Safety and Immunogenicity of Two Doses of a Tetravalent Influenza Vaccine in Adults Aged 18 Years and Above

This study has been completed.

Sponsor:	Novartis Vaccines
Collaborators:	
Information provided by (Responsible Party):	Novartis (Novartis Vaccines)
ClinicalTrials.gov Identifier:	NCT00620815

Purpose

Evaluate the immune response and reactogenicity of H5N1 vaccination in adults aged 18 years and above (as part of a tetravalent vaccine)

Condition	Intervention	Phase
Influenza	Biological/Vaccine: MF59-eTIV-H5N1+ placebo /pandemic influenza vaccine Biological/Vaccine: Pandemic influenza vaccine + placebo /MF59-eTIV-H5N1 Biological/Vaccine: Pandemic influenza vaccine + seasonal influenza vaccine / pandemic influenza vaccine Biological/Vaccine: Pandemic influenza vaccine + placebo / MF59-eTIV-H5N1 Biological/Vaccine: Pandemic influenza vaccine + seasonal influenza vaccine / pandemic influenza vaccine Biological/Vaccine: MF59-eTIV-H5N1 + Placebo/pandemic influenza vaccine	Phase 2

Study Type: Interventional
Study Design: Prevention, Parallel Assignment, Single Blind (Investigator), Randomized, Safety/Efficacy Study
Official Title: A Phase II, Randomized, Placebo-controlled, Observer-blind, Multi Center Study on the Safety and Immunogenicity of Novartis Tetravalent Influenza Vaccine (Containing Both Interpandemic Strains and H5N1) in Adults Aged 18 Years and Above

Further study details as provided by Novartis (Novartis Vaccines):

Primary Outcome Measure:

- To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43. [Time Frame: up to day 43] [Designated as safety issue: No]
  The antibody response was determined by SRH assay. Geometric mean areas (GMAs) and geometric mean ratios (GMRs) in the SRH assay were used to demonstrate the equivalence. The statistical analysis was done based on the GMRs.

Secondary Outcome Measures:

- Number of Subjects (Subjects ≤ 60 Years) With Reported Local Reactions After First Vaccination [Time Frame: Up to 7 days after 1st vaccination] [Designated as safety issue: Yes]
  Local reactions were collected up to 7 days after 1st vaccinations. All subjects were instructed to complete a diary card to record local reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization. The table represents local reactions after first vaccination in each arm differently.
- Number of Subjects (Subjects ≤60 Years) With Reported Local Reactions After Second Vaccination [Time Frame: Up to 7 days after 2nd vaccination] [Designated as safety issue: Yes]
  Local reactions were collected up to 7 days after 1st vaccinations. All subjects were instructed to complete a diary card to record local reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization.
- Number of Subjects (Subjects ≤ 60 Years) With Reported Systemic Reactions After 1st and 2nd Vaccinations. [Time Frame: 7 days after 1st and 2nd vaccinations each] [Designated as safety issue: Yes]
  Systemic reactions were collected upto 7 days after 1st and 2nd vaccinations. All subjects were instructed to complete a diary card to record systemic reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization.
- Percentages of Subjects Achieving Seroconversion/Significant Increase in Antibody Titre/ Area as Measured by SRH and (HI) and at Least 4 Fold Rise in Titres by MN Assay-H5N1 Strain [Time Frame: up to day 43] [Designated as safety issue: No]
  Measurement of immunogenicity in terms of significant increase in antibody titer and Seroconversion. Significant increase in antibody titer is defined as at least a four-fold increase from non-negative pre-vaccination serum (≥ 10) for HI or a 50% increase in area for SRH. Seroconversion is defined as negative pre-vaccination serum / post-vaccination titer ≥40 for HI (area ≥25 mm2 for SRH)
- Percentages of Subjects Achieving HI/MN ≥ 1:40 and SRH Area ≥ 25^mm2 [Time Frame: Up to 43 days] [Designated as safety issue: No]
  Measurement of immunogenicity in terms of percentage of subjects achieving a titre ≥ 40/area ≥ 25mm^2 after immunization as determined by HI (Haemagglutination Inhibition), MN(Microneutralization) and SRH assay.
- Antibody Response Determined by HI and MN Assay. [Time Frame: Up to 43 days] [Designated as safety issue: No]
  Measurement of immunogenicity in terms of Geometric mean titers (GMTs) as determined by HI and MN assay.
- Percentages of B-cell Antibodies Against H5N1 and H1N1 After Each Vaccination. [Time Frame: Three weeks after first vaccination (day 22) and three weeks after second vaccination (day 43)] [Designated as safety issue: No]
  The Cell Mediated Immunity (CMI) response was evaluated in a randomly selected subgroup of approximately 92 subjects from all the vaccine groups out of a total of 601 enrolled subjects. Frequency of circulating memory B cells (MBC), capable of differentiating in vitro into cell secreting IgG (Immunoglobulin G) antibodies specific for H5N1 (the subunit from A/Vietnam/1194/2004) or for H1N1 (the subunit from A/Solomon Island/3/2006) were determined by an ELISA-coupled limiting dilution assay.The frequency of H5N1-IgG MBC and H1N1-IgG MBC was expressed as percentages (%) of total IgG producing MBC
- Mean T-Cells Per Million Total Cells (95% CI) in Response to H5 Peptides and H5N1 Subunit [Time Frame: Three weeks after 1st vaccination (day 22) and three weeks after 2nd vaccination (day 43)] [Designated as safety issue: No]

