Sponsor:	Novartis Vaccines and Diagnostics
Investigational Product:	aH1N1, Adjuvanted monovalent H1N1 influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived)
Indication:	Prophylaxis of A (H1N1) 2009 Swine Origin Pandemic Influenza
Protocol Number:	V111_02
Protocol Title:	A Randomized, Single-blind, Dose-Ranging, Study to Evaluate Immunogenicity, Safety and Tolerability of Different Formulations of Adjuvanted and Unadjuvanted Egg-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 3

Study Period:

Date of first enrolment:	24 AUG 09
Date of last visit:	01 APR 11

Methodology:

Subjects were stratified into two age strata:

- Adults 18 to 60 years of age who were randomized at a 1:1:1 ratio to receive one of three vaccines (two adjuvanted and an unadjuvanted vaccine) followed by a booster vaccination with 2010/2011 seasonal flu vaccine (aTIV)
- Adults over 60 years who were randomized at a 1:1 ratio to receive either of the two adjuvanted vaccines followed by a booster vaccination with aTIV.
- Subjects received two priming doses of the aH1N1 vaccine at a 3-week interval. The booster vaccination with aTIV was given at 1 year after first dose. Blood samples to assess immunogenicity were collected at baseline, before first vaccination (day 1), before second vaccination (day 22) and three weeks after second vaccination (day 43) for the primary course; 1 year after the first vaccination just before the booster (day 366) and three weeks after booster vaccination (day 387). Sera were tested by Hemagglutination Inhibition (HI) and Microneutralization (MN) assays.

Number of Subjects (planned and analyzed):

Table 1: Planned and Actual Numbers of Subjects Enrolled

	18 to 60 years		Over 60 years	
	Planned	Actual	Planned	Actual
3.75_halfMF59[a]	120	137	120	126
7.5_fullMF59[b]	120	136	120	125
15_noMF59[c]	120	137	–	–

[a]3.75_halfMF59 = 3.75µg H1N1 antigen and half adjuvant MF59; [b]7.5_fullMF59 = 7.5µg H1N1 antigen and full adjuvant MF59; [c]15_noMF59 = 15µg H1N1antigen without adjuvant MF59

Study Centers: Eight sites in Germany, two sites in Belgium and two sites in Switzerland.

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

PMID: 22446638;

NCT00971906

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 aH1N1 vaccine in healthy adults based on Committee for Medical Products for Human use (CHMP)criteria and pairwise statistical comparisons for immunogenicity, and safety & tolerability.

Secondary Objectives:
Immunogenicity Objectives

- To evaluate immunogenicity against the A/California H1N1sw strain after a booster dose of aH1N1 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 dose of MF59) of aH1N1 vaccine to the corresponding GMTs of the full dose (7.5 µg of HA + full dose of MF59) of aH1N1 vaccine, after two doses administered 3 weeks apart in the pooled adult and elderly population.

Safety Objectives

- To evaluate safety and tolerability of aH1N1 vaccine for 3 weeks after first and second vaccination

- To evaluate safety and tolerability of aH1N1 vaccine up to 12 months after the first vaccination.
- To evaluate safety (up to 6 months) and tolerability of aTIV (containing the H1N1sw strain) administered as booster 12 months after the first dose of aH1N1 vaccine.

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

All three primary study vaccines - A/H1N1 - full (100%) MF59 refers to the adjuvant content of the European licensed seasonal influenza vaccine, aTIV.

The booster vaccine was the egg-derived, seasonal, trivalent MF59 adjuvanted vaccine aTIV. aTIV contained the same influenza virus surface antigen as in the H1N1sw vaccine used for priming vaccination (A/California/7/2009 (H1N1)-like virus), in combination with A/Perth/16/2009 (H3N2)-like virus and B/Brisbane/60/2008-like virus, as recommended for the 2010/2011 influenza season.

Table 2: Formulation of Vaccines

Group	Vaccine formulation			Lot No	Expiry date
	Antigen content (µg)	MF59 content (as mg squalene content)			
3.75_halfMF59[a]	3.75 µg	4.875 mg	50% (half)	Z56P18N1	Jul 2010
7.5_fullMF59[b]	7.5 µg	9.75 mg	100% (full)	Z56P18N1	Jul 2010
15_noMF59[c]	15 µg	-	0% (no)	Z53P22N1	Jul 2010
aTIV booster[d]	15 µg of each of the 3 strains	9.75 mg	100% (full)	104002E, 104601E, 104601A	Apr 2011 May 2011 May 2011

[a]3.75_halfMF59 = 3.75µg H1N1 antigen and half adjuvant MF59; [b]7.5_fullMF59 = 7.5µg H1N1 antigen and full adjuvant MF59; [c]15_noMF59 = 15µg H1N1antigen without adjuvant MF59; [d] aTIV=seasonal flu vaccine

Duration of Study:

Expected duration of individual subject's participation for the total study was about 18 months. Total duration of study was about 18 to 19 months.

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

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

Statistical Methods:

Primary and Secondary Analysis

Analysis of antibody titers: It was assumed that log-transformed antibody titers were normal distributed N (μi, $\sigma 2$) with μi denoting the unknown mean log10-transformed titer in the three vaccine groups, respectively and $\sigma 2$ the common variance.

Separated by age group least squares GMTs and two-sided 95% confidence intervals would be provided by visit using two-way analysis of variance (ANOVA) with factors for vaccine group and center. An interaction term would not be included. Log10-transformed antibody titers would be included as dependent variable.

Within group ratios were calculated in the same model using the log10-transformed ratios of post-baseline antibody titer and baseline titer as dependent variable.

Pairwise Comparisons: For the primary objective the following pairwise comparisons between vaccine groups were performed within each age group separately, and only with the immunogenicity results from the two priming vaccinations on Day 22 and Day 43:

- Difference (ratio) in percentage of subjects with seroconversion or significant increase in HI titer
- Difference (ratio) in percentage of subjects with HI titer ≥ 1:40
- Difference (ratio) in GMTs

Vaccine-group differences in seroconversion or significant increase in HI titer (defined as: HI ≥ 1:40 for subjects negative at baseline [< 1:10] or a minimum 4-fold increase in HI titer for subjects positive at baseline [HI ≥ 1:10]) and HI titer ≥ 1:40 were analyzed using log linear models with a factor for vaccine group, and vaccine-group differences in GMT were assessed using two-way ANOVA.

