Sponsor: Novartis Vaccines

Investigational Product: MF59-Adjuvanted, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine

Indication: Prophylaxis of A (H1N1) 2009 Pandemic Influenza

Protocol Number: V111_04

Protocol Title: A Phase II, Open Label Study to Evaluate the Immunogenicity, Tolerability and Safety of a MF59-Adjuvanted, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine in Healthy Subjects Aged 18 Years and Above

Phase of Development: Phase 2

Study Period:

Date of first enrolment: 26 AUG 09

Date of last visit: 21 OCT 09

Methodology:

The number of subjects enrolled is summarized in the section entitled Number of Subjects (planned and analyzed). For additional details, please refer to the Time and Events Table. At enrolment, subjects were stratified into two age groups:

- 18 to 60 years: of the four groups in the study, the first group, i.e., the group that previously received seasonal TIV was invited to participate in the present study and the other three groups were randomized at a 1:1:1 ratio to enrol similar number of participants to the first group. The first three groups received two 7.5µg H1N1 sw vaccination formulated with full MF59 (7.5_fullMF59: full MF59 refers to the adjuvant content of the European-licensed adjuvanted seasonal influenza vaccine, Fluad™) administered alone, concomitantly (first vaccination only), or sequentially to a 2009/10 formulation of unadjuvanted TIVs (TIV, Agrippal™). The fourth group was administered two 3.75µg H1N1 sw vaccinations formulated with half MF59 (3.75_halfMF59), concomitantly with TIV (first vaccination only).
- Over 60 years: of the three groups that participated in the study, the first and second groups that had previously received TIV or adjTIV, were invited to participate in the present study; a similar number of participants were enrolled to the third group. All the groups received 7.5_fullMF59 administered alone in this study.

Vaccinations were to be administered on day 1 and day 22. Blood samples were collected at day 1 (baseline, before the first vaccination), at day 22 (before the second vaccination),

at day 29 (one week after the second vaccination) and at day 43 (three weeks after the second vaccination). Sera were tested by Hemagglutination Inhibition (HI) and Microneutralization (MN) assays. Safety was assessed until 3 weeks after the first and second vaccination.

Number of Subjects (planned and analyzed):

Taking into account a drop-out rate of 10%, in order to analyze 50 evaluable subjects per vaccination group a total of up to 228 adult subjects aged 18 to 60 years and 176 adult subjects aged over 60 years were planned to be enrolled.

- 264 adults aged 18 to 60 years and 155 adults aged over 60 years were enrolled.
- 255 subjects aged 18 to 60 years and 153 subjects aged over 60 years were included in the per protocol set (PPS) for immunogenicity analysis
- 264 subjects aged 18 to 60 years and 154 subjects aged over 60 years were included in safety analysis.

In both adults 18 to 60 years and adults over 60 years, 98% subjects completed the study.

Study Centers:

Five sites in Italy

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

PMID - 20039974

Objectives:

Immunogenicity:

- To evaluate the immunogenicity of one and two intramuscular (IM) injections of the MF59-adjuvanted H1N1sw monovalent influenza vaccine in adult and elderly subjects previously exposed to 2009/10 NH formulation of Trivalent Influenza Vaccine and in those not yet vaccinated against seasonal influenza 2009/10, with respect to CHMP criteria.
- To evaluate immunogenicity of one and two IM injections of full and half dose of a H1N1sw monovalent influenza vaccine concomitantly administered with a single IM dose of a seasonal TIV in adult subjects not yet vaccinated against seasonal influenza 2009/10, with respect to CHMP criteria.
- To evaluate the immunogenicity of Trivalent Influenza Vaccine containing the three recommended strains for 2009/10 season (A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2)-like virus and B/Brisbane/60/2008-like virus) concomitantly administered with the first IM injection of full and half dose of the H1N1sw monovalent influenza vaccine in 18 to 60 year adult subjects not yet vaccinated with TIV (formulated with 2009/10).

Safety:

- To evaluate safety and tolerability of one and two IM injections of the MF59-adjuvanted H1N1sw monovalent influenza vaccine in adult and elderly subjects previously exposed to 2009/10 NH formulation of TIV and in those not yet vaccinated against seasonal influenza 2009/10, for 3 weeks after each vaccination.
- To evaluate safety and tolerability of one and two IM injections of full and half dose of a H1N1sw monovalent influenza vaccine, and of a single dose of a seasonal TIV concomitantly administered in adult subjects not yet vaccinated against seasonal influenza 2009/10, for 3 weeks after each H1N1sw vaccination.
- To evaluate safety and tolerability of a single IM injection of a seasonal TIV when concomitantly administered with one and two IM injections of full and half dose of a H1N1sw monovalent influenza vaccine in adult subjects not yet vaccinated against seasonal influenza 2009/10, for 3 weeks after each H1N1sw vaccination.