Frequency and functionality of vaccine antigen-specific CD4+ T cells was assessed in peripheral blood (PBMC) taken at days 1, 22 and 43 after in vitro stimulation with: Library of 70 peptides spanning the whole H5 A/Vietnam/1194/2004 protein (H5 pool of 70 Vietnam) H5N1 subunit from A/ Vietnam/1194/2004 (H5N1 Vietnam) H3N2 subunit from A/ Wisconsin/67/2005 (H3N2 Wisconsin) H1N1 subunit from A/Solomon Islands/3/2006 (H1N1 Solomon Islands) Polyclonal stimulus agonistic aCD3 mAb (aCD3) The change in frequency of T-cells was measured.

Enrollment: 601
Study Start Date: November 2007
Primary Completion Date: January 2008
Study Completion Date: December 2008

Arms	Assigned Interventions
Experimental: T/P-A One dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Aflunov (A) on day 22	Biological/Vaccine: MF59-eTIV-H5N1+ placebo /pandemic influenza vaccine Tetravalent influenza vaccine (MF59-eTIV-H5N1)and placebo on day 1 followed 3-5 weeks later by pandemic influenza vaccine, including serology blood draw at V1+V3.
Experimental: A/P-T One dose of the Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Tetravalent influenza vaccine (T) on day 22.	Biological/Vaccine: Pandemic influenza vaccine + placebo /MF59-eTIV-H5N1 Pandemic influenza vaccine plus placebo on day 1 followed 3-5 weeks later by tetravalent influenza vaccine (MF59-eTIV-H5N1), including serology blood draw at V1+V3.
Active Comparator: A/S-A One dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed Aflunov (A) on day 22.	Biological/Vaccine: Pandemic influenza vaccine + seasonal influenza vaccine /pandemic influenza vaccine Pandemic influenza vaccine plus seasonal influenza vaccine, 3-5 weeks later pandemic influenza vaccine , including serology blood draw at V1+V3.
Experimental: T/P-A (V2 blood draw) One dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by a blood draw at visit 2 (V2) prior to Aflunov (A) vaccination on day 22.	Biological/Vaccine: MF59-eTIV-H5N1 + Placebo/ pandemic influenza vaccine Tetravalent influenza vaccine (MF59-eTIV-H5N1)plus placebo followed 3-5 weeks later by pandemic influenza vaccine, including serology blood draw at V1, V2 and V3.
Experimental: A/P-T (V2 blood draw) One dose of the Aflunov(A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by additional blood draw at visit 2 (V2) prior to the Tetravalent influenza vaccination (T) on day 22.	Biological/Vaccine: Pandemic influenza vaccine + placebo / MF59-eTIV-H5N1 Pandemic influenza vaccine plus placebo followed 3-5 weeks later by tetravalent influenza vaccine (MF59-eTIV-H5N1), including serology blood draw at V1, V2 and V3.

Arms	Assigned Interventions
Active Comparator: A/S-A (V2 blood draw) One dose of Aflunov (A)and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed by an additional blood draw at visit 2 (V2) prior to Aflunov (A) vaccination on day 22.	Biological/Vaccine: Pandemic influenza vaccine + seasonal influenza vaccine / pandemic influenza vaccine Pandemic influenza vaccine plus seasonal influenza vaccine followed 3-5 weeks later by pandemic influenza vaccine, including serology blood draw at V1, V2 and V3.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Criteria

Inclusion Criteria:

- Healthy subjects (aged 18 years and above) who have signed an informed consent form

Exclusion Criteria:

- Any acute or chronic illness
- Receipt of seasonal influenza vaccine for the current season 2007/2008
- Known or suspected impairment/alteration of immune function
- Receipt of another vaccine within 3 weeks prior to Visit 1 or planned vaccination within 3 weeks following the last study vaccination
- Any serious disease
- Hypersensitivity to eggs, chicken protein, chicken feathers, influenza viral protein,neomycin or kanamycin or any other component of the study vaccine
- Receipt of blood, blood products or immunoglobulins 3 months prior to vaccination

Contacts and Locations

Locations
Germany
ATRIUM Gesundheitszentrum;
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Investigators
Study Chair: Novartis Vaccines and Diagnostics Novartis

More Information

Study Results

Participant Flow

Recruitment Details	Participants were enrolled at 2 sites in Germany
Pre-Assignment Details	All subjects were included in the trial. The data entered is for the overall study.