For the secondary objective, pairwise comparisons were conducted with the same model. Point estimates in terms of ratios of GMTs including 2-tailed 95% confidence intervals were calculated.

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 who were in good health as determined by the outcome of medical history, physical assessment and clinical judgment of the investigator;
3. Individuals who were able to comply with all study procedures and were available for all clinic visits scheduled in the study;
4. Individuals who were willing 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 with a history or any illness that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subjects due to participation in the study;
2. Individuals with any serious chronic or progressive disease according to the judgment of the investigator (including, but not limited to neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease);
3. Individuals with history of any anaphylaxis, serious vaccine reactions, or hypersensitivity to influenza viral proteins, to any excipients, and to eggs (including ovalbumin), and chicken proteins;
4. They were not eligible if they had documented confirmed or suspected influenza disease and received influenza vaccine within 3 months prior to day 1 or received another investigational products or any other vaccine within 4 weeks prior to enrollment;
5. Known or suspected impairment/alteration of immune function;
6. If female, of childbearing potential, and had not used any of the "acceptable contraceptive methods" for at least two months prior to study entry;
7. Females who were pregnant or nursing (breastfeeding) mothers, or females of childbearing potential who were sexually active and have not used or did not plan to use acceptable birth control measures during the first 3 weeks after vaccination;
8. Members of the research staff or their relatives. Hospital personnel, health care professionals and their relatives that were not involved in this clinical study were allowed for inclusion.

Criteria for Evaluation:

Immunogenicity Evaluation

Primary and secondary variables: HI assay parameters

The primary (priming vaccinations) and secondary (booster vaccination) immunogenicity criteria, determined by the strain-specific HI assay (using A/H1N1/California/7/2009 strain), were the CHMP criteria (according to EMEA/CPMP/VEG/4717/2003-Rev.1 pandemic guideline and EMEA/CHMP/VWP/263499/2006 pre-pandemic guideline), which are as follows:

For adults subjects aged 18-60 years:

- The percentage of subjects with seroconversion or significant increase in HI titer is > 40%
- The percentage of subjects achieving an HI titer ≥ 1:40 is > 70%
- The GMR is > 2.5

For elderly subjects aged ≥ 61 years:

- The percentage of subjects with seroconversion or significant increase in HI titer is > 30%
- The percentage of subjects achieving an HI titer ≥ 1:40 is > 60%
- The GMR is > 2.0

All three criteria as assessed at Day 43 should be met within each age group to fulfill regulatory requirements. Results collected at 21 days after the first dose were also evaluated against the CHMP criteria as presented above.

No predefined criteria were available to assess immunogenicity after booster vaccinations. However, the booster vaccine aTIV 2010/2011 (i.e., the seasonal influenza vaccine composition recommended for season 2010/2011) included the pandemic A/H1N1/California/7/2009 strain, and thus the CHMP criteria were applicable for the booster vaccination in this study. At least one criterion (assessed 3 weeks after the booster dose) should be met within each age group to fulfill regulatory requirements.

For Days 22, 43 and 366 seroconversion or significant increase in HI titer (after priming vaccination) would refer to the pre-vaccination titer on Day 1, whereas for Day 387 seroconversion or significant increase in HI titer (after booster vaccination) would refer to both the pre-vaccination titer on Day 1 and to the pre-booster vaccination titer on Day 366.

Primary variables: Pairwise comparisons between vaccine groups, after priming vaccinations (on Day 22 and 43, 3 weeks post first and second dose) and within each age group, were performed:

- Ratio of GMTs between vaccine groups at Day 22 and Day 43

- Difference between vaccine groups in terms of proportion of subjects achieving an HI titer ≥ 1:40 at Day 22 and Day 43
- Difference between vaccine groups in terms of proportion of subjects with seroconversion or significant increase in HI antibody at Day 22 and Day 43

The two-sided 95% CIs were calculated and assessed against a non-inferiority margin of 0.5. Subsequently the same non-inferiority hypothesis might have been tested using a non-inferiority margin of 0.67.

Secondary variables: The non-inferiority of the antibody response elicited by vaccine Groups A (3.75_half MF59) over Group B (7.5_full MF59), in the pooled age group (≥ 18 years), was determined for Day 22 and Day 43, by pairwise comparisons of GMT ratios.

Safety Evaluation

The safety variables and the Days on which they were assessed are presented in the table below (Table 3)

Table 3: Safety Measurements

Vaccination	Variables	Duration post vaccination	Study days
First vaccination	Solicited local and systemic reactions[a]	1 week	1-7
	All unsolicited AEs (including SAEs, onset of chronic disease, AEs leading to premature withdrawal, and prescription of medication) and solicited AEs continuing post Day 7	3 weeks	1-22
Second vaccination	Solicited local and systemic reactions[a]	1 week	22-28
	All unsolicited AEs (as above)	3 weeks	22-43
	Only SAEs, onset of chronic disease, AEs leading to withdrawal, and prescription of medication	6 weeks to 1 year post first vaccination	43-366
Booster vaccination	Solicited local and systemic reactions[a]	1 week	366-372
	All unsolicited AEs (as above)	3 weeks	366-387
	Only SAEs, onset of chronic disease, AEs leading to withdrawal, and prescription of medication	3 weeks to 6 months post booster	387-546

[a]Local Reactions: ecchymosis, erythema, induration, swelling, and pain (at injection site); Systemic Reactions: chills, malaise, myalgia, arthralgia, headache, sweating, fatigue, nausea, fever (defined as body temperature ≥ 38°C), body temperature > 40°C; Other Reactions (other indicators of reactogenicity): analgesic/antipyretic medication used, stayed at home due to reaction. Summarized according to the Brighton collaboration case definition (Bonhoeffer, Vaccine 2009; 27: 2282-2288)

Results:

Table 4: Overview of Populations Analyzed – Enrolled set, as randomized

	Adults (18 to 60 years)			Elderly (> 60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=137	**N=136**	**N=137**	**N=126**	**N=125**
Population					
Enrolled	137 (100%)	136 (100%)	137 (100%)	126 (100%)	125 (100%)
1st Vaccination	135 (99%)	132 (97%)	135 (99%)	125 (99%)	124 (99%)
2nd Vaccination	131 (96%)	129 (95%)	131 (96%)	124 (98%)	123 (98%)
3rd Vaccination [a](booster, aH1N1)	103 (75%)	106 (78%)	105 (77%)	104 (83%)	108 (86%)
Immunogenicity (HI Assay)					
[b]FAS (Day 1–43)	130 (95%)	126 (93%)	128 (93%)	124 (98%)	121 (97%)
[b]FAS (Day 1–366)	109 (80%)	115 (85%)	114 (83%)	107 (85%)	110 (88%)
[b]FAS (Day 1–387)	99 (72%)	105 (77%)	105 (77%)	102 (81%)	107 (86%)
[c]PPS (Day 1–43)	126 (92%)	120 (88%)	122 (89%)	117 (93%)	117 (94%)
[c]PPS (Day 1–366)	104 (76%)	112 (82%)	105 (77%)	104 (83%)	107 (86%)
[c]PPS (Day 1–387)	92 (67%)	95 (70%)	88 (64%)	92 (73%)	97 (78%)

[a]aH1N1, Adjuvanted monovalent H1N1 influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived); [b]FAS= Full Analysis Set; [c]PPS=Per Protocol Set

Table 5: Summary of Study Terminations - All Enrolled Subjects, Age Group: Adults 18-60 Yrs

	Number of Subjects (% of Total)		
Primary Withdrawal Reason	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59
Total Number Of Subjects Enrolled	137	136	137
Completed	98 (72%)	102 (75%)	103 (75%)
Completed Protocol	98 (72%)	102 (75%)	103 (75%)
Premature Withdrawal	39 (28%)	34 (25%)	34 (25%)
Death	0	0	0
Adverse Event	1 (< 1%)	3 (2%)	2 (1%)
Withdrawal Of Consent	17 (12%)	10 (7%)	15 (11%)
Lost To Follow-Up	10 (7%)	6 (4%)	10 (7%)
Inappropriate Enrollment	1 (< 1%)	2 (1%)	0
Administrative Reason	2 (1%)	0	0
Protocol Deviation/Violation	3 (2%)	4 (3%)	2 (1%)
Unable To Classify	5 (4%)	9 (7%)	5 (4%)

Table 6: Summary of Study Terminations - All Enrolled Subjects, Age Group: Elderly >= 61 Yrs

	Number of Subjects (% of Total)		
Primary Withdrawal Reason	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59
Total Number Of Subjects Enrolled	126	125	0
Completed	103 (82%)	108 (86%)	0
Completed Protocol	103 (82%)	108 (86%)	0
Premature Withdrawal	23 (18%)	17 (14%)	0
Death	0	2 (2%)	0
Adverse Event	1 (< 1%)	0	0
Withdrawal Of Consent	12 (10%)	9 (7%)	0
Lost To Follow-Up	2 (2%)	1 (< 1%)	0
Inappropriate Enrollment	2 (2%)	0	0
Administrative Reason	0	1 (< 1%)	0
Protocol Deviation/Violation	3 (2%)	1 (< 1%)	0
Unable To Classify	3 (2%)	3 (2%)	0

Table 7: Demography and Other Baseline Characteristics – Enrolled Set, as randomized

	Adults (18 to 60 years)			Elderly (> 60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=137	**N=136**	**N=137**	**N=126**	**N=125**
Age (Years):					
Mean±SD	38.5±11.6	38.3±11.8	38.9±11.1	68.0±5.2	67.0±4.6 (N=124)
Sex:					
Male	69 (50%)	73 (54%)	69 (50%)	71 (56%)	62 (50%)
Female	68 50%)	63 (46%)	68 (50%)	55 (44%)	62 (50%)
Race:					
Asian	0	0	1 (<1%)	0	0
Caucasian	135 (99%)	134 (99%)	135 (99%)	126 (100%)	124 (100%)
Other	2 (1%)	2 (1%)	1 (<1%)	0	0
Met Entry Criteria					
No	2 (1%)	4 (3%)	2 (1%)	1 (<1%)	1 (<1%)
Yes	135 (99%)	132 (97%)	135 (99%)	125 (99%)	124 (99%)

A=3.75_half MF59; **B**=7.5_full MF59; **C**=15_no MF59

Table 8: GMTs (95%CI) and GMRs (95% CI) of Adults (18 to 60 years) and Elderly (>60 years) after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=126	**N=120**	**N=122**	**N=117**	**N=117**
GMT Day 1	16 (13-19)	14 (12-17)	15 (13-18)	17 (14-21)	19 (15-23)
GMT Day 22	101 (75-135)	247 (184-332)	142 (106-190)	37 (28-49)	76 (57-101)
GMR Day 22 / Day 1	**6.45** (4.8-8.66)	**17** (13-23)	**9.37** (6.98-13)	**2.15** (1.66-2.78)	**4.02** (3.1-5.2)
GMT Day 43	158 (124-202)	326 (254-418)	174 (137-222)	61 (47-78)	129 (100-166)
GMR Day 43 / Day 1	**10** (7.71-13)	**23** (17-30)	**11** (8.76-15)	**3.51** (2.75-4.49)	**6.85** (5.36-8.75)
Prior to Booster	**N=104**	**N=112**	**N=105**	**N=104**	**N=107**
GMT Day 366	46 (33-66)	101 (72-141)	75 (54-105)	23 (17-31)	40 (30-54)
GMR Day 366 / Day 1	**2.93** (2.11-4.09)	**6.91** (5.04-9.49)	**4.84** (3.52-6.66)	1.43 (1.13-1.79)	**2.11** (1.68-2.66)
After Booster	**MF59-eTIV N=92**	**MF59-eTIV N=95**	**MF59-eTIV N=88**	**MF59-eTIV N=92**	**MF59-eTIV N=97**
GMT Day 387	419 (326-538)	559 (439-712)	358 (280-458)	225 (169-298)	266 (202-351)
GMR Day 387 / Day 1	27 (20-37)	40 (29-54)	23 (17-31)	14 (9.98-19)	15 (11-20)
GMR Day 387 /Day 366	**9.15** (6.58-13)	**5.44** (3.96-7.48)	**4.54** (3.28-6.28)	**10** (7.49-14)	**6.93** (5.12-9.38)
	Pooled Groups (A, B, C) Booster: MF59-eTIV (2010/2011)			**Pooled Groups (A, B) Booster: MF59-eTIV (2010/2011)**	
	N=275			**N=189**	
GMT Day 366	79 (65-96)			33 (27-40)	
GMT Day 387	466 (406-536)			247 (206-295)	
GMR Day 387 / Day 366	**5.91** (4.95-7.06)			**7.54** (6.17-9.21)	