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

All vaccines were administered IM in the deltoid muscle

1) Subunit monovalent influenza egg-derived vaccine containing 7.5µg HA of the H1N1sw influenza strain and the full dose (9.75mg) of MF59 in 0.5mL (7.5_fullMF59), Lot no. Z56P18N1B.
2) Subunit monovalent influenza egg-derived vaccine containing 3.75µg HA of the H1N1sw influenza strain and the half dose (4.875 mg) of MF59 in 0.25mL (3.75_halfMF59) Lot no. Z56P18N1B.
3) European-licensed unadjuvanted subunit trivalent influenza vaccine (Agrippal; Novartis Vaccines [TIV]) containing 15µg HA of each strain (A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2)-like virus, B/Brisbane/60/2008-like virus) recommended for the 2009/2010 NH influenza season.

Duration of Study:

Total duration of the study is eight weeks, which include two weeks for enrolment and 6 weeks for study participation.

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

As the study was designed to investigate concomitant and sequential administration of the H1N1 pandemic vaccines with European-licensed seasonal influenza vaccines, all study vaccines are described as test vaccines.

Statistical Methods:

There is no statistical null hypothesis associated with the immunogenicity objectives, which were analyzed descriptively. The immunogenicity parameters are grouped into two types:

- geometric mean titers (GMTs) and geometric mean titer ratios (GMRs)
- proportions computed from dichotomous variables (i.e. seroconversion [baseline seronegative subjects become seroprotected and baseline seropositive

subjects show at least a 4-fold titer increase]), and seroprotection [HI titers ≥40)

The sample size for each age stratum, allowing a 10% drop-out, was based on the sample size requirements of the current CHMP guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96).

All analyses are done separately for the two age strata. No multiplicity adjustment was done and the primary population for immunogenicity analysis is the PPS. Safety is assessed as numbers and percentages of subjects reporting local and systemic reactions and/or other AEs.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study population consisted of male and female healthy subjects aged ≥18 years who have not had H1N1sw influenza vaccination or documented H1N1sw influenza disease. Those with immunosuppressive conditions, including chronic use of oral or systemic steroids, were not included. Female individuals of reproductive potential were eligible for enrolment if they used birth control measures for at least 2 months before study participation and were committed to use birth control measures during at least the first 3 weeks after last study vaccination

Criteria for Evaluation:

Immunogenicity

For the monovalent H1N1sw vaccine, the immunogenicity criteria for success, as determined by HI, related to the EMEA/CPMP/VEG/4717/2003-Rev.1 (pandemic guideline) and EMEA/CHMP/VWP/263499/2006 (pre-pandemic guideline) are:

For subjects aged 18 to 60 years:

- The GMR is >2.5
- The percentage of subjects with seroconversion (HI ≥1:40 for subjects negative at baseline [<1:10] or at least a 4-fold increase in HI titer for subjects seropositive at baseline [HI ≥1:10]) is >40%
- The percentage of subjects achieving seroprotection (HI titer ≥40) is >70%.

For subjects aged over 60 years:

- The GMR is >2.0
- The percentage of subjects with seroconversion is >30%
- The percentage of subjects achieving seroprotection is >60%.

All three criteria should be met by the pandemic vaccine against the H1N1 pandemic strain (i.e A/California/7/2009) in each age stratum to fulfill regulatory requirements.

For TIV administered concomitantly with the first vaccinations of 3.75_halfMF59 and 7.5_fullMF59 in the 18 to 60 year age strata, the immunogenicity criteria for success, as determined by HI, related to the CHMP/BWP/214/96 guideline, are the same as listed

above. However it is sufficient that at least one criterion per each strain should be achieved to fulfil regulatory requirements.

Safety Measurements

Vaccination	Variables	Duration post vaccination	Study days
First Vaccination	Solicited local and systemic reactions[a]	1 week	1 – 7
	All unsolicited adverse events (incl serious adverse events, AEs that led to withdrawal of the subject, and prescription medication, and solicited reactions ongoing past day 7).	3 weeks	1 – 21
Second Vaccination	Solicited local and systemic reactions[a]	1 week	22 - 28
	All unsolicited AEs (incl SAEs, AEs that led to withdrawal of the subject, and prescription medication, and solicited reactions ongoing past day 7).	3 weeks	22 - 43

[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.

