day 1, day 22 and day 43 for the primary course, and on day 366 and day 387 for the booster;
2. Day 22/day 1, day 43/day 1, day 43/day 22, day 366/day 1, day 387/day 366 and day 387/day 1, geometric mean ratio (GMR) of MN;
3. Percentage of subjects with an MN titer ≥ 40, 80 and 160 on day 1, day 22, day 43, day 366 and day 387;
4. Percentage of subjects achieving at least a 4-fold increase in MN titer on day 22, day 43, day 366 and day 387, and the percentage of subjects achieving a 4-fold increase on day 387 referring to pre-booster values.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

1. Males and females 18 years of age and above on the day of enrollment;
2. Individuals in good health as determined by the outcome of medical history, physical assessment and clinical judgment of the investigator;

3. Individuals were able to comply with all study procedures and were available for all clinic visits scheduled in the study;
4. Willingness to allow for serum samples to be stored beyond the study period, for potential additional future testing to better characterize immune response.

Exclusion Criteria

1. Individuals who were unable to comprehend and to follow all required study procedures for the whole period of the study;
2. Individuals with history or any illness that, in the opinion of the investigator, might have interfered with the results of the study or posed additional risk to the subjects due to participation in the study;
3. Individuals with any serious chronic or progressive disease according to judgment of the investigator (including, but not limited to neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease);
4. History of any anaphylaxis, serious vaccine reactions, or hypersensitivity to influenza viral proteins, to any excipients, and to eggs (including ovalbumin), and chicken proteins;
5. Individuals who had received adjuvanted influenza vaccine or had documented confirmed or suspected[1] influenza disease within 3 months prior to day 1;
6. Receipt of another investigational agent within 4 weeks prior to enrollment, or before completion of the safety follow-up period in this or in another study; unwilling to refuse participation in another clinical study through the end of this study;
7. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who were planning to receive any vaccine within 4 weeks from the study vaccines; the only exception being plain seasonal influenza vaccines which were allowed until 1 week prior to and after 1 week for the first two study vaccinations. Individuals who had received any influenza vaccine for the 2010 / 2011 season or for the 2010 Southern Hemisphere season less than 8 months before the booster dose. Individuals who had received the monovalent H1N1 pandemic vaccine outside this protocol less that 8 months before the booster dose;
8. Individuals who had received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks;
9. Individuals with axillary temperature ≥ 38 degrees Celsius (≥ 100.4° F) or oral temperature ≥ 38.5° Celsius (≥ 101.3° F) within 3 days of intended study vaccination;

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[1] "Laboratory-confirmed" includes:

a. Positive serology result
b. Positive viral culture
c. Positive rapid antigen test

"Suspected" influenza disease includes: subjects with influenza-like illness within the past 3 months with a household/intimate contact with "laboratory-confirmed" influenza disease

10. Known or suspected impairment/alteration of immune function, for example resulting from:
    a. receipt of immunosuppressive therapy such as systemic corticosteroids known to be associated with the suppression of hypothalamic-pituitary-adrenal (HPA) axis (10 mg/day of prednisone or its equivalent) or chronic use of inhaled high-potency corticosteroids (e.g. budesonide 800µg/day or fluticasone 750µg/day) within 60 days prior to Visit 1,
    b. cancer chemotherapy,
    c. receipt of immunostimulants within 60 days prior to Visit 1,
    d. receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Visit 1 or planned during the full length of the study,
    e. known HIV infection or HIV-related disease;
11. History of progressive or severe neurological disorders (including Guillain-Barré syndrome and convulsions, but excluding febrile convulsions);
12. History of or clinically suspected developmental delay;
13. Bleeding diathesis;
14. Surgery planned during the study period that in the Investigator's opinion would have interfered with the study visits schedule;
15. If female, of childbearing potential, had not used any of the "acceptable contraceptive methods" for at least 2 months prior to study entry
    a. Female of childbearing potential is defined as a post onset of menarche or pre-menopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: (1) menopause at least 2 years earlier, (2) tubal ligation at least 1 year earlier, or (3) total hysterectomy.
    b. Acceptable birth control methods were defined as one or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring)
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse
        iii. Intrauterine device (IUD)
        iv. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least six months prior to the subject's study entry;
16. Females who were pregnant or nursing (breastfeeding) mothers, or females of childbearing potential who were sexually active and had not used or did not plan to use acceptable birth control measures during the first 3 weeks after vaccination;
17. Members of the research staff or their relatives (research staff are individuals with direct contact with trial subjects, or study site personnel who had access to any study documents containing subject information, including: e.g. receptionists, persons

scheduling appointments or making screening calls, regulatory specialists, laboratory technicians). Hospital personnel, health care professionals and their relatives that were not involved in this clinical study were allowed for inclusion.

Criteria for Evaluation:

Primary Immunogenicity Endpoints:

The primary response endpoints based on HI were as follows:

1. The percentage of subjects with seroconversion or a significant increase at day 22 and day 43;
2. The percentage of subjects achieving seroprotection (ie, HI titer ≥ 40) at day 22 and day 43;
3. The GMT and GMR at day 22 and day 43.

These 3 criteria were evaluated based on Committee for Medicinal Products for Human Use (CHMP) criteria for adults and the elderly.

Separated by age group, pairwise between-group comparisons were made for day 22 and day 43 for the following:

- Ratio of GMTs
- Proportion of subjects achieving an HI titer ≥ 40
- Proportion of subjects with seroconversion or significant increase in HI antibody titers.

Separated by age group, pairwise within-group comparisons (one versus two doses) were made for day 22 and day 43 for the following:

- GMT ratio: day 22 to day 43
- Proportion of subjects achieving an HI titer ≥ 40: day 22 to day 43
- Proportion of subjects with seroconversion or significant increase in HI antibody titers: day 22 to day 43.

For each comparison, a 2-sided 95%CI was provided.

Safety Endpoints

The safety measurements presented in the Clinical Study Report are given in the table below.

Table 3: Safety Measurements

Vaccination	Variables	Duration post vaccination	Study days
First Vaccination	Solicited local and systemic reactions[a]	1 wk	1 – 7
	All unsolicited AEs (incl. SAEs, new onset of chronic disease, AEs that led to withdrawal of the subject and prescription medication)	3 wks	1 – 22
Second vaccination	Solicited local and systemic reactions[a]	1 wk	22 – 28
	All unsolicited AEs (as above)	3 wks	22 – 43
	Only SAEs, onset of chronic disease, AEs that led to withdrawal of the subjects and prescription medication	6 wks to 12 months after first vaccination	43-366
Booster	Solicited local and systemic reactions[a]	1 wk	366-372
	All unsolicited AEs (as above)	3 wks	366-387
	Only SAEs, onset of chronic disease, AEs that led to withdrawal of the subjects and prescription medication	3 wks to 6 months post-booster	387-546

[a] Local (ecchymosis, erythema, induration, swelling, pain at injection site) and systemic reactions: (headache, arthralgia, chills, fatigue, malaise, myalgia, nausea, sweating, and fever) were summarized according to the Brighton collaboration case definition (Bonhoeffer J *et al*, Vaccine 2009; 27: 2282-2288).