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Overall Study

	T/P-A	A/P-T	A/S-A
Started	199	203	199
Completed	195	192	192
Not Completed	4	11	7
Adverse Event	1	1	2
Withdrawal by Subject	1	2	0
Lost to Follow-up	1	6	3
Inappropriate enrolment	0	0	1
Protocol Violation	1	2	1

Baseline Characteristics

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal(S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Baseline Measures

	T/P-A	A/P-T	A/S-A	Total
Number of Participants	199	203	199	601
Age, Customized [1] [units: participants]				
≤60 years	196	202	198	596
≥ 61 Years	3	1	0	4
Gender, Customized [2] [units: participants]				
Female (≤60 years of age)	126	129	114	369
Male (≤60 years of age)	70	73	84	227
Female (≥61 years of age)	1	1	0	2
Male (≥61 years of age)	2	0	0	2

[1] A total of 601 subjects were enrolled and randomized, 199 to the T/P-A group, 203 to the A/P-T group and 199 to the A/S-A group. One subject in the A/S-A group did not meet entry criteria and so did not receive any vaccination.

[2] Analysis was done on Full Analysis Set

Outcome Measures

1. Primary Outcome Measure:

Measure Title	To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.
Measure Description	The antibody response was determined by SRH assay. Geometric mean areas (GMAs) and geometric mean ratios (GMRs) in the SRH assay were used to demonstrate the equivalence. The statistical analysis was done based on the GMRs.
Time Frame	up to day 43
Safety Issue?	No

Analysis Population Description

The analysis was done on Per Protocol Set (PPS)

Reporting Groups

	Description
T/P-A	One dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Aflunov (A) on day 22
A/P-T	One dose of the Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Tetravalent influenza vaccine (T) on day 22
A/S-A	One dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed Aflunov (A) on day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	194	202	198
To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43. [units: Area (mm^2)] Geometric Mean (95% Confidence Interval)			
Day 1	4.64 (4.17 to 5.17)	4.10 (3.69 to 4.56)	4.61 (4.14 to 5.13)
Day 22 (N= 31, 31, 30)	14 (10 to 19)	12 (8.51 to 16)	16 (12 to 23)
Day 43 (N=181, 189, 189)	41 (36 to 47)	35 (31 to 40)	39 (34 to 44)

Statistical Analysis 1 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/P-T
	Comments	(On day 1) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.
Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Group Mean Ratio]
	Estimated Value	1.13
	Confidence Interval	(2-Sided) 96.67% 1.02 to 1.25
	Estimation Comments	[Not specified]

Statistical Analysis 2 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/S-A
	Comments	(On day 1) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.
Statistical Test of Hypothesis	P-Value	

	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	1.01
	Confidence Interval	(2-Sided) 96.67% 0.91 to 1.12
	Estimation Comments	[Not specified]

Statistical Analysis 3 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	A/P-T, A/S-A
	Comments	(On day 1)Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.

Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratio]
	Estimated Value	0.89
	Confidence Interval	(2-Sided) 96.67% 0.80 to 0.99
	Estimation Comments	[Not specified]

Statistical Analysis 4 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/P-T
	Comments	(On day 22) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.
Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	1.19
	Confidence Interval	(2-Sided) 96.67% 0.74 to 1.93
	Estimation Comments	[Not specified]

Statistical Analysis 5 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/S-A
	Comments	(On day 22) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.
Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	0.85
	Confidence Interval	(2-Sided) 96.67% 0.52 to 1.38
	Estimation Comments	[Not specified]

Statistical Analysis 6 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	A/P-T, A/S-A
	Comments	(On day 22) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.

Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	0.71
	Confidence Interval	(2-Sided) 96.67% 0.44 to 1.15
	Estimation Comments	[Not specified]

Statistical Analysis 7 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/P-T
	Comments	(On day 43) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].

	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.

Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	1.14
	Confidence Interval	(2-Sided) 96.67% 1.01 to 1.30
	Estimation Comments	[Not specified]

Statistical Analysis 8 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	T/P-A, A/S-A
	Comments	(On day 43) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.

Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	1.05

	Confidence Interval	(2-Sided) 96.67% 0.93 to 1.19
	Estimation Comments	[Not specified]

Statistical Analysis 9 for To Demonstrate the Equivalence of Antibody Response Against A/H5N1 Strain Elicited by the Three Different Immunization Schedules on Day 43.