Table 1: Time and Events

Clinic Visit? (Yes/No)	**Visit 1 Yes**	**Visit 2 No**	**Visit 3 Yes**	**Visit 4 Yes**	**Visit 5 Yes**
Study Day	1	8	22	29	43
Study Visit Window	-	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
ICF	X				
Exclusion/Inclusion	X				
Medical history	X				
Physical assessment	X		X	X	X
Urine pregnancy test	X		X		X
Serology Blood draw (10mL)	X		X	X	X
Vaccine administered	X		X		
Diary Card Dispensed	X		X	X	
Diary Card Collected and/or Reviewed		X	X	X	X
Assess Local/ Systemic Reactions	X	X		X	
Assess AEs and SAEs	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Study Termination					X

RESULTS

Table 2: Populations Analyzed

	Adults aged 18 to 60 years				Adults Over 60 Years		
	TIV→ 7.5_fullMF59	7.5_fullMF59	7.5_fullMF59 + TIV	3.75_half MF59 + TIV	TIV→ 7.5_fullMF59	adjTIV→ 7.5_fullMF59	7.5_fullMF59
	N=50	N=71	N=71	N=72	N=49	N=46	N=60
Enrolled Population	50 (100%)	71(100%)	71(100%)	72 (100%)	49 (100%)	46 (100%)	59 (100%)
Full Analysis Set	50 (100%)	71(100%)	70 (99%)	69 (96%)	49 (100%)	46 (100%)	59 (98%)
Per Protocol Set	50 (100%)	70 (99%)	67 (94%)	68 (94%)	49 (100%)	46 (100%)	58 (97%)

Table 3: Summary of Study Terminations - Adults 18 to 60 Years

	TIV→ 7.5_full MF59	7.5_fullMF59	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV
Enrolled (N)	50	71	71	72
Completed study (%)	50 (100%)	71 (100%)	69 (97%)	68 (94%)
Premature withdrawals [a]	0	0	2 (3%)	4 (6%)
Adverse Event	0	0	0	1 (1%)
Withdrew consent (%)	0	0	1 (1%)	1 (1%)
Lost to follow-up	0	0	1 (1%)	1 (1%)
Inappropriate enrolment (%)	0	0	0	1 (1%)

[a]Primary Reason

Table 4: Summary of Study Terminations - Adults over 60 Years

	TIV→7.5_full MF59	adjTIV→7.5_full MF59	7.5_fullMF59
Enrolled (N)	49	46	60
Completed study (%)	49 (100%)	46 (100%)	59 (99%)
Premature withdrawals [a]	0	0	1 (2%)
Withdrew consent (%)	0	0	1 (2%)

[a]Primary Reason

Table 5: Demography and other Baseline Characteristics in Adults 18 to 60 Years-Enrolled Set

	TIV→ 7.5_fullMF59	7.5_fullMF59	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV	Total
	N=50	N=71	N=71	N=72	N=264
Age	46.5 ± 9.7	40.7 ±12.1	40.5 ± 12.3	38.5 ± 12.1	41.2 ±12.0
Female	33 (66%)	40 (56%)	38 (54%)	40 (56%)	151 (57%)
Male	17 (34%)	31 (44%)	33 (46%)	32 (44%)	113 (43%)
Ethnic Origin: Black	0	1(1%)	0	0	1 (<1%)
Caucasian	50 (100%)	69 (97%)	71 (100%)	72 (100%)	262 (99%)
Hispanic	0	1 (1%)	0	0	1 (<1%)
Weight (kg)	74.80 ± 13.97	69.03 ± 15.34	70.60 ± 17.45	68.53 ± 14.97	70.41 ±15.68
Height (cm)	166.2 ± 8.1	168.5 ± 10	169.9 ± 9.4	168.7 ± 9.2	168.5 ±9.3
Female of Childbearing Potential	22 (44%)	28 (39%)	33 (46%)	34 (47%)	117 (44%)
Participation in Prev Infl. Study	50 (100%)	0	0	0	50 (19%)
Met Study Entry Criteria	50 (100%)	71 (100%)	71 (100%)	71 (99%)	263 (100%)

Categorical parameters: N(%), non-categorical parameters: Mean ± Std

Table 6: Demography and other Baseline Characteristics in Adults over 60 years-Enrolled Set

	TIV→ 7.5_full MF59	adjTIV→ 7.5_full MF59	7.5_fullMF59	Total
	N=49	N=46	N=60	N=155
Age	69.2 ± 7.3	72.8 ± 5.9	70.5 ± 7.4	70.7 ±7.1
Gender: Female	27 (55%)	19 (41%)	26 (43%)	72(46%)
Male	22 (45%)	27 (59%)	34 (57%)	83 (54%)
Ethnic Origin: Caucasian	49 (100%)	46 (100%)	60 (100%)	155 (100%)
Weight (kg)	74.05 ± 12.70	75.54 ± 12.35	73.45 ± 10.88	74.26 ±
Height (cm)	165.0 ± 7.9	164.3 ± 7.3	166.6 ± 7.2	165.4 ± 7.4
Participation in Prev Infl. Study	49 (100%)	46 (100%)	0	95 (61%)
Met Study Entry Criteria	49 (100%)	46 (100%)	60 (100%)	155 (100%)

Categorical parameters: N(%), non-categorical parameters: Mean±Std

Table 7: GMTs and GMRs (95% CI) in Adults 18 to 60 Years after First and Second Vaccination: PPS and HI Assay, A/H1N1 California Strain