Table 4: Time and Events

Clinic Visit? (Yes/No)[a]	**Visit 1 Yes**	**Visit 2 No**	**Visit 3 Yes**	**Visit 4 No**	**Visit 5 Yes**	**Visit 6 No**	**Visit 7 Yes**	**Visit 8 No**	**Visit 9 Yes**	**Visit 10 No**
Study Day	**1**	**8**	**22**	**29**	**43**	**202**	**366**	**373**	**387**	**546**
Study Visit Window[b]	-	7 to 10 days after first vaccination	18 to 28 days after first vaccination	7 to 10 days after second vaccination	18 to 28 days after second vaccination	165 to 195 days after second vaccination	350 to 380 days after first vaccination	7 to 10 days after booster vaccination	18 to 28 days after booster vaccination	165 to 195 days after booster vaccination
ICF	x									
Exclusion/Inclusion[c]	x						x			
Medical history	x						x			
Physical assessment[c; d]	x		x		x		x		x	
Urine pregnancy test[e]	x		x		x		x		x	
Serology Blood draw (approx. 20mL)[c]	x		x		x		x		x	
Investigational vaccine administered	x		x				x			
Diary Card Dispensed	x		x		x[g]		x		x[g]	
Diary Card Collected and/or Reviewed [f]		x	x	x	x	x	x	x	x	x
Assess Local/ Systemic Reactions	x	x	x	x			x	x		
Assess AEs and SAEs [f]	x	x	x	x	x	x[h]	x	x	x	x[h]
Concomitant medications[j]	x	x	x	x	x	x	x	x	x	x
Study Termination										x

a. Clinic visit "no" refers to telephone contact only with subject
b. All per-protocol study visit time points and related visit windows were re-adjusted based on the actual date of the last preceding vaccination
c. Performed prior to vaccination
d. Physical assessment was performed by a physician or qualified health professional according to local regulations, designated within the Site Responsibility Delegation Log. History driven physical assessment was performed on day 1 and on day 366. Brief history driven physical assessment was performed at each clinic visit
e. Urine pregnancy test was performed for females of childbearing potential at Visits 1, 3, 5, 7 and 9
f. Data on 7-day data post-vaccination was discussed at Visit 2, at day 8 at Visit 4, at day 29, and at Visit 8 on day 373. Adverse events from day 8 to day 21 were reviewed at Visit 3 on day 22. Adverse events from day 29 to day 42 were reviewed at Visit 5 on day 43. Adverse events from day 373 to day 386 were reviewed at Visit 9 on day 387.
g. Memory aids were dispensed. Memory aids dispensed at Visit 5 were returned to sites at Visit 7. Memory aids dispensed at Visit 9 were not returned to sites.
h. Only SAEs, AEs leading to withdrawal from study and onset of chronic diseases
i. Collect concomitant medications/vaccines according to "Other Concomitant Treatment or Vaccines".

Results:

Table 5: Overview of Analysis Sets, Day 43, Day 366 and Day 387 - Enrolled Population

		3.75ug_halfMF59	7.5ug_fullMF59	15ug_noMF59	Total
		N=183	N=179	N=182	N=544
Adults 18-60 Yrs	Population Total:				
	Enrolled	183 (100%)	179 (100%)	182 (100%)	544 (100%)
	1st Vaccination	183 (100%)	178 (99%)	180 (99%)	541 (99%)
	2nd Vaccination	178 (97%)	176 (98%)	178 (98%)	532 (98%)
	3rd Vaccination (1st aTIV)	162 (89%)	151 (84%)	154 (85%)	467 (86%)
	Full Analysis Set (HI) Day 43	180 (98%)	177 (99%)	179 (98%)	536 (99%)
	Full Analysis Set (HI) Day 366	164 (90%)	157(88%)	157 (86%)	478 (88%)
	Full Analysis Set (HI) Day 387	160 (87%)	151 (84%)	150 (82%)	461 (85%)
	Per Protocol Set (HI) Day 43	173 (95%)	170 (95%)	167 (92%)	510 (94%)
	Per Protocol Set (HI) Day 366	154 (84%)	145 (81%)	140 (77%)	439 (81%)
	Per Protocol Set (HI) Day 387	143 (78%)	135 (75%)	128 (70%)	406 (75%)
		N=135	N=133	NA	N=268
Adults Over 60 Yrs	Population Total:				
	Enrolled	135 (100%)	133 (100%)		268 (100%)
	1st Vaccination	135 (100%)	132 (99%)		267 (100%)
	2nd Vaccination	135 (100%)	130 (98%)		265 (99%)
	3rd Vaccination (1st aTIV)	123 (91%)	118 (89%)		241 (90%)
	Full Analysis Set (HI) Day 43	135 (100%)	132 (99%)		267 (100%)
	Full Analysis Set (HI) Day 366	125 (93%)	120 (90%)		245 (91%)
	Full Analysis Set (HI) Day 387	121 (90%)	118 (89%)		239 (89%)
	Per Protocol Set (HI) Day 43	129 (96%)	126 (95%)		255 (95%)
	Per Protocol Set (HI) Day 366	116 (86%)	114 (86%)		230 (86%)
	Per Protocol Set (HI) Day 387	108 (80%)	106 (80%)		214 (80%)

Table 6: Summary of Study Terminations - Enrolled Population

	18 to 60 years			Over 60 years	
Vaccine administered	3.75_halfMF59	7.5_fullMF59	15_noMF59	3.75_halfMF59	7.5_fullMF59
Enrolled	183	179	182	135	133
Completed protocol	160 (87%)	152 (85%)	150 (82%)	123 (91%)	118 (89%)
Premature withdrawals[a]	23 (13%)	27 (15%)	32 (18%)	12 (9%)	15 (11%)
Withdrew consent	9 (5%)	14 (8%)	14 (8%)	9 (7%)	10 (8%)
Lost to follow-up	9 (5%)	7 (4%)	9 (5%)	0	0
Protocol violation	1 (<1%)	2 (1%)	1 (<1%)	2 (1%)	0
Inappropriate enrollment	0	1 (<1%)	2 (1%)	0	0
Adverse event	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (2%)
Unable to classify	2 (1%)	2 (1%)	3 (2%)	0	2 (2%)
Administrative reason	1 (<1%)	0	2 (1%)	0	0