Bold = CHMP criterion met

Table 9: Pairwise Comparisons of GMTs (95% CI) in Adults (18 to 60 years) and Elderly (> 60 years) on Days 22 and 43 – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)		Elderly (>60 years)	
	Comparisons of Group:		Comparisons of Group:	
	3.75_halfMF59 to 7.5_fullMF59	3.75_halfMF59 to 15_noMF59	7.5_fullMF59 to 15_ noMF59	3.75_halfMF59 to 7.5_fullMF59
Day 22 (from Day 1)	**0.41** (0.28-0.6)	0.71 (0.48-1.04)	***1.74*** (1.18-2.57)	**0.49** (0.34-0.71)
Day 43 (from Day 1)	**0.48** (0.35-0.67)	**0.91 (0.66-1.25)**	***1.87*** (1.35-2.59)	**0.47** (0.34-0.65)

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 10: Percentage (95%CI) of Adults (18 to 60 years) and Elderly (>60 years) with Seroconversiona after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)			**Elderly (>60 years)**	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=126	**N=120**	**N=122**	**N=117**	**N=117**
Day 22 (from Day 1)	**64%** (55-73%)	**88%** (81-93%)	**70%** (61-78%)	26% (18-35%)	**43%** (34-52%)
Day 43 (from Day 1)	**77%** (69-84%)	**95%** (89-98%)	**78%** (69-85%)	**43%** (34-52%)	**62%** (53-71%)
Prior to Booster	**N=104**	**N=112**	**N=105**	**N=104**	**N=107**
Day 366 (from Day 1)	46% (36-56%)	65% (56-74%)	53% (43-63%)	9% (4-16%)	28% (20-38%)
After Booster	**aH1N1 N=92**	**aH1N1 N=95**	**aH1N1 N=88**	**aH1N1 N=92**	**aH1N1 N=97**
Day 387 (from Day 1)	91% (84-96%)	98% (93-100%)	92% (84-97%)	78% (68-86%)	84% (75-90%)
Day 387 (from Day 366)	**65%** (55-75%)	**59%** (48-69%)	**53%** (42-64%)	**70%** (59-79%)	**64%** (54-73%)
	Pooled Groups (A, B, C) Booster: aTIV **(2010/2011)**			**Pooled Groups (A, B) Booster:** aTIV **(2010/2011)**	
	N=275			**N=189**	
Day 387 (from Day 1)	94% (90-96%)			81% (75-86%)	
Day 387 (from Day 366)	**59%** (53-65%)			**67%** (59-73%)	

Bold percentage of subjects with seroconversion = CHMP criterion met.
[a]Seroconversion defined as: HI ≥ 1:40 for subjects negative at baseline (< 1:10) or a minimum 4-fold increase in HI titer for subjects positive at baseline (HI ≥ 1:10)

Table 11: Pairwise Comparisons of Percentage (95%CI) of Adults (18 to 60 years) and Elderly (>60 years) with Seroconversion[a] on Days 22 and 43 – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)			Elderly (>60 years)
	Comparisons of Group:			Comparisons of Group:
	3.75_halfMF59 to 7.5_fullMF59	3.75_halfMF59 to 15_noMF59	7.5_fullMF59 to 15_ noMF59	3.75_halfMF59 to 7.5_fullMF59
Day 22 (from Day 1)	**-24%** (-34% - -14%)	-5% (-17% - 6%)	***19%*** (9% - 29%)	**-17%** (-29% - -5%)
Day 43 (from Day 1)	**-18%** (-26% - -10%)	-1% (-11% - 10%)	***17%*** (9% - 25%)	**-20%** (-32% - -7%)

[a]Seroconversion defines as: HI ≥ 1:40 for subjects negative at baseline (< 1:10) or a minimum 4-fold increase in HI titer for subjects positive at baseline (HI ≥ 1:10).
Bold % difference with negative value = the second vaccine group, of the respective pair being compared, is **statistically superior** to the first vaccine group (95% CI completely below 0).
Bold Italic % difference with positive value = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 0).

Table 12: Percentage (95%CI) of Adults (18 to 60 years) and Elderly (>60 years) with Seroprotection after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=126	**N=120**	**N=122**	**N=117**	**N=117**
Day 1	22% (15-30%)	18% (11-25%)	27% (19-36%)	26% (19-35%)	24% (17-33%)
Day 22	**75%** (67-83%)	**96%** (91-99%)	**84%** (77-90%)	57% (48-66%)	**73%** (64-80%)
Day 43	**93%** (87-97%)	**100%** (97-100%)	**89%** (82-94%)	**74%** (65-81%)	**88%** (81-93%)
Prior to Booster	**N=104**	**N=112**	**N=105**	**N=104**	**N=107**
Day 366	61% (51-70%)	87% (79-92%)	70% (61-79%)	37% (27-47%)	54% (44-64%)
After Booster	**aTIV N=92**	**aTIV N=95**	**aTIV N=88**	**aTIV N=92**	**aTIV N=97**
Day 387	**98%** (92-100%)	**100%** (96-100%)	**95%** (89-99%)	**95%** (88-98%)	**99%** (94-100%)
	Pooled Groups (A, B, C) Booster: aTIV (2010/2011)			**Pooled Groups (A, B) Booster: aTIV (2010/2011)**	
	N=275			**N=189**	
Day 387	**98%** (95-99%)			**97%** (93-99%)	

A=3.75_half MF59; **B**=7.5_full MF59; **C**=15_no MF59
Bold percentage of subjects with HI titer ≥ 1:40= CHMP criterion met.