	TIV→7.5_fullMF59	**7.5_fullMF59**	**7.5_fullMF59 + TIV**	**3.75_halfMF59 + TIV**
	N=50	**N=70**	**N=67**	**N=68**
Day 1	11 (7.87-17)	8.08 (6.36-10)	9.67 (7.56-12)	8.61 (6.74-11)
Day 22	451 (265-768)	431 (307-606)	465 (328-658)	270 (192-382)
Day 22 to Day 1	**39** (22-72)	**53** (36-78)	**48** (32-71)	**31** (21-46)
Day 29	407 (263-630)	390 (295-516)	374 (281-498)	257 (193-341)
Day 29 to Day 1	36 (21-61)	48 (34-68)	39 (27-55)	30 (21-42)
Day 43	391 (261-586)	371 (286-480)	325 (250-423)	247 (190-322)
Day 43 to Day 1	**34** (21-56)	**46** (34-63)	**34** (24-46)	**29** (21-40)

Bold font: CHMP criteria met; *GMR >2.5

Table 8: Percentages (95%CI) of Adults Aged 18 to 60 Years with Seroconversion after First and Second Vaccination: PPS and HI Assay, A/H1N1 California strain

	TIV→ 7.5_full MF59	**7.5_fullMF59**	**7.5_fullMF59 + TIV**	**3.75_halfMF59 + TIV**
	N=50	**N=70**	**N=67**	**N=68**
Day 22	47 (**94%**) (83-99)	62 (**89%**) (79-95)	66 (**99%**) (92-100)	62 (**91%**) (82-97)
Day 29	45 (90%) (78-97)	65 (93%) (84-98)	61 (91%) (82-97)	62 (91%) (82-97)
Day 43	48 (**96%**) (86-100)	66 (**94%**) (86-98)	61 (**91%**) (82-97)	65 (**96%**) (88-99)

Bold font: CHMP criteria met; *The percentage of subjects with seroconversion (HI ≥1:40 for subjects negative at baseline [<1:10] or at least a 4-fold increase in HI titer for subjects seropositive at baseline [HI ≥1:10]) >40%

Table 9: Percentages (95%CI) of Seroprotected Adults Aged 18 to 60 Years after First and Second Vaccination: PPS and HI Assay, A/H1N1 California Strain

	TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=70	N=67	N=68
Day 1	13 (26%) (15-40)	5 (7%) (2-16)	8 (12%) (5-22)	5 (7%) (2-16)
Day 22	48 (**96%**) (86-100)	67 (**96%**) (88-99)	67 (**100%**) (95-100)	65 (**96%**) (88-99)
Day 29	50 (**100%**) (93-100)	68 (**97%**) (90-100)	65 (**97%**) (90-100)	67 (**99%**) (92-100)
Day 43	50 (**100%**) (93-100)	70 (**100%**) (95-100)	65 (**97%**) (90-100)	67 (**99%**) (92-100)

Table 10: GMTs and GMRs (95% CI) in Adults over 60 Years after First and Second Vaccination: PPS and HI Assay, A/H1N1 California Strain

	TIV→7.5_full MF59	adjTIV→7.5_full MF59	7.5_fullMF59
	N=49	N=46	N=58
Day 1	11 (5.68-20)	14 (7.39-25)	10 (6.61-17)
Day 22	81 (29-226)	79 (29-215)	71 (34-152)
Day 22 to Day 1	**7.63** (3.05-19)	**5.81** (2.38-14)	**6.8** (3.46-13)
Day 29	128 (55-299)	118 (52-270)	167 (89-312)
Day 29 to Day 1	12 (5.04-29)	8.65 (3.71-20)	16 (8.39-30)
Day 43	198 (89-443)	131 (60-286)	168 (93-304)
Day 43 to Day 1	**19** (7.84-44)	**9.59** (4.12-22)	**16** (8.46-30)

Bold font: CHMP criteria met; *GMR >2.0

Table 11: Percentages (95%CI) of Adults aged Over 60 Years with Seroconversion after First and Second Vaccination: PPS and HI Assay, A/H1N1 California Strain

	TIV→7.5_full MF59 N=49	adjTIV→7.5_full MF59 N=46	7.5_fullMF59 N=58
Day 22	35 (**71%**) (57-83)	32 (**70%**) (54-82)	44 (**76%**) (63-86)
Day 29	35 (**71%**) (57-83)	31 (**67%**) (52-80)	50 (**86%**) (75-94)
Day 43	38 (**78%**) (63-88)	32 (**70%**) (54-82)	52 (**90%**) (79-96)

Bold font: CHMP criteria met; * The percentage of subjects with seroconversion (HI ≥1:40 for subjects negative at baseline [<1:10] or at least a 4-fold increase in HI titer for subjects seropositive at baseline [HI ≥1:10]) >30%

Table 12: Percentages (95%CI) of Seroprotected Adults aged over 60 Years after First and Second Vaccination: PPS and HI Assay, A/H1N1 California Strain

	TIV→7.5_full MF59 N=49	adjTIV→7.5_full MF59 N=46	7.5_full MF59 N=58
Day 1	4 (8%) (2-20)	7 (15%) (6-29)	4 (7%) (2-17)
Day 22	44 (**90%**) (78-97)	41 (**89%**) (76-96)	49 (**84%**) (73-93)
Day 29	44 (**90%**) (78-97)	40 (**87%**) (74-95)	54 (**93%**) (83-98)
Day 43	45 (**92%**) (80-98)	42 (**91%**) (79-98)	57 (**98%**) (91-100)

Bold font: CHMP criteria met; *The percentage of subjects achieving seroprotection >60%.