Statistical Analysis Overview	Comparison Groups	A/P-T, A/S-A
	Comments	(On day 43) Null hypothesis representing non-equivalence was rejected if the two-sided (1-2α)*100% CI on one GMA ratio is completely within the equivalence range [0.5, 2.0].
	Non-Inferiority or Equivalence Analysis?	Yes
	Comments	To show statistical equivalence was, confidence intervals (CIs) of all 3 pair wise ratios of the GMAs were inspected.

Statistical Test of Hypothesis	P-Value	
	Comments	P-values were not calculated for the equivalence tests due to lack of appropriate statistical software
	Method	ANOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Geometric Mean Ratios]
	Estimated Value	0.92
	Confidence Interval	(2-Sided) 96.67% 0.81 to 1.04
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Number of Subjects (Subjects ≤ 60 Years) With Reported Local Reactions After First Vaccination
Measure Description	Local reactions were collected up to 7 days after 1st vaccinations. All subjects were instructed to complete a diary card to record local reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization. The table represents local reactions after first vaccination in each arm differently.
Time Frame	Up to 7 days after 1st vaccination
Safety Issue?	Yes

Analysis Population Description

The analysis was performed on Safety Population

Reporting Groups

	Description
T/P-A: In Arm Receiving Tetravalent Vaccine (T)	Local reactions after first vaccination in arm receiving tetravalent influenza vaccine in group receiving one dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Aflunov (A) on day 22
T/P-A: In Arm Receiving Placebo (P)	Local reactions after first vaccination in arm receiving placebo in group receiving one dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Aflunov (A) on day 22
A/P-T: In Arm Receiving Aflunov (A)	Local reactions after first vaccination in arm receiving Aflunov in group receiving one dose of the Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Tetravalent influenza vaccine(T) on day 22
A/P-T: In Arm Receiving Placebo (P)	Local reactions after first vaccination in arm receiving Placebo in group receiving one dose of the Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed by Tetravalent influenza vaccine (T) on day 22
A/S-A: In Arm Receiving Aflunov (A)	Local reactions after first vaccination in arm receiving Aflunov in group receiving one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed Aflunov (A) bon day 22
A/S-A: In Arm Receiving Seasonal Influenza Vaccine (S)	Local reactions after first vaccination in arm receiving seasonal influenza vaccination in group receiving one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed Aflunov (A) on day 22

Measured Values

	T/P-A: In Arm Receiving Tetravalent Vaccine (T)	T/P-A: In Arm Receiving Placebo (P)	A/P-T: In Arm Receiving Aflunov (A)	A/P-T: In Arm Receiving Placebo (P)	A/S-A: In Arm Receiving Aflunov (A)	A/S-A: In Arm Receiving Seasonal Influenza Vaccine (S)
Number of Participants Analyzed	195	194	201	201	197	196
Number of Subjects (Subjects ≤ 60 Years) With Reported Local Reactions After First Vaccination [units: Participants]						
Erythema	10	0	5	0	6	5
Induration	22	1	5	0	9	3
Swelling	19	1	6	0	7	3

	T/P-A: In Arm Receiving Tetravalent Vaccine (T)	T/P-A: In Arm Receiving Placebo (P)	A/P-T: In Arm Receiving Aflunov (A)	A/P-T: In Arm Receiving Placebo (P)	A/S-A: In Arm Receiving Aflunov (A)	A/S-A: In Arm Receiving Seasonal Influenza Vaccine (S)
Ecchymosis	2	1	2	0	2	1
Pain	164	30	138	32	131	80

3. Secondary Outcome Measure:

Measure Title	Number of Subjects (Subjects ≤60 Years) With Reported Local Reactions After Second Vaccination
Measure Description	Local reactions were collected up to 7 days after 1st vaccinations. All subjects were instructed to complete a diary card to record local reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization.
Time Frame	Up to 7 days after 2nd vaccination
Safety Issue?	Yes

Analysis Population Description

The analysis was performed on Safety Population

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal(S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	188	192	192
Number of Subjects (Subjects ≤60 Years) With Reported Local Reactions After Second Vaccination			

	T/P-A	A/P-T	A/S-A
[units: Participants]			
Erythema (N=188,192,191)	2	7	5
Induration	7	10	7
Swelling	5	8	6
Ecchymosis	3	3	2
Pain	98	136	91

4. Secondary Outcome Measure:

Measure Title	Number of Subjects (Subjects ≤ 60 Years) With Reported Systemic Reactions After 1st and 2nd Vaccinations.
Measure Description	Systemic reactions were collected upto 7 days after 1st and 2nd vaccinations. All subjects were instructed to complete a diary card to record systemic reactions starting on the day of vaccination (after 6 hours) and for each of the 6 days following each immunization.
Time Frame	7 days after 1st and 2nd vaccinations each
Safety Issue?	Yes