Table 13: Pairwise Comparisons of Percentage (95%CI) of Adults (18 to 60 years) and Elderly (>60 years) with Seroprotection on Days 22 and 43 – PPS, HI Assay, A/H1N1/California/7/2009 Strain

	Adults (18 to 60 years)			Elderly (>60 years)
	Comparisons of Group:			Comparisons of Group:
	3.75_halfMF59 to 7.5_fullMF59	3.75_halfMF59 to 15_noMF59	7.5_fullMF59 to 15_ noMF59	3.75_halfMF59 to 7.5_fullMF59
Day 22 (from Day 1)	**-20%** (-29% - -12%)	-9% (-19% - 1%)	***11%*** (4% - 19%)	**-15%** (-27% - -3%)
Day 43 (from Day 1)	**-7%** (-12% - -3%)	4% (-4% - 11%)	***11%*** (5% - 16%)	**-15%** (-24% - -5%)

Bold % difference with negative value = the second vaccine group, of the respective pair being compared, is **statistically superior** to the first vaccine group (95% CI completely below 0).
Bold Italic % difference with positive value = the first vaccine group, of the respective pair being compared, is ***statistically superior*** to the second vaccine group (95% CI completely above 0).

Table 14: Non-inferiority Analysis of GMTs in both Adjuvanted Groups after Priming Vaccinations - Pooled Population (≥18 years), HI Assay, A/H1N1 California 2009 strain

	Pooled Adults and Elderly (≥ 18 years)		
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Comparisons of Group:**
	N=243	**N=237**	**3.75_halfMF59 to7.5_fullMF59**
GMTs Day 22	63 (51-78)	142 (115-175)	0.45 (0.34-0.59)
GMTs Day 43	101 (85-121)	213 (179-254)	0.48 (0.37-0.61)

Table 15: Overview of Adults (18-60 years) and Elderly (>60 years) with Solicited AEs after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – Safety Set

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=134	**N=134**	**N=130**	**N=124**	**N=123**
	First Priming Vaccination (A/H1N1sw)				
Any	78 (58%)	93 (69%)	67 (52%)	54 (44%)	58 (47%)
Local	57 (43%)	74 (55%)	29 (22%)	30 (24%)	35 (28%)
Systemic	55 (41%)	64 (48%)	59 (45%)	40 (32%)	41 (33%)
Other	13 (10%)	12 (9%)	10 (8%)	6 (5%)	5 (4%)
	Second Priming Vaccination (A/H1N1sw)				
	N=131	**N=131**	**N=128**	**N=123**	**N=123**
Any	60 (46%)	80 (61%)	59 (46%)	39 (32%)	52 (42%)
Local	39 (30%)	65 (50%)	30 (23%)	21 (17%)	31 (25%)
Systemic	35 (27%)	49 (37%)	42 (33%)	27 (22%)	27 (22%)
Other	16 (12%)	15 (11%)	12 (9%)	11 (9%)	12 (10%)
	Booster Vaccination (aTIV [2010/2011]), by Priming Vaccine Group				
	aTIV N=105	**aTIV N=107**	**aTIV N=102**	**aTIV N=103**	**aTIV N=108**
Any	77 (73%)	82 (77%)	75 (74%)	53 (51%)	61 (56%)
Local	72 (69%)	73 (68%)	69 (68%)	40 (39%)	49 (45%)
Systemic	47 (45%)	52 (49%)	49 (48%)	31 (30%)	36 (33%)
Other	11 (10%)	11 (10%)	10 (10%)	4 (4%)	9 (8%)
	Booster Vaccination (aTIV [2010/2011]), Pooled				
	N=314			**N=211**	
Any	234 (75%)			114 (54%)	
Local	214 (68%)			89 (42%)	
Systemic	148 (47%)			67 (32%)	
Other	32 (10%)			13 (6%)	

A=3.75_half MF59; **B**=7.5_full MF59; **C**=15_no MF59

Table 16: Numbers (%) of Adults (18 to 60 years) with Solicited AEs after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – Safety Set

		First Priming Vaccination			Second Priming Vaccination			Booster Vaccination			
		Group A 3.75_ half MF59 **N=134**	**Group B** 7.5_ full MF59 **N=134**	**Group C** 15_ no MF59 **N=130**	**Group A** 3.75_ half MF59 **N=131**	**Group B** 7.5_ full MF59 **N=131**	**Group C** 15_ no MF59 **N=128**	3.75_ half MF59 **aTIV N=105**	7.5_ full MF59 **aTIV N=107**	15_ no MF59 **aTIV N=102**	**Pooled aTIV N=314**
Local Reactions	Ecchymosis	6 (4%)	8 (6%)	7 (5%)	4 (3%)	1 (1%)	2 (2%)	3 (3%)	4 (4%)	3 (3%)	10 (3%)
	>100mm	0	0	0	0	0	0	0	0	0	0
	Erythema	17 (13%)	13 (10%)	10 (8%)	13 (10%)	11 (8%)	10 (8%)	20 (19%)	18 (17%)	13 (13%)	51 (16%)
	>100mm	0	0	0	0	0	0	1 (1%)	0	0	1 (<1%)
	Induration	12 (9%)	17 (13%)	3 (2%)	7 (5%)	15 (11%)	4 (3%)	25 (24%)	19 (18%)	16 (16%)	60 (19%)
	>100mm	0	0	0	0	0	0	1 (1%)	0	0	1 (<1%)
	Swelling	6 (4%)	11 (8%)	8 (6%)	4 (3%)	12 (9%)	4 (3%)	21 (20%)	16 (15%)	12 (12%)	49 (16%)
	>100mm	0	0	0	0	0	0	0	0	0	0
	Pain	45 (34%)	64 (48%)	21 (16%)	31 (24%)	57 (44%)	23 (18%)	70 (67%)	68 (64%)	68 (67%)	206 (66%)
	Severe	0	0	0	0	0	0	4 (4%)	3 (3%)	1 (1%)	8 (3%)
Systemic Reactions	Chills	3 (2%)	1 (1%)	1 (1%)	4 (3%)	8 (6%)	2 (2%)	5 (5%)	5 (5%)	9 (9%)	19 (6%)
	Severe	1 (1%)	0	0	0	0	0	1 (1%)	1 (1%)	0	2 (1%)
	Malaise	13 (10%)	13 (10%)	13 (10%)	8 (6%)	15 (11%)	6 (5%)	17 (16%)	12 (11%)	12 (12%)	41 (13%)
	Severe	2 (1%)	0	1 (1%)	0	1 (1%)	1 (1%)	1 (1%)	3 (3%)	2 (2%)	6 (2%)
	Myalgia	23 (17%)	26 (19%)	10 (8%)	13 (10%)	16 (12%)	8 (6%)	28 (27%)	26 (24%)	29 (28%)	83 (26%)
	Severe	0	0	0	0	0	0	3 (3%)	1 (1%)	1 (1%)	5 (2%)
	Arthralgia	9 (7%)	9 (7%)	3 (2%)	4 (3%)	12 (9%)	5 (4%)	13 (12%)	11 (10%)	11 (11%)	35 (11%)
	Severe	0	0	0	1 (1%)	0	0	2 (2%)	2 (2%)	2 (2%)	6 (2%)
	Headache	32 (24%)	29 (22%)	30 (23%)	22 (17%)	28 (21%)	28 (22%)	30 (29%)	22 (21%)	24 (24%)	76 (24%)
	Severe	3 (2%)	1 (1%)	3 (2%)	3 (2%)	5 (4%)	3 (2%)	2 (2%)	3 (3%)	2 (2%)	7 (2%)
	Sweating	12 (9%)	13 (10%)	12 (9%)	5 (4%)	9 (7%)	5 (4%)	4 (4%)	13 (12%)	11 (11%)	28 (9%)
	Severe	1 (1%)	1 (1%)	0	0	2 (2%)	0	0	2 (2%)	0	2 (1%)
	Fatigue	27 (20%)	27 (20%)	43 (33%)	13 (10%)	29 (22%)	18 (14%)	28 (27%)	25 (23%)	27 (26%)	80 (25%)
	Severe	2 (1%)	1 (1%)	2 (2%)	1 (1%)	1 (1%)	0	3 (3%)	2 (2%)	1 (1%)	6 (2%)
	Nausea	4 (3%)	6 (4%)	6 (5%)	2 (2%)	6 (5%)	4 (3%)	6 (6%)	5 (5%)	9 (9%)	20 (6%)
	Severe	1 (1%)	0	1 (1%)	0	0	0	0	2 (2%)	1 (1%)	3 (1%)
Other	Fever (≥38°C)	1 (1%)	1 (1%)	0	1 (1%)	3 (2%)	0	1 (1%)	3 (3%)	1 (1%)	5 (2%)
	≥40°C	0	0	0	0	0	0	0	0	0	0
	Stayed home	1 (1%)	0	1 (1%)	1 (1%)	4 (3%)	2 (2%)	1 (1%)	3 (3%)	3 (3%)	7 (2%)
	Analg/antipyr	12 (9%)	12 (9%)	9 (7%)	15 (11%)	15 (11%)	11 (9%)	10 (10%)	10 (9%)	9 (9%)	29 (9%)