[a] primary reason

Table 7: Demography and Other Baseline Characteristics by Age Group - Enrolled Population

		3.75ug_halfMF 59	7.5ug_fullMF59	15ug_noMF59	Total
		N=183	N=179	N=182	N=544
Adults 18-60 Yrs	Age (Years):	37.3±11.8	33.7±11.2	36.8±12.3	36.0±11.8
	Gender:				
	Male	82 (45%)	84 (47%)	75 (41%)	241 (44%)
	Female	101 (55%)	95 (53%)	107 (59%)	303 (56%)
	Ethnic Origin:				
	Asian	1 (<1%)	1 (<1%)	0	2 (<1%)
	Black	1 (<1%)	0	2 (1%)	3 (<1%)
	Caucasian	178 (97%)	178 (99%)	179 (98%)	535 (98%)
	Hispanic	1 (<1%)	0	0	1 (<1%)
	Other	2 (1%)	0	1 (<1%)	3 (<1%)
	Weight (kg):	74.87±17.81	73.54±16.09	72.53±14.97	73.65±16.33
	Height (cm):	173.7±9.3	173.7±9.9	172.3±9.1	173.2±9.5
	Body Mass Index:	24.72±5.22	24.25±4.20	24.34±4.35	24.44±4.61
	Female of Childbearing Potential:				
	No	20 (20%)	10 (11%)	26 (24%)	56 (18%)
	Yes	81 (80%)	85 (89%)	81 (76%)	247 (82%)
	Pregnancy Test:				
	Negative	81 (99%)	85 (98%)	81 (99%)	247 (98%)
	Not Done	1 (1%)	2 (2%)	1 (1%)	4 (2%)
	Birth Period:				
	Born Before or During 1951	6 (3%)	5 (3%)	10 (5%)	21 (4%)
	Born After 1951	177 (97%)	174 (97%)	172 (95%)	523 (96%)
	Previous Influenza Vaccination:				
	No	90 (49%)	103 (58%)	88 (48%)	281 (52%)
	Unknown	0	0	2 (1%)	2 (<1%)
	Yes	93 (51%)	76(42%)	92 (51%)	261 (48%)
	Year of Last Influenza Vaccination:				
	Unknown	90 (49%)	103 (58%)	90 (49%)	283 (52%)
	1999	0	2 (1%)	2 (1%)	4 (<1%)
	2001	0	1 (<1%)	0	1 (<1%)
	2002	0	1 (<1%)	0	1 (<1%)
	2003	0	1 (<1%)	1 (<1%)	2 (<1%)
	2004	0	2 (1%)	3 (2%)	5 (<1%)
	2005	4 (2%)	0	1 (<1%)	5 (<1%)
	2006	2 (1%)	4 (2%)	6 (3%)	12 (2%)
	2007	15 (8%)	13 (7%)	9 (5%)	37 (7%)
	2008	66 (36%)	51 (28%)	66 (36%)	183 (34%)
	2009	6 (3%)	1 (<1%)	4 (2%)	11 (2%)

Met Entry Criteria:				
No	0	3 (2%)	2 (1%)	5 (<1%)
Yes	183 (100%)	176 (98%)	180 (99%)	539 (99%)

Adults Over 60 Yrs

	N=135	**N=133**	**N=NA**	**N=268**
Age (Years):	66.4±3.9	67.9±5.4		67.1±4.8
Gender:				
Male	75 (56%)	72 (54%)		147 (55%)
Female	60 (44%)	61 (46%)		121 (45%)
Ethnic Origin:				
Caucasian	135 (100%)	133 (100%)		268 (100%)
Weight (kg):	78.29±15.95	76.66±14.65		77.48±15.31
Height (cm):	170.3±8.8	170.3±8.4		170.3±8.6
Body Mass Index:	26.86±4.38	26.38±4.53		26.62±4.45
Female of Childbearing Potential:				
No	61 (98%)	61 (98%)		122 (98%)
Not determined	1 (2%)	1 (2%)		2 (2%)
Birth Period:				
Born Before or During 1951	135 (100%)	133 (100%)		268 (100%)
Previous Influenza Vaccination:				
No	21 (16%)	14 (11%)		35 (13%)
Unknown	0	2 (2%)		2 (<1%)
Yes	114 (84%)	117 (88%)		231 (86%)
Year of Last Influenza. Vaccination:				
Unknown	21 (16%)	16 (12%)		37 (14%)
2001	1 (<1%)	0		1 (<1%)
2005	0	1 (<1%)		1 (<1%)
2006	2 (1%)	1 (<1%)		3 (1%)
2007	7 (5%)	7 (5%)		14 (5%)
2008	97 (72%)	102 (77%)		199 (74%)
2009	7 (5%)	6 (5%)		13 (5%)
Met Entry Criteria:				
No	0	2 (2%)		2 (<1%)
Yes	135 (100%)	131 (98%)		266 (99%)

Categorical parameters: N (%), non-categorical parameters: Mean±Standard Deviation.

Table 8: GMTs and GMRs (95% CI) After Primary Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults 18-60 Years: PPS and HI Assay, A/California H1N1 Strain

	Adult 18 to 60 Years		
	3.75ug_halfMF59	**7.5ug_fullMF59**	**15ug_noMF59**
Primary	**N=173**	**N=170**	**N=167**
GMT Day 1	7.4 (6.5-8.5)	7.6 (6.6-8.7)	8.0 (7.0-9.2)
GMT Day 22	90 (69-117)	146 (111-191)	107 (81-140)
GMR Day 22 /Day 1	**12** (9.4-15)	**19** (15-25)	**13** (10-17)
GMT Day 43	170 (138-208)	310 (252-380)	158 (128-194)
GMR Day 43/Day 1	**23** (19-28)	**41** (33-50)	**20** (16-24)
GMR Day 43/Day 22	1.89 (1.63-2.19)	2.12 (1.84-2.46)	1.48 (1.27-1.71)
Booster	**aTIV N=143**	**aTIV N=135**	**aTIV N=128**
GMT Day 1	7.59 (6.5-8.87)	7.52 (6.42-8.81)	7.95 (6.75-9.36)
GMT Day 366	44 (34-58)	61 (47-80)	50 (38-66)
GMT Day 387	369 (314-434)	423 (358-498)	291 (245-344)
GMR Day 387/Day 366	**8.32** (6.54-11)	**6.92** (5.42-8.83)	**5.76** (4.48-7.42)
GMR Day 387/Day 1	49 (40-60)	56 (46-69)	37 (30-45)

Bold = CHMP criteria met

Table 9: GMTs and GMRs (95% CI) Pre and Post-Booster Vaccination (Day 387) in Adults 18-60 Years: PPS, HI Assay - A/California H1N1 Strain