Analysis Population Description

The analysis was performed on Per Protocol Safety Population

Reporting Groups

	Description
T/P-A: After 1st Vaccination	Systemic reactions after first vaccination after one dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed 3 to 5 weeks later by Aflunov (A)
A/P-T: After 1st Vaccination	Systemic reactions after first vaccination after one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed 3 to 5 weeks later by tetravalent influenza vaccine (T)
A/S-A: After 1st Vaccination	Systemic reactions after first vaccination after one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed 3 to 5 weeks later by Aflunov (A)
T/P-A: After 2nd Vaccination	Systemic reactions after second vaccination after one dose of the tetravalent influenza vaccine (T) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed 3 to 5 weeks later by Aflunov (A)
A/P-T: After 2nd Vaccination	Systemic reactions after second vaccination after one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of placebo (P) on day 1, followed 3 to 5 weeks later by tetravalent influenza vaccine (T)

	Description
A/S-A: After 2nd Vaccination	Systemic reactions after second vaccination after one dose of Aflunov (A) and concomitantly, but in a different arm, one dose of licensed seasonal vaccine (S) on day 1, followed 3 to 5 weeks later by Aflunov (A)

Measured Values

	T/P-A: After 1st Vaccination	A/P-T: After 1st Vaccination	A/S-A: After 1st Vaccination	T/P-A: After 2nd Vaccination	A/P-T: After 2nd Vaccination	A/S-A: After 2nd Vaccination
Number of Participants Analyzed	195	201	196	188	192	192
Number of Subjects (Subjects ≤ 60 Years) With Reported Systemic Reactions After 1st and 2nd Vaccinations. [units: Participants]						
Chills (N=195,201,196,187,192,192)	24	8	9	6	11	3
Malaise (N=195,201,196,187,192,192)	62	29	28	15	38	15
Myalgia (N=195,201,196,187,192,192)	68	47	42	22	53	27
Arthralgia (N=195,201,196,187,192,192)	34	14	12	6	15	6
Headache (N=195, 201, 196, 187, 192, 192)	70	52	43	33	50	27
Sweating (N=195,201,196,187,192,192)	13	16	10	6	13	7
Fatigue (N=195,201,196,187,192,192)	79	58	52	32	60	35
Nausea (N=195,201,196,187,192,192)	24	16	8	7	16	6
Coughing (N=195,201,196,187,192,192)	14	16	16	13	12	13
Fever (>= 38 C) [N=195,201,195,188,192,192]	8	1	3	2	5	0
Body Temp. (< 38C)[N=195,201,195,188,192,192]	187	200	192	186	187	192
Stayed home due to reactions	8	7	2	1	8	1
Analgesic, Antipyretic Medicines Used	27	21	15	6	16	6

5. Secondary Outcome Measure:

Measure Title	Percentages of Subjects Achieving Seroconversion/Significant Increase in Antibody Titre/ Area as Measured by SRH and (HI) and at Least 4 Fold Rise in Titres by MN Assay-H5N1 Strain

Measure Description	Measurement of immunogenicity in terms of significant increase in antibody titer and Seroconversion. Significant increase in antibody titer is defined as at least a four-fold increase from non-negative pre-vaccination serum (≥ 10) for HI or a 50% increase in area for SRH. Seroconversion is defined as negative pre-vaccination serum / post-vaccination titer ≥40 for HI (area ≥25 mm2 for SRH)
Time Frame	up to day 43
Safety Issue?	No

Analysis Population Description

The population was analyzed on per protocol set.

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	181	189	189
Percentages of Subjects Achieving Seroconversion/ Significant Increase in Antibody Titre/ Area as Measured by SRH and (HI) and at Least 4 Fold Rise in Titres by MN Assay-H5N1 Strain [units: Percentage of subjects] Number (95% Confidence Interval)			
Seroconversion/significant rise SRH(N=181,189,189)	90 (84 to 94)	86 (80 to 90)	86 (80 to 91)
Seroconversion/significant rise HI (N=180,186,184)	69 (62 to 76)	67 (59 to 73)	75 (68 to 81)
Four fold increase MN (N=181,189,189)	90 (84 to 94)	86 (80 to 90)	89 (84 to 93)

6. Secondary Outcome Measure:

Measure Title	Percentages of Subjects Achieving HI/MN ≥ 1:40 and SRH Area ≥ 25^mm2
Measure Description	Measurement of immunogenicity in terms of percentage of subjects achieving a titre ≥ 40/area ≥ 25mm^2 after immunization as determined by HI (Haemagglutination Inhibition), MN(Microneutralization) and SRH assay.
Time Frame	Up to 43 days
Safety Issue?	No