Table 13: GMTs and GMRs (95% CI) against the Seasonal Strains after TIV Vaccination in Adults 18 to 60 Years: PPS and HI Assay

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV
	N=67	N=68	N=67	N=68	N=67	N=68
Day 1	27 (19-37)	28 (20-38)	24 (17-34)	29 (21-41)	12 (9.82-15)	15 (12-18)
Day 22	153 (117-199)	165 (127-214)	142 (106-190)	135 (101-180)	54 (43-68)	68 (54-86)
Day 22 over Day 1	5.69 (4.07-7.95)	5.92 (4.25-8.26)	5.96 (4.1-8.65)	4.64 (3.2-6.71)	4.41 (3.31-5.89)	4.66 (3.5-6.21)

Table 14: Percentages (95%CI) of Adults Aged 18 to 60 Years with Seroconversion against the Seasonal Strains after TIV Vaccination: PPS and HI Assay

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=67	N=68	N=67	N=68	N=67	N=68
Day 22	**57%** (44%-69%)	**65%** (52%-76%)	**55%** (43%-67%)	**51%** (39%-64%)	**57%** (44%-69%)	**59%** (46%-71%)

Table 15: Percentages (95%CI) of Adults Aged 18 to 60 Years with Seroprotection against the Seasonal Strains after TIV Vaccination: PPS and HI Assay

	A/Brisbane/59/2007 (H1N1)-like virus		A/Brisbane/10/2007 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=67	N=68	N=67	N=68	N=67	N=68
Day 1	29 (43%) (31-56)	32 (47%) (35-60)	31 (46%) (34-59)	30 (44%) (32-57)	11 (16%) (8-27)	16 (24%) (14-35)
Day 22	62 (**93%**) (83-98)	65 (**96%**) (88-99)	57 (**85%**) (74-93)	63 (**93%**) (84-98)	53 (**79%**) (67-88)	56 (**82%**) (71-91)

Table 16: Numbers (%) of Subjects Reporting Solicited Local and Systemic Reactions after First and Second Vaccination in Adults 18 - 60 Years of Age: Safety Set

	TIV→ 7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
First Vaccination	**N=50**	**N=71**	**N=71**	**N=72**
Any	32 (64%)	55 (77%)	51 (72%)	51 (71%)
Local	25 (50%)	43 (61%)	43 (61%)	41 (57%)
Systemic	23 (46%)	45 (63%)	36 (51%)	36 (50%)
Other[a]	2 (4%)	11 (15%)	6 (8%)	9 (13%)
Second Vaccination	**N=50**	**N=71**	**N=70**	**N=69**
Any	24 (48%)	53 (75%)	48 (69%)	37 (54%)
Local	18 (36%)	43 (61%)	38 (54%)	28 (41%)
Systemic	15 (30%)	36 (51%)	32 (46%)	26 (38%)
Other[a]	4 (8%)	6 (8%)	6 (9%)	8 (12%)

[a]Other= Analgesic and/or antipyretics use

Table 17: Numbers (%) of Adults 18 to 60 Year Old with Any (and Severe/>100 mm) Local And Systemic Reaction to Pandemic Vaccines within 7 Days after First Vaccination: Safety Set

			TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
			N=50	N=71	N=71	N=72
Local Reactions	Ecchymosis(mm)	Any	0	1(1)	1(1)	0
		> 100 mm	0	0	0	0
	Erythema (mm)	Any	5 (10%)	0	0	0
		> 100 mm	0	0	0	0
	Induration (mm)	Any	2 (4%)	3 (4%)	1 (1%)	1 (1%)
		> 100 mm	0	0	0	0
	Swelling (mm)	Any	2 (4%)	3 (4%)	1 (1%)	0
		> 100 mm	0	0	0	0
	Pain	Any	25 (50%)	43 (61%)	43 (61%)	41 (57%)
		Severe	1 (2%)	1 (1%)	1 (1%)	0
Systemic Reactions	Chills	Any	3 (6%)	5 (7%)	4 (6%)	4 (6%)
		Severe	0	0	0	0
	Malaise	Any	8 (16%)	16 (23%)	11 (15%)	10 (14%)
		Severe	0	1(1)	0	0
	Myalgia	Any	7 (14%)	15 (21%)	14 (20%)	15 (21%)
		Severe	0	0	0	0
	Arthralgia	Any	6 (12%)	9 (13%)	10 (14%)	12 (17%)
		Severe	0	0	0	0
	Headache	Any	13 (26%)	26 (37%)	14 (20%)	22 (31%)
		Severe	1 (2%)	4 (6%)	0	1 (1%)
	Sweating	Any	7 (14%)	15 (21%)	14 (20%)	8 (11%)
		Severe	0	0	0	0
	Fatigue	Any	8 (16%)	25 (35%)	23 (32%)	26 (36%)
		Severe	0	2 (3%)	0	1 (1%)
	Nausea	Any	6 (12%)	12 (17%)	3 (4%)	7 (10%)
		Severe	0	0	0	0
	Fever (≥ 38C)		0	0	0	0
Other	Analg. Antip. Used		2 (4%)	11 (15%)	6 (8%)	9 (13%)