	Adults 18-60 Years
	Pooled aTIV N=406
GMT Day 1	7.6 (6.97-8.29)
GMT Day 366	49 (42-57)
GMT Day 387	327 (297-359)
GMR Day 387 to Day 366	**6.69** (5.81-7.69)
GMR Day 387 to Day 1	43 (38-48)

Bold = CHMP criteria met

Table 10: Pairwise Comparisons of GMTs (95% CI) Between Vaccine Groups After Each Primary Vaccination (Day 22 and Day 43) in Adults 18-60 Years: PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences		
	3.75_half : 7.5ug_full	**3.75ug_half : 15ug_no**	**7.5ug_full: 15ug_no**
GMT Day 22	**0.61** (**0.43-0.88**)	0.84 (0.58-1.21)	1.37 (0.95-1.96)
GMT Day 43	**0.55** (**0.42-0.72**)	1.07 (0.82-1.41)	***1.96*** *(1.49-2.59)*

Ratio Bold = the first vaccine group, of the respective pair being compared, is **statistically inferior** to the second vaccine group (95% CI completely below 1).

Ratio Bold Italic = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 1).

All Bold = the first vaccine group, of the respective pair being compared, is **statistically non-inferior** to the second vaccine group (lower bound 95% CI >0.5 and upper bound 95% CI >1 but <2).

Table 11: Percentage of Subjects (95% CI) with Seroconversion or Significant Increase After Primary Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults 18-60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adults 18-60 Years		
	3.75_halfMF59	**7.5_fullMF59**	**15_noMF59**
Primary	**N=173**	**N=170**	**N=167**
Day 22 / Day 1	**73%** (66-79)	**82%** (75-87)	**70%** (63-77)
Day 43/Day 1	**93%** (88-96)	**96%** (92-98)	**81%** (75-87)
Booster	**aTIV N=143**	**aTIV N=135**	**aTIV N=128**
Day 387/Day 366	**76%** (68-82)	**64%** (56-72)	**63%** (54-71)

Bold = CHMP criteria met

Table 12: Percentage of Subjects (95% CI) with Seroconversion or Significant Increase After Booster (Day 387) in Adults 18-60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adults 18-60 Years
	Pooled aTIV N=406
Day 387/Day 366	**68%** (63-72)

Bold = CHMP criteria met

Table 13: Pairwise Comparisons of Percentage of Subjects (95% CI) with Seroconversion or Significant Increase After Primary Vaccination (Day 22 and Day 43) in Adults 18-60 Years – PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences		
	3.75_half - 7.5_full	**3.75_half - 15_no**	**7.5_full - 15_no**
Day 22 to Day 1	-9% (-18-0)	3% (-7-12)	**12% (3-21)**
Day 43 to Day 1	-3% (-8-2)	**12% (5-19)**	**14% (8-21)**

Ratio Bold = the first vaccine group, of the respective pair being compared, is **statistically inferior** to the second vaccine group (95% CI completely below 1).

Ratio Bold Italic = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 1).

All Bold = the first vaccine group, of the respective pair being compared, is **statistically non-inferior** to the second vaccine group (lower bound 95% CI >0.5 and upper bound 95% CI >1 but <2).

Table 14: Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥ 40) After Primary Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults 18-60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adult 18-60 Years		
	3.75ug_halfMF59	**7.5ug_fullMF59**	**15ug_noMF59**
Primary	**N=173**	**N=170**	**N=167**
Day 1	8% (4-13)	9% (5-14)	11% (7-16)
Day 22	**77%** (70-83)	**83%** (76-88)	**73%** (66-80)
Day 43	**95%** (91-98)	**97%** (93-99)	**85%** (79-90)
Booster	**aTIV**	**aTIV**	**aTIV**
Day 366	60% (52-68) (N=154)	66% (58-74) (N=145)	56% (48-65) (N=140)
Day 387	**99%** (96-100) N=143	**100%** (97-100) N=135	**99%** (96-100) N=128

Bold= CHMP criteria met

Table 15: Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥40) After Booster (Day 387) in Adults 18-60 Years - Per-Protocol Set, A/California H1N1 Strain

	Adults 18-60 Years
	Pooled aTIV N=406
Day 387	**100%** (98-100)

Bold= CHMP criteria met

Table 16: Vaccine Group Differences in the Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥ 40) After Primary vaccinations (Day 22 and Day 43) in Adults 18-60 Years - PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences		
	3.75ug_half - 7.5ug_full	**3.75ug_half - 15ug_no**	**7.5ug_full - 15ug_no**
Day 1	-1% (-7 - 4)	-3% (-9 - 3)	-2% (-8 - 4)
Day 22	-5% (-14 - 3)	4% (-5 - 14)	**10% (1 - 19)**
Day 43	-2% (-6 - 2)	**10% (4 - 17)**	**12% (6 - 18)**

Bold = statistically significant

Table 17: GMTs and GMRs (95% CI) After Priming Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults Over 60 Years: PPS and HI Assay, A/California H1N1 Strain

	Adults Over 60 Years	
	3.75_halfMF59	**7.5_fullMF59**
Primary	**N=129**	**N=126**
GMT Day 1	7.36 (6.38-8.49)	8.2 (7.1-9.47)
GMT Day 22	25 (20-32)	41 (32-53)
GMR Day 22/Day 1	**3.42** (2.7-4.33)	**5** (3.93-6.35)
GMT Day 43	66 (53-82)	107 (86-134)
GMR Day 43/Day 1	**8.97** (7.14-11)	**13** (10-16)
GMR Day 43/Day 22	2.62 (2.15-3.21)	2.61 (2.13-3.2)
Booster	**aTIV N=108**	**aTIV N=106**
GMT Day 366	20 (16-25)	22 (18-28)
GMT Day 387	174 (137-220)	193 (152-246)
GMR Day 387/Day 366	**8.66** (6.71-11)	**8.61** (6.6-11)
GMR Day 387/Day 1	24 (18-31)	24 (18-32)

Bold = CHMP criteria met

Table 18: GMTs and GMRs (95% CI) in Subjects with Post Booster Vaccination (Day 387) in Adults Over 60 Years: PPS, HI Assay - A/California H1N1 Strain

	Adults Over 60 Years
	Pooled aTIV N=214
GMT Day 387	167 (143-195)
GMR Day 387/Day 366	**8.01** (6.72-9.54)

Bold = CHMP criteria met

Table 19: Pairwise Comparisons of GMTs and GMRs (95% CI) After Each Primary Vaccination (Day 22 and Day 43) in Adults Over 60 Years: PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences
	3.75_halfMF59/7.5_fullMF59
GMT Day 1	0.9 (0.75-1.08)
GMT Day 22	**0.61 (0.44-0.85)**
GMR Day 22/Day 1	**0.68 (0.5-0.93)**
GMT Day 43	**0.62 (0.46-0.82)**
GMR Day 43/Day 1	**0.69 (0.51-0.92)**
GMR Day 43/Day 22	1 (0.77-1.3)

Ratio Bold = the first vaccine group, of the respective pair being compared, is **statistically inferior** to the second vaccine group (95% CI completely below 1).