Analysis Population Description

The analysis was done on Per Protocol Set

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	196	202	198
Percentages of Subjects Achieving HI/MN ≥ 1:40 and SRH Area ≥ 25^mm2 [units: Percentages of subjects] Number (95% Confidence Interval)			
SRH-Day 1 (N=194,202,198)	4 (1 to 7)	0 (0 to 2)	4 (2 to 8)
SRH-Day 43 (N=181,189,189)	93 (88 to 96)	86 (80 to 90)	89 (84 to 93)
HI-Day 1 (N=192,198,193)	2 (0 to 4)	0 (0 to 2)	2 (0 to 4)
HI-Day 43 (N=181,187,186)	70 (62 to 76)	66 (59 to 73)	74 (67 to 80)
MN-Day 1 (N=194,202,198)	1 (0 to 4)	3 (1 to 6)	3 (1 to 6)
MN-Day 43 (N=181,189,189)	90 (85 to 94)	87 (82 to 92)	89 (84 to 93)

7. Secondary Outcome Measure:

Measure Title	Antibody Response Determined by HI and MN Assay.
Measure Description	Measurement of immunogenicity in terms of Geometric mean titers (GMTs) as determined by HI and MN assay.
Time Frame	Up to 43 days
Safety Issue?	No

Analysis Population Description

The population was analyzed on Per protocol set

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	192	198	193
Antibody Response Determined by HI and MN Assay. [units: titers] Mean (95% Confidence Interval)			
HI-Day 1	5.93 (5.49 to 6.40)	5.58 (5.18 to 6.02)	5.85 (5.42 to 6.32)
HI-Day 22 (N=31,31,30)	8.36 (5.79 to 12)	6.76 (4.68 to 9.77)	9.66 (6.65 to 14)
HI-Day 43 (N=181,187,186)	46 (30 to 70)	33 (22 to 50)	49 (32 to 75)
MN-Day 1 (N=194,202,198)	10 (9.28 to 11)	10 (9.67 to 11)	10 (9.55 to 11)
MN-Day 22 (N=31,31,30)	14 (11 to 19)	16 (12 to 22)	17 (13 to 23)
MN-Day 43 (N=181,189,189)	141 (110 to 180)	111 (87 to 141)	133 (105 to 169)

8. Secondary Outcome Measure:

Measure Title	Percentages of B-cell Antibodies Against H5N1 and H1N1 After Each Vaccination.
Measure Description	The Cell Mediated Immunity (CMI) response was evaluated in a randomly selected subgroup of approximately 92 subjects from all the vaccine groups out of a total of 601 enrolled subjects. Frequency of circulating memory B cells (MBC), capable of differentiating in vitro into cell secreting IgG (Immunoglobulin G) antibodies specific for H5N1 (the subunit from A/Vietnam/1194/2004) or for H1N1 (the subunit from A/Solomon Island/3/2006) were determined by an ELISA-coupled limiting dilution assay.The frequency of H5N1-IgG MBC and H1N1-IgG MBC was expressed as percentages (%) of total IgG producing MBC
Time Frame	Three weeks after first vaccination (day 22) and three weeks after second vaccination (day 43)
Safety Issue?	No

Analysis Population Description

The analysis was done on Full analysis set

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal(S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	30	30	29
Percentages of B-cell Antibodies Against H5N1 and H1N1 After Each Vaccination. [units: Percentages of B-cell antibodies] Mean (95% Confidence Interval)			
H5N1-IgG MBC - Day 1 (N=30, 30, 29)	0.7 (0.11 to 1.28)	0.42 (-0.168 to 1.01)	0.53 (-0.073 to 1.12)
H5N1-IgG MBC - Day 22 (N=30, 30, 28)	5.39 (2.66 to 8.11)	6.08 (3.36 to 8.8)	7.58 (4.77 to 10)
H5N1-IgG MBC - Day 43 (N=30, 30, 29)	6.67 (4.71 to 8.64)	7.21 (5.24 to 9.18)	6.84 (4.84 to 8.83)

	T/P-A	A/P-T	A/S-A
H1N1-IgG MBC - Day 1 (N=30, 30, 29)	2.35 (0.81 to 3.89)	2.64 (1.1 to 4.18)	1.61 (0.039 to 3.18)
H1N1-IgG MBC - Day 22 (N=30, 30, 28)	13 (9.29 to 17)	8.55 (4.76 to 12)	15 (11 to 19)
H1N1-IgG MBC - Day 43 (N=30, 30, 29)	12 (6.98 to 17)	16 (11 to 21)	15 (10 to 20)