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

Table 18: Numbers (%) of Adults 18 to 60 Year Old with Any (and Severe/>100 mm) Local and Systemic Reaction to Pandemic Vaccines within 7 Days after Second Vaccination: Safety Set

			TIV→ 7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
			N=50	N=71	N=71	N=72
Local Reactions	Ecchymosis (mm)	Any	0	0	0	0
		> 100 mm	0	0	0	0
	Erythema (mm)	Any	6 (12%)	1 (1%)	3/70 (4%)	4/69(6%)
		> 100 mm	0	0	0	0
	Induration (mm)	Any	2 (4%)	2 (3%)	4/70 (6%)	4/69 (6%)
		> 100 mm	0	0	0	0
	Swelling (mm)	Any	3 (6%)	3 (4%)	1/70 (1%)	4/69 (6%)
		> 100 mm	0	0	0	0
	Pain	Any	17 (34%)	42 (59%)	38/70 (54%)	27/69 (39%)
		Severe	0	0	0	0
Systemic Reactions	Chills	Any	2 (4%)	3 (4%)	2/70 (3%)	5/69 (7%)
		Severe	0	0	0	0
	Malaise	Any	4 (8%)	14 (20%)	11/70 (16%)	8/69 (12%)
		Severe	0	0	0	0
	Myalgia	Any	8 (16%)	13 (18%)	11/70 (16%)	10/69 (14%)
		Severe	1 (2%)	0	0	0
	Arthralgia	Any	6 (12%)	16 (23%)	13/70 (19%)	10/69 (14%)
		Severe	0	0	0	0
	Headache	Any	9 (18%)	19 (27%)	13/70 (19%)	16/69 (23%)
		Severe	0	3 (4%)	0	1/69 (1%)
	Sweating	Any	2 (4%)	6 (8%)	5/70 (7%)	3/69 (4%)
		Severe	0	0	0	0
	Fatigue	Any	3 (6%)	21 (30%)	20/70 (29%)	21/69 (30%)
		Severe	0	0	0	0
	Nausea	Any	2 (4%)	5 (7%)	7/70 (10%)	3/69 (4%)
		Severe	0	0	0	0
	Fever (≥ 38C)	Yes	1 (2%)	0	0	0
Other	Analg. Antip. Used	Yes	4 (8%)	6 (8%)	6/70 (9%)	8/69 (12%)

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

Table 19: Numbers (%) of Subjects Reporting Solicited Local and Systemic Reactions after First and Second Vaccination in Adults over 60 Years of Age: Safety Set

	TIV→7.5_fullMF59	adjTIV→7.5_fullMF59	7.5_fullMF59
First Vaccination	**N=49**	**N=46**	**N=59**
Any	18 (37%)	9 (20%)	28 (47%)
Local	9 (18%)	3 (7%)	15 (25%)
Systemic	15 (31%)	8 (17%)	20 (34%)
Other[a]	3 (6%)	1 (2%)	3 (5%)
Second Vaccination	**N=49**	**N=46**	**N=59**
Any	16 (33%)	13 (28%)	24 (41%)
Local	5 (10%)	7 (15%)	19 (32%)
Systemic	11 (22%)	9 (20%)	16 (27%)
Other[a]	2 (4%)	0	2 (3%)

Table 20: Numbers (%) of Adults over 60 Year Old with Any (and Severe/>100 mm) Local And Systemic Reaction to Pandemic Vaccines within 7 Days after First Vaccination: Safety Set

			TIV→7.5_fullMF59	adjTIV→7.5_full MF59	7.5_fullMF59
			N=49	**N=46**	**N=59**
Local Reactions	Ecchymosis (mm)	Any	0	0	1(2)
		> 100 mm	0	0	0
	Erythema (mm)	Any	1 (2%)	1 (2%)	1 (2%)
		> 100 mm	0	0	0
	Induration (mm)	Any	1 (2%)	0	1 (2%)
		> 100 mm	0	0	0
	Swelling (mm)	Any	1 (2%)	0	2 (3%)
		> 100 mm	0	0	0
	Pain	Any	9 (18%)	2 (4%)	14 (24%)
		Severe	0	0	0
Systemic Reactions	Chills	Any	3 (6%)	0	1 (2%)
		Severe	0	0	0
	Malaise	Any	5 (10%)	1 (2%)	6 (10%)
		Severe	1 (2%)	0	0
	Myalgia	Any	5 (10%)	2 (4%)	6 (10%)
		Severe	0	0	0
	Arthralgia	Any	8 (16%)	0	8 (14%)