Ratio Bold Italic = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 1).

All Bold = the first vaccine group, of the respective pair being compared, is **statistically non-inferior** to the second vaccine group (lower bound 95% CI >0.5 and upper bound 95% CI >1 but <2)

Table 20: Percentage of Subjects (95% CI) with Seroconversion or Significant Increase After Priming Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults Over 60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adults Over 60 Years	
Primary	**3.75ug_halfMF59 N=129**	**7.5ug_fullMF59 N=126**
Day 22/Day 1	**35% (**27-44)	**52% (**43-61)
Day 43/Day 1	**69% (**60-77)	**79% (**71-86)
Booster	**aTIV N=108**	**aTIV N=106**
Day 387/Day 366	**77%** (68-84)	**72%** (62-80)

Bold= CHMP criteria met

Table 21: Percentage of Subjects (95% CI) with Seroconversion or Significant Increase After Booster (Day 387) in Adults Over 60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adults Over 60 Years
	Pooled aTIV N=214
Day 387/Day 366	**74%** (68-80)

Bold= CHMP criteria met

Table 22: Vaccine Group Differences in the Percentage of Subjects (95% CI) with Seroconversion or a Significant Increase After Primary Vaccinations (Day 22 and Day 43) in Adults Over 60 Years - PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences
	3.75ug_half - 7.5ug_full
Day 22/Day 1	**-17% (-29 to -6%)**
Day 43/Day 1	-10% (-21 to 0%)

Ratio Bold = the first vaccine group, of the respective pair being compared, is **statistically inferior** to the second vaccine group (95% CI completely below 1).

Ratio Bold Italic = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 1).

All Bold = the first vaccine group, of the respective pair being compared, is **statistically non-inferior** to the second vaccine group (lower bound 95% CI >0.5 and upper bound 95% CI >1 but <2)

Table 23: Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥ 40) After Priming Vaccinations (Day 22 and Day 43) and Booster (Day 387) in Adults Over 60 Years - PPS and HI Assay, A/California H1N1 Strain

	Adults Over 60 Years	
	3.75ug_halfMF59	**7.5ug_fullMF59**
Primary	**N=129**	**N=126**
Day 1	6% (3-12)	12% (7-19)
Day 22	44% (35-53)	60% (51-69)
Day 43	**76%** (68-83)	**87%** (80-93)
Booster	**aTIV N=116**	**aTIV N=114**
Day 366	30% (22-39)	37% (28-46)
Day 387	**95%** (90-98) N=108	**93%** (87-97) N=106

Bold = CHMP criteria met

Table 24: Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥ 40) After Booster (Day 387) in Adults Over 60 Years - Per-Protocol Set, Day 387, A/California H1N1 Strain

	Adults Over 60 Years
	Pooled aTIV N=214
Day 387	**94%** (90-97)

Bold = CHMP criteria met

Table 25: Pairwise Comparisons of the Percentage of Subjects (95% CI) with Seroprotection (HI Titer ≥ 40) After Primary Vaccinations (Day 22 and Day 43) in Adults Over 60 Years - PPS and HI Assay, A/California H1N1 Strain

	Vaccine Group Differences
	3.75ug_half - 7.5ug_full
Day 1	-6% (-13 to 1)
Day 22	**-16% (-28-to -4)**
Day 43	**-11% (-21 to -2)**

Ratio Bold = the first vaccine group, of the respective pair being compared, is **statistically inferior** to the second vaccine group (95% CI completely below 1).
Ratio Bold Italic = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 1).
All Bold = the first vaccine group, of the respective pair being compared, is **statistically non-inferior** to the second vaccine group (lower bound 95% CI >0.5 and upper bound 95% CI >1 but <2)

Table 26: GMTs (95% CI) non-inferiority Analysis of the Adjuvanted Groups After Primary Vaccinations (Day 22 and Day 43) - Pooled Age Groups, PPS, HI assay, A/California/7/2009 strain

	A/California/7/2009 (H1N1)v		
	3.75ug_halfMF59 N=302	**7.5ug_fullMF59 N=296**	**3.75_half : 7.5_full**
Day 22	48 (39-59)	78 (64-96)	0.61 (0.47-0.8)
Day 43	114 (97-133)	197 (168-231)	0.58 (0.47-0.71)

Table 27: Number (%) of Subjects Reporting Solicited Reactions During the 7-Day Period After Each Vaccination - Adults 18-60 Years - Safety Set

	First Vaccination			Second Vaccination			Booster Vaccination			
	3.75ug_ halfMF59	7.5ug_ fullMF59	15ug_ noMF59	3.75ug_ halfMF59	7.5ug_ fullMF59	15ug_ noMF59	3.75ug_ halfMF59 → aTIV	7.5ug_ fullMF59 → aTIV	15ug_ noMF59 → aTIV	aTIV pooled
	N=185	N=178	N=178	N=180	N=176	N=174	N=163	N=151	N=153	N=467
Any	147 (79)	157 (88)	125 (70)	101 (56)	115 (65)	97 (56)	138 (85)	133 (88)	127 (83)	398 (85)
Local	123 (66)	141 (79)	87 (49)	85 (47)	99 (56)	72 (41)	135 (83)	125 (83)	119 (78)	379 (81)
Systemic	95 (51)	102 (57)	92 (52)	53 (29)	67 (38)	65 (37)	71 (44)	80 (53)	66 (43)	217 (46)
Other	21 (11)	20 (11)	24 (13)	15 (8)	10 (6)	19 (11)	16 (10)	22 (15)	19 (12)	57 (12)

Table 28: Number (%) of Subjects Reporting Solicited Reactions During the 7-Day Period After Each Vaccination - Adults Over 60 Years - Safety Set

	First Vaccination		Second Vaccination		Booster Vaccination		
	3.75ug_ halfMF59	7.5ug_ fullMF59	3.75ug_ halfMF59	7.5ug_ fullMf59	3.75ug_ halfMF59 → aTIV	7.5ug_ fullMF59 → aTIV	aTIV pooled
	N=135	N=132	N=135	N=130	N=123	N=118	N=241
Any	69 (51)	77 (58)	48 (36)	49 (38)	70 (57)	68 (58)	138 (57)
Local	43 (32)	54 (41)	31 (23)	39 (30)	59 (48)	55 (47)	114 (47)
Systemic	45 (33)	49 (37)	30 (22)	26 (20)	34 (28)	37 (31)	71 (29)
Other	5 (4)	4 (3)	5 (4)	5 (4)	4 (3)	7 (6)	11 (5)