9. Secondary Outcome Measure:

Measure Title	Mean T-Cells Per Million Total Cells (95% CI) in Response to H5 Peptides and H5N1 Subunit
Measure Description	Frequency and functionality of vaccine antigen-specific CD4+ T cells was assessed in peripheral blood (PBMC) taken at days 1, 22 and 43 after in vitro stimulation with: Library of 70 peptides spanning the whole H5 A/Vietnam/1194/2004 protein (H5 pool of 70 Vietnam) H5N1 subunit from A/Vietnam/1194/2004 (H5N1 Vietnam) H3N2 subunit from A/ Wisconsin/67/2005 (H3N2 Wisconsin) H1N1 subunit from A/Solomon Islands/3/2006 (H1N1 Solomon Islands) Polyclonal stimulus agonistic aCD3 mAb (aCD3) The change in frequency of T-cells was measured.
Time Frame	Three weeks after 1st vaccination (day 22) and three weeks after 2nd vaccination (day 43)
Safety Issue?	No

Analysis Population Description

Analysis was done on full analysis set

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Measured Values

	T/P-A	A/P-T	A/S-A
Number of Participants Analyzed	31	31	30

	T/P-A	A/P-T	A/S-A
Mean T-Cells Per Million Total Cells (95% CI) in Response to H5 Peptides and H5N1 Subunit [units: Mean cells per million total cells] Mean (95% Confidence Interval)			
H5 Pool of 70 Vietnam Day 1 (N=30, 31, 30)	162 (106 to 218)	175 (120 to 230)	167 (111 to 223)
H5 Pool of 70 Vietnam Day 22 (N=31, 31, 30)	273 (198 to 348)	358 (284 to 431)	365 (290 to 440)
H5 Pool of 70 Vietnam Day 43 (N=31, 31, 30)	311 (246 to 376)	328 (264 to 392)	290 (225 to 355)
H5N1 Vietnam Day 1 (N=31, 31, 30)	136 (93 to 178)	180 (137 to 222)	155 (112 to 198)
H5N1 Vietnam Day 22 (N=31, 31, 30)	604 (420 to 788)	711 (526 to 895)	938 (752 to 1124)
H5N1 Vietnam Day 43 (N=31, 31, 30)	784 (615 to 952)	813 (644 to 982)	750 (579 to 921)
H3N2 Wisconsin Day 1 (N=31, 31, 30)	329 (266 to 392)	344 (281 to 407)	349 (285 to 413)
H3N2 Wisconsin Day 22 (N=31, 31, 30)	1050 (853 to 1247)	616 (419 to 813)	1129 (929 to 1329)
H3N2 Wisconsin Day 43 (N=31, 31, 30)	910 (750 to 1071)	1034 (874 to 1195)	814 (651 to 978)
H1N1 Solomon Islands Day 1 (N=30, 31, 30)	275 (186 to 365)	427 (339 to 515)	331 (241 to 420)
H1N1 Solomon Islands Day 22 (N=30, 30, 30)	998 (795 to 1201)	729 (528 to 930)	1040 (842 to 1237)
H1N1 Solomon Islands Day 43 (N=30, 30, 29)	930 (735 to 1125)	973 (781 to 1166)	792 (599 to 984)
aCD3 Day 1 (N=31, 31, 30)	38714 (29922 to 47505)	32703 (23912 to 41494)	27824 (18887 to 36760)
aCD3 Day 22 (N=31, 31, 30)	29134 (26356 to 31911)	27324 (24571 to 30077)	32324 (29504 to 35144)
aCD3 Day 43 (N=31, 31, 30)	31001 (27850 to 34153)	29327 (26203 to 32451)	34680 (31480 to 37880)

Reported Adverse Events

Time Frame	Throughout the entire study period
Additional Description	Data provided in the "other Adverse Events (>5%)" includes solicited local and systemic reactions along with unsolicited AEs that persisted for more than 7 days after each study vaccination.

Reporting Groups

	Description
T/P-A	one dose of the tetravalent (T) influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by Aflunov, on study day 22
A/P-T	one dose of the Aflunov (A; A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, with one dose of the placebo (P) control, on study day 1, followed by the tetravalent (T) influenza vaccine, on study day 22
A/S-A	one dose of the Aflunov (A, A/H5N1) avian influenza vaccine administered concomitantly, in a different arm, one dose of licensed seasonal (S) vaccine, on study day 1, followed by Aflunov (A), on study day 22

Serious Adverse Events

	T/P-A	A/P-T	A/S-A
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	2/196 (1.02%)	3/202 (1.49%)	4/198 (2.02%)
Eye disorders			
Retinal Detachment [A] *	0/196 (0%)	1/202 (0.5%)	0/198 (0%)
Gastrointestinal disorders			
Diarrhoea [A] *	0/196 (0%)	1/202 (0.5%)	0/198 (0%)
Intestinal Polyp [A] *	1/196 (0.51%)	0/202 (0%)	0/198 (0%)
Hepatobiliary disorders			
Bile Duct Stenosis [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Infections and infestations			
Pyelonephritis [A] *	0/196 (0%)	1/202 (0.5%)	0/198 (0%)
Investigations			
Endoscopic Retrograde Cholangiopancreatography [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian Cancer [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Nervous system disorders			
Cerebral Haemorrhage [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)