Table 17: Numbers (%) of Elderly (>60 years) with Solicited AEs after Priming and Booster Vaccinations, by Priming Vaccine Groups and Pooled – Safety Set

		First Priming Vaccination		Second Priming Vaccination		Booster Vaccination		
		Group A 3.75_halfMF59 **N=124**	**Group B** 7.5_fullMF59 **N=123**	**Group A** 3.75_halfMF59 **N=123**	**Group B** 7.5_fullMF59 **N=123**	3.75_halfMF59 **aTIV N=103**	7.5_fullMF59 **aTIV N=108**	Pooled **aTIV N=211**
Local Reactions	Ecchymosis	8 (6%)	3 (2%)	2 (2%)	4 (3%)	4 (4%)	3 (3%)	7 (3%)
	>100mm	0	0	0	0	0	0	0
	Erythema	13 (10%)	12 (10%)	7 (6%)	14 (11%)	16 (16%)	13 (12%)	29 (14%)
	>100mm	0	0	0	0	0	0	0
	Induration	3 (2%)	7 (6%)	4 (3%)	5 (4%)	11 (11%)	12 (11%)	23 (11%)
	>100mm	0	0	0	0	0	0	0
	Swelling	3 (2%)	7 (6%)	1 (1%)	6 (5%)	6 (6%)	7 (6%)	13 (6%)
	>100mm	0	0	0	0	0	0	0
	Pain	12 (10%)	23 (19%)	13 (11%)	17 (14%)	27 (26%)	40 (37%)	67 (32%)
	Severe	0	0	0	0	0	2 (2%)	2 (1%)
Systemic Reactions	Chills	3 (2%)	3 (2%)	1 (1%)	2 (2%)	3 (3%)	2 (2%)	5 (2%)
	Severe	0	0	0	0	0	0	0
	Malaise	9 (7%)	11 (9%)	8 (7%)	7 (6%)	7 (7%)	1 (1%)	8 (4%)
	Severe	1 (1%)	1 (1%)	1 (1%)	0	0	0	0
	Myalgia	13 (10%)	11 (9%)	7 (6%)	7 (6%)	13 (13%)	17 (16%)	30 (14%)
	Severe	0	0	0	0	0	0	0
	Arthralgia	7 (6%)	6 (5%)	7 (6%)	5 (4%)	13 (13%)	8 (7%)	21 (10%)
	Severe	0	0	0	1 (1%)	0	0	0
	Headache	17 (14%)	15 (12%)	16 (13%)	13 (11%)	16 (16%)	13 (12%)	29 (14%)
	Severe	0	1 (1%)	0	1 (1%)	1 (1%)	1 (1%)	2 (1%)
	Sweating	13 (10%)	14 (11%)	7 (6%)	6 (5%)	9 (9%)	10 (9%)	19 (9%)
	Severe	2 (2%)	1 (1%)	1 (1%)	1 (1%)	0	1 (1%)	1 (<1%)
	Fatigue	24 (19%)	20 (16%)	15 (12%)	11 (9%)	17 (17%)	16 (15%)	33 (16%)
	Severe	2 (2%)	1 (1%)	1 (1%)	2 (2%)	0	1 (1%)	1 (<1%)
	Nausea	6 (5%)	1 (1%)	4 (3%)	2 (2%)	1 (1%)	3 (3%)	4 (2%)
	Severe	0	0	0	0	0	0	0
Other	Fever (≥38°C)	0	0	1 (1%)	0	0	1 (1%)	1 (<1%)
	≥40°C	0	0	0	0	0	0	0
	Stayed home	2 (2%)	1 (1%)	2 (2%)	2 (2%)	1 (1%)	1 (1%)	2 (1%)
	Analg/antipyr	4 (3%)	4 (3%)	10 (8%)	11 (9%)	4 (4%)	8 (7%)	12 (6%)