Table 29: Number (%) of Subjects with Any Severe Local Reactions During the 7-Day Period After Each Vaccination - Safety Set

Age Group: Adults 18-60 Years											
		First Vaccination			**Second Vaccination**			**Booster**			
		3.75_ halfMF59	**7.5_ fullMF59**	**15_ noMF59**	**3.75_ halfMF59**	**7.5_ fullMF59**	**15_ noMF59**	**3.75_halfMF59→ aTIV**	**7.5_fullMF59→ aTIV**	**15_noMF59→ aTIV**	**aTIV pooled**
		N=185	**N=178**	**N=178**	**N=180**	**N=176**	**N=174**	**N=163**	**N=151**	**N=153**	**N=467**
Ecchymosis(mm)	Any	7 (4)	12 (7)	13 (7)	5 (3)	6 (3)	11 (6)	9 (6)	7 (5)	10 (7)	26 (6)
	> 100 mm	0	0	0	0	0	0	0	0	0	0
Erythema (mm)	Any	19 (10)	31 (17)	29 (16)	11 (6)	24 (14)	18 (10)	28 (17)	28 (19)	28 (18)	84 (18)
	> 100 mm	0	0	0	0	0	0	2 (1)	1 (1)	0	3 (1)
Induration (mm)	Any	17 (9)	32 (18)	15 (8)	9 (5)	20 (11)	14 (8)	34 (21)	38 (25)	34 (22)	106 (23)
	> 100 mm	0	0	0	0	0	0	1 (1)	0	0	1 (<1)
Swelling (mm)	Any	11 (6)	22 (12)	12 (7)	9 (5)	15 (9)	8 (5)	33 (20)	32 (21)	27 (18)	92 (20)
	> 100 mm	0	0	0	0	0	0	1 (1)	0	0	1 (<1)
Pain	Any	110 (59)	128 (72)	64 (36)	78 (43)	85 (48)	55 (32)	125 (77)	115 (76)	111 (73)	351 (75)
	Severe	0	2 (1)	0	2 (1)	2 (1)	0	5 (3)	2 (1)	4(3)	11 (2)
Age Group: Adults Over 60 Years											
		First Vaccination			**Second Vaccination**			**Booster**			
		N=135	**N=132**	**NA**	**N=135**	**N=130**	**NA**	**N=123**	**N=118**	**NA**	**N=241**
Ecchymosis(mm)	Any	7 (5)	5 (4)		5 (4)	3 (2)		4 (3)	2 (2)		6 (2)
	> 100 mm	0	0		0	0		0	0		0
Erythema (mm)	Any	15 (11)	19 (14)		10 (7)	15 (12)		24 (20)	16 (14)		40 (17)
	> 100 mm	0	0		0	0		1 (1)	1 (1)		2 (1)
Induration (mm)	Any	8 (6)	18 (14)		8 (6)	12 (9)		16 (13)	19 (16)		35 (15)
	> 100 mm	0	0		0	0		0	0		0
Swelling (mm)	Any	7 (5)	11 (8)		8 (6)	8 (6)		15 (12)	11 (9)		26 (11)
	> 100 mm	0	0		0	0		0	0		0
Pain	Any	29 (21)	40 (30)		19 (14)	27 (21)		41 (33)	41 (35)		82 (34)
	Severe	0	0		0	0		0	1 (1)		1 (<1)

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

Table 30: Number (%) of Subjects with Any Systemic Reactions During the 7-Day Period After Each Vaccination - Safety Set

		Age Group: Adults 18-60 Years									
		First Vaccination			Second Vaccination			Booster			
		3.75_ halfMF59	7.5_ fullMF59	15_ noMF59	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59	3.75_ halfMF59 →aTIV	7.5_ fullMF59 →aTIV	15_ noMF59 →aTIV	aTIV pooled
		N=185	N=178	N=178	N=180	N=176	N=174	N=163	N=151	N=153	N=467
Systemic											
Chills	Any	6 (3)	5 (3)	3 (2)	1 (1)	4 (2)	5 (3)	8 (5)	12 (8)	10 (7)	30 (6)
	Severe	0	0	0	0	0	0	2 (1)	0	2 (1)	4 (1)
Malaise	Any	14 (8)	17 (10)	13 (7)	17 (9)	17 (10)	14 (8)	24 (15)	27 (18)	16 (10)	67 (14)
	Severe	1 (1)	0	0	0	1 (1)	0	3 (2)	1 (1)	2 (1)	6 (1)
Myalgia	Any	44 (24)	49 (28)	31 (17)	22 (12)	29 (16)	23 (13)	42 (26)	45 (30)	42 (27)	129 (28)
	Severe	1 (1)	1 (1)	0	0	2 (1)	0	4 (2)	2 (1)	2 (1)	8 (2)
Arthralgia	Any	16 (9)	19 (11)	11 (6)	11 (6)	10 (6)	7 (4)	21 (13)	24 (16)	18 (12)	63 (13)
	Severe	0	1 (1)	1 (1)	0	0	0	0	1 (1)	0	1 (<1)
Headache	Any	45 (24)	50 (28)	46 (26)	27 (15)	27 (15)	39 (22)	36 (22)	42 (28)	32 (21)	110 (24)
	Severe	4 (2)	4 (2)	5 (3)	2 (1)	3 (2)	3 (2)	3 (2)	3 (2)	4 (3)	10 (2)
Sweating	Any	18 (10)	15 (8)	17 (10)	3 (2)	7 (4)	10 (6)	17 (10)	16 (11)	11 (7)	44 (9)
	Severe	1 (1)	0	1 (1)	0	0	0	3 (2)	2 (1)	0	5 (1)
Fatigue	Any	47 (25)	53 (30)	43 (24)	29 (16)	34 (19)	35 (20)	38 (23)	43 (28)	42 (27)	123 (26)
	Severe	2 (1)	3 (2)	3 (2)	3 (2)	2 (1)	0	2 (1)	2 (1)	1 (1)	5 (1)
Nausea	Any	11 (6)	16 (9)	11 (6)	12 (7)	13 (7)	9 (5)	12 (7)	10 (7)	6 (4)	28 (6)
	Severe	0	1 (1)	1 (1)	0	2 (1)	0	4 (2)	0	1 (1)	5 (1)
Fever (≥ 38ºC)	Yes	4 (2)	0	1 (1)	0	1 (1)	0	2 (1)	3 (2)	0	5 (1)
Other											
Temp. (ºC)	<38.0	181 (98)	178 (100)	177 (99)	180 (100)	175 (99)	174 (100)	161 (99)	148 (98)	153 (100)	462 (99)
	≥ 40.0	0	0	0	0	0	0	0	0	0	0
Stayed Home	Yes	2 (1)	4 (2)	3 (2)	2 (1)	0	3 (2)	6/162 (4)	6 (4)	2/152 (1)	14/465 (3)
Analg. Antipyr. Med.Used	Yes	21 (11)	18 (10)	23 (13)	14 (8)	10 (6)	18 (10)	12 (7)	21 (14)	18 (12)	51 (11)