		Severe	0	0	0
	Headache	Any	7 (14%)	3 (7%)	7 (12%)
		Severe	1 (2%)	0	0
	Sweating	Any	6 (12%)	3 (7%)	7 (12%)
		Severe	0	0	0
	Fatigue	Any	5 (10%)	2 (4%)	12 (20%)
		Severe	0	0	1(2)
	Nausea	Any	1 (2%)	0	3 (5%)
		Severe	0	0	0
	Fever (≥ 38C)	Yes	0	0	0
Other	Analg. Antip. Used	Yes	3 (6%)	1 (2%)	3 (5%)

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

Table 21: Numbers (%) of Adults over 60 Year Old with Any (and Severe/>100 mm) Local And Systemic Reaction to Pandemic Vaccines within 7 Days after Second Vaccination: Safety Population

			TIV→7.5_fullMF59	adjTIV→7.5_full MF59	7.5_fullMF59
			N=49	N=46	N=59
Local Reactions	Ecchymosis (mm)	Any	0	0	1(2)
		> 100 mm	0	0	0
	Erythema (mm)	Any	0	3 (7%)	3 (5%)
		> 100 mm	0	0	0
	Induration (mm)	Any	1 (2%)	2 (4%)	1 (2%)
		> 100 mm	0	0	0
	Swelling (mm)	Any	0	2 (4%)	1 (2%)
		> 100 mm	0	0	0
	Pain	Any	5 (10%)	5 (11%)	18 (31%)
		Severe	0	0	0
Systemic Reactions	Chills	Any	1 (2%)	0	2 (3%)
		Severe	0	0	1 (2%)
	Malaise	Any	2 (4%)	2 (4%)	5 (8%)
		Severe	0	0	1 (2%)
	Myalgia	Any	6 (12%)	3 (7%)	6 (10%)
		Severe	0	0	0
	Arthralgia	Any	7 (14%)	2 (4%)	7 (12%)
		Severe	0	0	0
	Headache	Any	1 (2%)	3 (7%)	6 (10%)
		Severe	0	0	0
	Sweating	Any	3 (6%)	3 (7%)	5 (8%)
		Severe	0	0	1(2)
	Fatigue	Any	7 (14%)	5 (11%)	8 (14%)
		Severe	0	0	0
	Nausea	Any	2 (4%)	0	2 (3%)
		Severe	0	0	0
	Fever (≥ 38C)	Yes	0	0	0
Other	Analg. Antip.Used	Yes	2 (4%)	0	2 (3%)

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

Table 22: Number (%) of Subjects Reporting All Unsolicited AEs after First and Second Vaccination in Adults 18 - 60 Years of Age: Safety Set

	TIV→ 7.5_fullMF59	7.5_fullMF59	7.5_fullMF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=71	N=71	N=72
Any AE	8 (16%)	27(38%)	28 (39%)	34 (47%)
Possibly/Prob. Related AE	2 (4%)	3 (4%)	5 (7%)	4 (6%)
Any SAE	0	0	0	1 (1%)
Possibly/Prob Related SAEs	0	0	0	0
AE leading to withdrawal	0	0	0	1 (1%)

Table 23: Number (%) of Subjects Reporting Unsolicited AEs after First and Second Vaccination in Adults over 60 Years of Age: Safety Set

	TIV→ 7.5_full MF59	adjTIV→ 7.5_full MF59	7.5_fullMF59
	N=49	N=46	N=59
Any AE	8 (16%)	3 (7%)	14 (24%)
Possibly/Prob. Related AE	4 (8%)	1 (2%)	5 (8%)
Any SAE	0	0	1 (2%)
Possibly/Prob Related SAEs	0	0	0
AE leading to withdrawal	0	0	0

Table 24: Serious AEs after any Vaccination, by Age Group, until Study Termination

		Number (%) of Subjects				
MedDRA SOC	**SAE**	**TIV→ 7.5_ fullMF59**	**AdjTIV→ 7.5_ fullMF59**	**7.5_ fullMF59**	**7.5_ fullMF59 + TIV**	**3.75_ halfMF59 + TIV**
18 to 60 years						
Infections & Infestations	Influenza	0	NA	0	0	1 (<1%)
Over 60 years						
Injury & Poisoning	Head Injury	0	0	1 (2%)	NA	NA
Injury & Poisoning	Skin Laceration	0	0	1 (2%)	NA	NA
Nervous System Disorders	Syncope	0	0	1 (2%)	NA	NA