Table 18: Overview of Unsolicited AEs in Adults (18-60 years) and Elderly (>60 years) after Priming Vaccinations, by Safety Monitoring Period – Safety Set

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59	**Group A** 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=134	**N=134**	**N=130**	**N=124**	**N=123**
Priming Vaccinations, Day 1–43					
AEs: all	53 (40%)	51 (38%)	52 (40%)	39 (31%)	44 (36%)
related (poss./prob.)	24 (18%)	29 (22%)	24 (18%)	23 (19%)	16 (13%)
SAEs: all	0	1 (1%)	0	1 (1%)	2 (2%)
related (poss./prob.)	0	0	0	0	0
AEs leading to premature withdrawal	1 (1%)	0	0	0	0
related (poss./prob.)	1 (1%)	0	0	0	0
New onset of chronic diseases	1 (1%)	3 (2%)	2 (2%)	1 (1%)	1 (1%)
related (poss./prob.)	0	1 (1%)0	1 (1%)	0	0
Priming Vaccinations, Day 43–366					
SAEs: all	3 (2%)	4 (3%)	4 (3%)	9 (7%)	13 (11%)
related (poss./prob.)	0	0	0	0	0
AEs leading to premature withdrawal	0	4 (3%)	2 (2%)	2 (2%)	3 (2%)
related (poss./prob.)	0	0	2 (2%)	0	0
New onset of chronic diseases	1 (1%)	4 (3%)	2 (2%)	3 (2%)	2 (2%)
related (poss./prob.)	0	0	1 (1%)	0	0
Death	0	0	0	0	2 (2%)
related (poss./prob.)	0	0	0	0	0

Table 19: Overview of Unsolicited AEs in Adults (18-60 years) and Elderly (>60 years) after Booster Vaccinations, by Priming Vaccine Groups and Safety Monitoring Period – Safety Set

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**	**Group C** 15_noMF59 **aTIV**	**Group A** 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**
	N=105	**N=107**	**N=102**	**N=103**	**N=108**
Booster Vaccination by priming vaccine group, Day 366–387					
AEs: all	15 (14%)	19 (18%)	21 (21%)	18 (17%)	21 (19%)
related (poss./prob.)	9 (9%)	8 (7%)	9 (9%)	12 (12%)	9 (8%)
SAEs: all	0	0	0	1 (1%)	0
related (poss./prob.)	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0	0
related (poss./prob.)	0	0	0	0	0
New onset of chronic diseases	0	0	1 (1%)	1 (1%)	1 (1%)
related (poss./prob.)	0	0	0	1 (1%)	0
Booster Vaccination by priming vaccine group, Day 387–546					
SAEs: all	3 (3%)	0	1 (1%)	5 (5%)	4 (4%)
related (poss./prob.)	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0	0
related (poss./prob.)	0	0	0	0	0
New onset of chronic diseases	1 (1%)	1 (1%)	0	0	1 (1%)
related (poss./prob.)	0	0	0	0	0

Table 20: Overview of Unsolicited AEs in Adults (18-60 years) and Elderly (>60 years) after Booster Vaccinations, Pooled, by Safety Monitoring Period – Safety Set

	Adults (18 to 60 years)			Elderly (>60 years)	
	Group A 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**	**Group C** 15_noMF59 **aTIV**	**Group A** 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**
	N=105	**N=107**	**N=102**	**N=103**	**N=108**
		N=314		**N=211**	
Booster Vaccination, pooled, Day 366–387					
AEs: all		55 (18%)		39 (18%)	
related (poss./prob.)		26 (8%)		21 (10%)	
SAEs: all		0		1 (1%)	
related (poss./prob.)		0		0	
AEs leading to premature withdrawal		0		0	
related (poss./prob.)		0		0	
New onset of chronic diseases		1 (<1%)		2 (1%)	
related (poss./prob.)		0		1 (<1%)	
Booster Vaccination, pooled, Day 387–546					
SAEs: all		4 (1%)		9 (4%)	
related (poss./prob.)		0		0	
AEs leading to premature withdrawal		0		0	
related (poss./prob.)		0		0	
New onset of chronic diseases		2 (<1%)		1 (<1%)	
related (poss./prob.)		0		0	

Table 21: Serious Adverse events by Preferred Term sorted by System Organ Class-From Day 1 to Day 366, Age Group: Adults 18-60 Yrs

	Number(%) of Subjects		
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_noMF59
	N=134	**N=134**	**N=130**
Any Serious Adverse Event	3 (2%)	5 (4%)	4 (3%)
Cardiac Disorders			
Atrial Fibrillation	1 (1%)	0	0
Myocarditis	0	1 (1%)	0
Congen. & Famil./Genetic Disorders			
Hip Dysplasia	0	0	1 (1%)
Gastrointestinal Disorders			
Gastritis	0	1 (1%)	0
Immune System Disorders			
Anaphylactic Reaction	0	1 (1%)	0
Infections & Infestations			
Appendicitis	0	0	1 (1%)
Diverticulitis	1 (1%)	0	0
Injury & Poisoning			
Ankle Fracture	0	0	1 (1%)
Musculo, Connect. Tis. & Bone Dis.			
Intervertebral Disc Protrusion	1 (1%)	0	1 (1%)
Neo. Ben./Malig.(Inc. Cysts/Polyps)			
Breast Cancer	0	1 (1%)	0
Renal & Urinary Disorders			
Renal Colic	0	1 (1%)	0

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 22: Serious Adverse events by Preferred Term sorted by System Organ Class-From Day 1 to Day 366, Age Group: Elderly >= 61 Yrs

	Number(%) of Subjects	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=124	**N=123**
Any Serious Adverse Event	10 (8%)	15 (12%)
Cardiac Disorders		
Cardiac Arrest	0	1 (1%)
Cardiac Tamponade	0	1 (1%)
Supraventricular Tachyarrhythmia	0	1 (1%)
Gastrointestinal Disorders		
Haemorrhoids	0	1 (1%)
Inguinal Hernia	1 (1%)	0
Infections & Infestations		
Osteomyelitis	1 (1%)	0
Sinusitis Fungal	0	1 (1%)
Urinary Tract Infection	0	1 (1%)
Wound Infection	1 (1%)	0
Injury & Poisoning		
Clavicle Fracture	0	1 (1%)
Meniscus Lesion	0	1 (1%)
Tendon Rupture	0	1 (1%)
Tibia Fracture	1 (1%)	0
Upper Limb Fracture	1 (1%)	1 (1%)
Metabolism & Nutrition Disorders		
Diabetes Mellitus	0	1 (1%)
Hyperglycaemia	0	1 (1%)
Musculo., Connect. Tis. & Bone Dis.		
Bursitis	0	1 (1%)
Osteoarthritis	2 (2%)	2 (2%)