	T/P-A	A/P-T	A/S-A
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Intracranial Aneurysm [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous [A] *	1/196 (0.51%)	0/202 (0%)	0/198 (0%)
Psychiatric disorders			
Bulimia Nervosa [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Depression Suicidal [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Surgical and medical procedures			
Eye Operation [A] *	0/196 (0%)	1/202 (0.5%)	0/198 (0%)
Hysterosalpingo-Oophorectomy [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)
Lymphadenectomy [A] *	0/196 (0%)	0/202 (0%)	1/198 (0.51%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	T/P-A	A/P-T	A/S-A
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	190/196 (96.94%)	185/202 (91.58%)	183/198 (92.42%)
Gastrointestinal disorders			
Diarrhoea [A] *	9/196 (4.59%)	11/202 (5.45%)	9/198 (4.55%)
Nausea [A] †	30/196 (15.31%)	29/202 (14.36%)	14/198 (7.07%)
Toothache [A] [1] *	1/3 (33.33%)	0/1 (0%)	0/0
General disorders			
Chills [A] †	30/196 (15.31%)	19/202 (9.41%)	11/198 (5.56%)
Fatigue [A] [1] †	1/3 (33.33%)	1/1 (100%)	0/0

	T/P-A	A/P-T	A/S-A
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Fatigue [A] †	88/196 (44.9%)	92/202 (45.54%)	71/198 (35.86%)
Injection Site Erythema [A] †	10/196 (5.1%)	10/202 (4.95%)	11/198 (5.56%)
Injection Site Haematoma [A] [1] *	1/3 (33.33%)	0/1 (0%)	0/0
Injection Site Haemorrhage [A] *	13/196 (6.63%)	11/202 (5.45%)	8/198 (4.04%)
Injection Site Haemorrhage [A] [1] *	1/3 (33.33%)	0/1 (0%)	0/0
Injection Site Induration [A] †	22/196 (11.22%)	14/202 (6.93%)	12/198 (6.06%)
Injection Site Pain [A] †	172/196 (87.76%)	164/202 (81.19%)	155/198 (78.28%)
Injection Site Pain [A] [1] †	2/3 (66.67%)	0/1 (0%)	0/0
Injection Site Swelling [A] †	21/196 (10.71%)	12/202 (5.94%)	11/198 (5.56%)
Injection Site Swelling [A] [1] †	1/3 (33.33%)	0/1 (0%)	0/0
Malaise [A] †	66/196 (33.67%)	55/202 (27.23%)	38/198 (19.19%)
Malaise [A] [1] †	1/3 (33.33%)	1/1 (100%)	0/0
Pyrexia [A] †	12/196 (6.12%)	11/202 (5.45%)	6/198 (3.03%)
Infections and infestations			
Nasopharyngitis [A] *	39/196 (19.9%)	38/202 (18.81%)	26/198 (13.13%)
Nasopharyngitis [A] [1] *	1/3 (33.33%)	0/1 (0%)	0/0
Tinea Pedis [A] [1] *	1/3 (33.33%)	0/1 (0%)	0/0
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	37/196 (18.88%)	29/202 (14.36%)	19/198 (9.6%)
Arthralgia [A] [1] †	0/3 (0%)	1/1 (100%)	0/0
Back Pain [A] *	1/3 (33.33%)	0/1 (0%)	0/0
Myalgia [A] †	75/196 (38.27%)	77/202 (38.12%)	57/198 (28.79%)

	T/P-A	A/P-T	A/S-A
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Myalgia A [1] †	1/3 (33.33%)	0/1 (0%)	0/0
Osteoarthritis A [2] *	1/3 (33.33%)	0/1 (0%)	0/0
Nervous system disorders			
Headache A †	90/196 (45.92%)	86/202 (42.57%)	60/198 (30.3%)
Headache A [1] †	1/3 (33.33%)	1/1 (100%)	0/0
Respiratory, thoracic and mediastinal disorders			
Cough A †	30/196 (15.31%)	28/202 (13.86%)	26/198 (13.13%)
Cough A [1] †	1/3 (33.33%)	0/1 (0%)	0/0
Oropharyngeal Pain A *	8/196 (4.08%)	12/202 (5.94%)	13/198 (6.57%)
Skin and subcutaneous tissue disorders			
Hyperhidrosis A *	19/196 (9.69%)	25/202 (12.38%)	15/198 (7.58%)
Hyperhidrosis A [1] *	1/3 (33.33%)	0/1 (0%)	0/0
Surgical and medical procedures			
Wisdom teeth Removal A [1] *	1/3 (33.33%)	0/1 (0%)	0/0

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA

[1] In subjects >= 61 years of age.
[2] In subjects >= 61 years of age

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:
Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is more than 60 days but less than or equal to 180 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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