Table 31: Number (%) of Subjects with Any Systemic Reactions During the 7-Day Period After Each Vaccination - Safety Set

		First Vaccination		Second Vaccination		Booster			
		3.75_ halfMF59	7.5_ fullMF59	3.75_ halfMF59	7.5_ fullMF59	3.75_ halfMF59 →aTIV	7.5_ fullMF59 →aTIV	15_ noMF59 →aTIV	aTIV pooled
		N=135	N=132	N=135	N=130	N=123	N=118	NA	N=241
Systemic									
Chills	Any	1 (1)	0	3 (2)	1 (1)	1 (1)	0		1 (<1)
	Severe	0	0	0	0	0	0		0
Malaise	Any	10 (7)	5 (4)	5 (4)	3 (2)	1 (1)	6 (5)		7 (3)
	Severe	1 (1)	1 (1)	0	0	0	0		0
Myalgia	Any	12 (9)	16 (12)	8 (6)	9 (7)	10 (8)	12 (10)		22 (9)
	Severe	1 (1)	1 (1)	0	0	0	0		0
Arthralgia	Any	2 (1)	8 (6)	8 (6)	9 (7)	9 (7)	7 (6)		16 (7)
	Severe	0	0	0	0	0	0		0
Headache	Any	11 (8)	22 (17)	14 (10)	8 (6)	11 (9)	14 (12)		25 (10)
	Severe	1 (1)	0	2 (1)	0	0	0		0
Sweating	Any	19 (14)	18 (14)	5 (4)	3 (2)	7 (6)	6 (5)		13 (5)
	Severe	3 (2)	2 (2)	0	0	0	0		0
Fatigue	Any	21 (16)	26 (20)	15 (11)	15 (12)	16 (13)	22 (19)		38 (16)
	Severe	0	2 (2)	0	2 (2)	0	1 (1)		1 (<1)
Nausea	Any	6 (4)	3 (2)	4 (3)	0	1 (1)	3 (3)		4 (2)
	Severe	1 (1)	1 (1)	0	0	0	0		0
Fever (≥ 38ºC)	Yes	0	0	0	0	2 (2)	0		2 (1)
Other									
Temp. (ºC)	<38.0	135 (100)	132 (100)	135 (100)	130 (100)	121 (98)	118 (100)		239 (99)
	≥ 40.0	0	0	0	0	0	0		0
Stayed Home	Yes	2 (1)	0	1/134 (1)	0	0	2 (2)		2 (1)
Analg. Antipyr. Med.Used	Yes	3 (2)	4 (3)	5 (4)	5 (4)	4 (3)	6 (5)		10 (4)

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

Table 32: Number (%) of Subjects Reporting Unsolicited AEs by Age Cohort - Safety Set

		Day 1 to Day 43			Day 366 to Day 387			
		3.75_ halfMF59	**7.5_ fullMF59**	**15_ noMF59**	**3.75_ halfMF59 → aTIV**	**7.5_ fullMF59 →aTIV**	**15_ noMF59 →aTIV**	**aTIV pooled**
Adults 18-60 YRS		**N=185**	**N=178**	**N=178**	**N=163**	**N=151**	**N=153**	**N=467**
	Any AEs	82 (44)	75 (42%)	76 (43%)	28 (17%)	25 (17%)	23 (15%)	76 (16%)
	At least possibly related AEs	37 (20%)	40 (22%)	39 (22%)	20 (12)	17 (11%)	12 (8%)	49 (10%)
	AEs leading to withdrawal	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)
	AEs leading to onset of chronic disease	2 (<1%)	0	0	0	0	0	0
	Serious AEs	0	3 (2)	0	0	1 (1)	0	1 (<1)
	At least possibly related SAEs	0	0	0	0	0	0	0
Adults Over 60 YRS		**N=135**	**N=132**	**NA**	**N=123**	**N=118**	**NA**	**N=241**
	Any AEs	46 (34)	30 (23)		7 (6)	19 (16)		26 (11)
	At least possibly related AEs	16 (12)	15 (11)		3 (2)	6 (5)		9 (4)
	AEs leading to withdrawal	0	0		0	0		0
	AEs leading to onset of chronic disease	2 (<1%)	0		0	0		0
	Serious AEs	1 (1)	2 (2)		0	0		0
	At least possibly related SAEs	0	0		0	0		0

Table 33: Serious Adverse events by Preferred Term sorted by System Organ Class - from Day 1 to Day 366, Age Group: Adults 18-60 Years

	Number(%) of Subjects[1]		
MedDRA System Organ Class MedDRA Preferred Term	**3.75ug_50 (N=185)**	**7.5ug_100 (N=178)**	**15ug_0 (N=178)**
Any Serious Adverse Event	11 (6%)	6 (3%)	6 (3%)
Gastrointestinal Disorders	2 (1%)	0	1 (1%)
Abdominal Pain	1 (1%)	0	0
Gastritis	0	0	1 (1%)
Pancreatitis Acute	1 (1%)	0	0
Gen. Disorders & Admin. Site Cond.	1 (1%)	0	1 (1%)
Chest Pain	0	0	1 (1%)
Hernia	1 (1%)	0	0
Infections & Infestations	3 (2%)	1 (1%)	0
Appendicitis	2 (1%)	1 (1%)	0
H1N1 Influenza	1 (1%)	0	0
Tonsillitis	1 (1%)	0	0
Injury & Poisoning	3 (2%)	2 (1%)	1 (1%)
Accident	1 (1%)	0	0
Ankle Fracture	1 (1%)	0	0
Decompression Sickness	0	1 (1%)	0
Fall	0	0	1 (1%)
Fibula Fracture	1 (1%)	0	0
Testicular Injury	0	1 (1%)	0
Vaccination Failure	1 (1%)	0	0
Musculo., Connect. Tis. & Bone Dis	1 (1%)	1 (1%)	0
Intervertebral Disc Protrusion	0	1 (1%)	0
Osteoarthritis	1 (1%)	0	0
Neo. Ben./Malig.(Inc. Cysts/Polyps)	1 (1%)	1 (1%)	1 (1%)
Basal Cell Carcinoma	0	1 (1%)	0
Breast Cancer	1 (1%)	0	0
Uterine Leiomyoma	0	0	1 (1%)
Psychiatric Disorders	0	1 (1%)	0
Depression	0	1 (1%)	0
Renal & Urinary Disorders	0	0	1 (1%)
Stress Urinary Incontinence	0	0	1 (1%)
Reproduct. Sys. & Breast Disorders	1 (1%)	0	0
Dysmenorrhea	1 (1%)	0	0
Menorrhagia	1 (1%)	0	0
Resp., Thoracic & Mediastinal Dis.	0	0	1 (1%)
Pneumothorax	0	0	1 (1%)
Surgical & Medical Procedures	2 (1%)	0	0
Adhesiolysis	1 (1%)	0	0
Knee Arthroplasty	1 (1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%.