	Number(%) of Subjects	
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59
	N=124	**N=123**
Rotator Cuff Syndrome	0	1 (1%)
Neo. Ben./Malig.(Inc. Cysts/Polyps)		
Gastric Cancer	0	1 (1%)
Prostate Cancer	1 (1%)	0
Prostate Cancer Stage 0	0	1 (1%)
Nervous System Disorders		
Cerebrovascular Accident	1 (1%)	0
Reproduct. Sys. & Breast Disorders		
Benign Prostatic Hyperplasia	0	1 (1%)
Uterine Prolapse	1 (1%)	0
Resp., Thoracic & Mediastinal Dis.		
Pulmonary Embolism	0	1 (1%)
Surgical & Medical Procedures		
Cataract Operation	1 (1%)	0
Hip Arthroplasty	0	1 (1%)
Vascular Disorders		
Hypertensive Crisis	1 (1%)	0

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 23: Serious Adverse events by Preferred Term sorted by System Organ Class-From Day 366 to Day 546, Age Group: Adults 18-60 Yrs

	Number (%) of Subjects			
	Group A 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**	**Group C** 15_noMF59 **aTIV**	**Pooled aTIV**
	N=105	**N=107**	**N=102**	**N=314**
Any Serious Adverse Event	3 (3%)	0	1 (1%)	4 (1%)
Gastrointestinal Disorders				
Anal Fissure	1 (1%)	0	0	1 (<1%)
Hepato-Biliary Disorders				
Cholelithiasis	1 (1%)	0	0	1 (<1%)
Musculo., Connect. Tis. & Bone Dis.				
Pathological Fracture	1 (1%)	0	0	1 (<1%)
Neo. Ben./Malig.(Inc. Cysts/Polyps)				
Lung Cancer Metastatic	1 (1%)	0	0	1 (<1%)
Lung Neoplasm Malignant	1 (1%)	0	0	1 (<1%)
Surgical & Medical Procedures				
Foot Operation	0	0	1 (1%)	1 (<1%)

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 24-: Serious Adverse events by Preferred Term sorted by System Organ Class-From Day 366 to Day 546, Age Group: Elderly >= 61 Yrs

	Number(%) of Subjects		
	Group A 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**	**Pooled aTIV**
	N=103	**N=108**	**N=211**
Any Serious Adverse Event	6 (6%)	4 (4%)	10 (5%)
Eye Disorders			
Eye Disorder	1 (1%)	0	1 (<1%)
Eyelid Ptosis	1 (1%)	0	1 (<1%)
Scotoma	1 (1%)	0	1 (<1%)
Infections & Infestations			
Bronchitis	0	1 (1%)	1 (<1%)
Neo. Ben./Malig.(Inc. Cysts/Polyps)			
Colon Cancer	0	1 (1%)	1 (<1%)
Metastatic Uterine Cancer	1 (1%)	0	1 (<1%)
Pancreatic Carcinoma	1 (1%)	0	1 (<1%)
Renal & Urinary Disorders			
Calculus Bladder	1 (1%)	0	1 (<1%)
Surgical & Medical Procedures			
Hip Arthroplasty	0	1 (1%)	1 (<1%)
Knee Operation	0	1 (1%)	1 (<1%)

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 25: 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 Yrs

	Number(%) of Subjects		
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_no MF59
	N=134	**N=134**	**N=130**
Any Adverse Event	53 (40%)	51 (38%)	52 (40%)
Infections & Infestations			
Nasopharyngitis	9 (7%)	11 (8%)	10 (8%)
Rhinitis	8 (6%)	3 (2%)	4 (3%)
Nervous System Disorders			
Headache	10 (7%)	9 (7%)	5 (4%)
Resp., Thoracic & Mediastinal Dis			
Oropharyngeal Pain	9 (7%)	3 (2%)	5 (4%)

Vaccinatio group X ug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 26: 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 Yrs

	Number(%) of Subjects		
	Group A 3.75_halfMF59	**Group B** 7.5_fullMF59	**Group C** 15_no MF59
	N=124	**N=123**	**N=0**
Any Adverse Event	39 (31%)	44 (36%)	0
Gen. Disorders & Admin. Site Cond.			
Fatigue	7 (6%)	5 (4%)	0

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 27: 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 Yrs

	Number(%) of Subjects			
	Group A 3.75_halfMF59 **aTIV**	**Group B** 7.5_fullMF59 **aTIV**	**Group A** 15_noMF59 **aTIV**	**Pooled aTIV**
	N=105	**N=107**	**N=102**	**N=314**
Any Adverse Event	15 (14%)	19 (18%)	21 (21%)	55 (18%)
Infections & Infestations				
Nasopharyngitis	5 (5%)	6 (6%)	4 (4%)	15 (5%)

Vaccination group Xug_Y contains X ug A/H1N1 antigen and an MF59 dose level of Y%

Table 28: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class-From Day 366 to Day 387, Age Group: Elderly >= 61 Yrs

None Reported

Conclusion:

This was a pivotal dose-ranging study designed to evaluate safety, tolerability and immunogenicity of 3 different formulations of the aH1N1 vaccine with and without MF59 adjuvant in a population of healthy adults (18 to 60 years) and of two different formulations of aH1N1 vaccine with MF59 adjuvant in a population of healthy elderly (>60 years).

- Overall, all vaccine formulations had a very good long term safety profile.
- Immunogenicity results after both priming (primary immune response) and booster vaccinations (boostability, secondary immune response), indicated that the adjuvant MF59 permits a reduction of the antigen content (15µg in the seasonal vaccine aTIV) in this aH1N1 vaccine by one half (7.5µg) or even by one quarter (3.75µg) 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 boost ability, the strength of the booster/secondary immunogenicity observed in elderly matched or exceeded the one observed in the adult subjects.

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