Table 25: Unsolicited AEs Reported by >5% of Subjects by Decreasing Frequency until Study Termination

Number (%) of Subjects						
MedDRA SOC	**AE**	**TIV→ 7.5_ fullMF59**	**AdjTIV→ 7.5_ fullMF59**	**7.5_ fullMF59**	**7.5_ fullMF59 + TIV**	**3.75_ halfMF59 + TIV**
18 to 60 years						
Resp., Thoracic & Mediastinal Dis.	Oropharyngeal Pain	3 (6%)	NA	5 (7%)	4 (6%)	8 (11%)
Infections & Infestations	Nasopharyngitis	1 (2%)	NA	1 (1%)	6(8%)	7 (10%)
Nervous System Disorders	Headache	2 (4%)	NA	6 (8%)	6 (8%)	7 (10%)
Resp., Thoracic & Mediastinal Dis.	Cough	3 (6%)	NA	0	3 (4%)	2 (3%)
Reproduct. Sys. & Breast Disorders	Dysmenorrhoea	0	NA	1 (1%)	4 (6%)	3 (4%)
Musculo., Connect. Tis. & Bone Dis.	Neck Pain	0	NA	2 (3%)	0	4 (6%)
Over 60 Years						
Infections & Infestations	Rhinitis	0	0	4 (7%)	NA	NA
Nervous System Disorders	Headache	3 (6%)	0	1 (2%)	NA	NA

Conclusion:

The H1N1 sw vaccination programs are being rolled out. Due to medical needs, vaccination will be given to individuals previously exposed to adjuvanted or unadjuvanted seasonal influenza vaccines (adjTIV and TIV in the over 60 year age stratum and TIV in the 18 to 60 year age group). In addition, there would be logistic advantages to administer H1N1 sw vaccine concomitantly with seasonal influenza vaccines. However, information on immunogenicity and safety following sequential or concomitant use of H1N1 sw vaccines with TIV/adjTIV remains scanty.

In the 18 to 60 years age statum, 7.5_fullMF59 met all the three CHMP criteria against the vaccine strain (A/H1N1 California-like) after the first vaccination when administered alone, or concomitantly or sequentially with TIV. In addition, the half dose H1N1 sw vaccine (3.75_halfMF59) also met all three CHMP criteria after the first vaccination when administered concomitantly with TIV. The CHMP criteria were also met in H1N1 disease-vulnerable subjects who were seronegative or not seroprotected at baseline. The immune responses to TIV administered concomitantly with 3.75_halfMF59 and 7.5_fullMF59 also met all three CHMP criteria against all three seasonal strains. It is not clear why none of the second H1N1 vaccinations induced further increases in GMTs, although there were generally slight increases in seroprotected and seroconverted subjects. Nonetheless, the 31- to 53-fold increases in GMTs induced by the first H1N1 sw vaccinations far exceeded the CHMP requirements.

In the over 60 year age stratum, 7.5_fullMF59 met all the three CHMP criteria against the vaccine strain (A/H1N1 California-like) after the first vaccination when administered alone or sequentially with adjTIV or TIV, with no statistically significant differences between the immune responses. Further increases in the immune responses were induced by the second H1N1 vaccinations. The CHMP criteria were met after the first vaccination regardless of whether these over 60 year subjects were seropositive or seroprotected at baseline.

The reactogenicity profile of all vaccines evaluated in this study was acceptable. In both age strata, the reactogenicity profile of the 7.5_fullMF59 vaccine after sequential or concomitant administration of adjTIV or TIV was at least as good as when 7.5_fullMF59 was administered alone. In addition, in the 18 to 60 year age stratum the reactogenicity profiles after concomitant vaccination of 7.5_fullMF59 or 3.75_halfMF59 with TIV were at least as good as the second vaccination, when 7.5_fullMF59 or 3.75_halfMF59 when administered alone. The vast majority of solicited reactions were mild and self-limiting. Other AEs were reported by relatively few subjects, and most were mild. None of the other AEs indicated that there was increased risk to individuals who had either concomitant or sequential vaccination with H1N1 sw and seasonal influenza vaccines.

No deaths were reported. Two subjects reported non-related SAEs. One of these subjects withdrew after the SAE. No other subject with an AE withdrew from the study.

Overall, it can be concluded that the H1N1 sw vaccine can be safely administered concomitantly or sequentially with currently licensed seasonal adjuvanted or unadjuvanted seasonal influenza vaccines in healthy adults with no loss of immunogenicity. All CHMP criteria for the pandemic vaccine were met after a single dose of vaccine in all adults with all tested formulations regardless of age stratification. In adults 18 to 60 years of age, however, there may be no advantage to the second H1N1 sw vaccination as no clear immunologic benefit was seen. These results suggest that the medical and logistical needs to vaccinate against H1N1 sw in individuals previously immunized against seasonal influenza or, vaccinate concomitantly with the seasonal influenza vaccine can be met.