Table 34: Serious Adverse events by Preferred Term sorted by System Organ Class - from Day 1 to Day 366, Age Group: Elderly >= 61 Years

	Number(%) of Subjects[1]	
MedDRA System Organ Class MedDRA Preferred Term	**3.75ug_50 (N=135)**	**7.5ug_100 (N=132)**
Any Serious Adverse Event	10 (7%)	12 (9%)
Blood & Lymphatic System Disorders	0	1 (1%)
Anemia	0	1 (1%)
Cardiac Disorders	1 (1%)	0
Atrial Fibrillation	1 (1%)	0
Congen. & Famil./Genetic Disorders	1 (1%)	1 (1%)
Adenomatous Polyposis Coli	0	1 (1%)
Hydrocele	1 (1%)	0
Gastrointestinal Disorders	0	1 (1%)
Gastrointestinal Necrosis	0	1 (1%)
Gen. Disorders & Admin. Site Cond.	0	1 (1%)
Device Dislocation	0	1 (1%)
Hepato-Biliary Disorders	0	1 (1%)
Cholelithiasis	0	1 (1%)
Immune System Disorders	0	1 (1%)
Drug Hypersensitivity	0	1 (1%)
Infections & Infestations	2 (1%)	0
Pharyngitis	1 (1%)	0
Pneumonia	1 (1%)	0
Injury & Poisoning	2 (1%)	4 (3%)
Clavicle Fracture	0	1 (1%)
Fall	0	1 (1%)
Femoral Neck Fracture	0	1 (1%)
Forearm Fracture	1 (1%)	0
Joint Dislocation	1 (1%)	0
Pelvic Fracture	0	1 (1%)
Radius Fracture	0	1 (1%)
Investigations	1 (1%)	0
Arthroscopy	1 (1%)	0
Musculo., Connect. Tis. & Bone Dis.	0	3 (2%)
Musculoskeletal Pain	0	1 (1%)
Osteoarthritis	0	2 (2%)
Neo. Ben./Malig.(Inc. Cysts/Polyps)	1 (1%)	0
Prostate Cancer	1 (1%)	0
Nervous System Disorders	2 (1%)	1 (1%)
Facial Paresis	0	1 (1%)
Loss of Consciousness	1 (1%)	0
Restless Legs Syndrome	1 (1%)	0
Renal & Urinary Disorders	1 (1%)	0

Urinary Tract Disorder	1 (1%)	0
Reproduct. Sys. & Breast Disorders	1 (1%)	1 (1%)
Benign Prostatic Hyperplasia	1 (1%)	1 (1%)
Resp., Thoracic & Mediastinal Dis.	1 (1%)	1 (1%)
Chronic Obstructive Pulmonary Disease	1 (1%)	0
Pulmonary Embolism	0	1 (1%)
Vascular Disorders	0	1 (1%)
Thrombophlebitis	0	1 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts. Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%.

Table 35: Serious Adverse events by Preferred Term sorted by System Organ Class - from Day 366 to Day 546, Age Group: Adults 18-60 Years

	Number(%) of Subjects[1]			
MedDRA System Organ Class MedDRA Preferred Term	**3.75ug_50 + aTIV (N=163)**	**7.5ug_100 + aTIV (N=151)**	**15ug_0 + aTIV (N=153)**	**aTIV (N=467)**
Any Serious Adverse Event	0	1 (1%)	0	1 (<1%)
Infections & Infestations	0	1 (1%)	0	1 (<1%)
Cellulitis	0	1 (1%)	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts maynot sum to overall counts. Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 36: Serious Adverse events by Preferred Term sorted by System Organ Class - from Day 366 to Day 546, Age Group: Elderly >= 61 Years

MedDRA System Organ Class MedDRA Preferred Term	**3.75ug_50 + aTIV (N=123)**	**7.5ug_100 + aTIV (N=118)**	**aTIV (N=241)**
Any Serious Adverse Event	3 (2%)	2 (2%)	5 (2%)
Infections & Infestations	1 (1%)	0	1 (<1%)
Diverticulitis	1 (1%)	0	1 (<1%)
Injury & Poisoning	1 (1%)	1 (1%)	2 (1%)
Contusion	1 (1%)	0	1 (<1%)
Patella Fracture	0	1 (1%)	1 (<1%)
Musculo., Connect. Tis. & Bone Dis	0	1 (1%)	1 (<1%)
Osteoporotic Fracture	0	1 (1%)	1 (<1%)
Vascular Disorders	1 (1%)	0	1 (<1%)
Hypertension	1 (1%)	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts. Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%.

Table 37: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class-with Onset before Study Day 43 (within the allowed window), Age Group: Adults 18-60 Years

MedDRA System Organ Class MedDRA Preferred Term	3.75ug_50 (N=185)	7.5ug_100 (N=178)	15ug_0 (N=178)
Gastrointestinal Disorders	17 (9%)	16 (9%)	19 (11%)
Diarrhea	7 (4%)	10 (6%)	7 (4%)
Nervous System Disorders	15 (8%)	17 (10%)	19 (11%)
Headache	12(6%)	10 (6%)	11 (6%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts. Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%.

Table 36: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class-with Onset before Study Day 43 (within the allowed window), Age Group: Elderly >= 61 Years

None Reported

Table 37: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class - from Day 366 to Day 387, Age Group: Adults 18-60 Years

None Reported

Table 38: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class- from Day 366 to Day 546, Age Group: Elderly >= 61 Years

None Reported

Conclusion:

In conclusion:

- Overall, all vaccine formulations have a very good long term safety profile.
- Immunogenicity results after both priming and booster vaccinations have indicated that the adjuvant MF59 permits a reduction of the antigen content (15 µg in the seasonal vaccine aTIV) in this A/H1N1 vaccine by one half (7.5 µg) or even by one quarter (3.75 µg) in both age groups. For a pandemic setting, this would considerably increase the number of available doses, and thus protect a much broader population.
- As expected, adults (18 to 60 years) had a stronger primary immune response than elderly (> 60 years); however, in terms of boostability, the strength of the booster immunogenicity observed in elderly matched or exceeded the one observed in the adult subjects.

Date of Clinical Trial Report: **07 JUN 11**