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Study No.: 106622
Title: An observational study to investigate the incidence of influenza, downstream complications of influenza and hospitalizations, in elderly subjects vaccinated with GSK Biologicals' influenza vaccine (Fluarix™) administered intramuscularly. Fluarix™ (Flu): GlaxoSmithKline (GSK) Biologicals' inactivated influenza split vaccine.
Rationale: The aim of this study was to investigate the incidence of influenza disease and various possible downstream complications, such as pneumonia, ischemic Heart Disease (HD) (unstable angina or myocardial infarction (MI)), congestive heart failure, acute cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD) exacerbation and hospitalizations or emergency room (ER) visits, and to evaluate the feasibility of health outcome surveillance and the validity of using questionnaires, after routine annual vaccination of the elderly population with Flu vaccine.
Phase: Epidemiology.
Study Period: 29 March 2006 to 14 December 2006.
Study Design: Multi-centre, open-label, observational study with 1 study group.
Centres: 2 centres in Brazil and 9 centres in Australia.
Indication: Immunization against influenza in male and female subjects aged 65 years and over.
Treatment: All subjects received a single dose of Flu vaccine by intramuscular injection into the deltoid region of the non-dominant arm.
<p>Objectives:</p> <p><i>Epidemiology</i></p> <ul style="list-style-type: none"> • To evaluate the incidence of influenza like illness (ILI) in elderly adults after vaccination with Flu vaccine, during the influenza season*. • To evaluate the incidence of laboratory confirmed influenza in elderly adults after vaccination with Flu vaccine; laboratory confirmation was done by detection of influenza A and /or B by virus culture and/or Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) in nasal and throat swab specimens or equivalent specimen. • To evaluate the incidence of hospitalization or emergency room visits due to ILI in subjects vaccinated with Flu vaccine. • To evaluate the incidence of hospitalization or emergency room visit due to laboratory confirmed influenza in subjects vaccinated with Flu vaccine. • To evaluate the incidence of hospitalization or emergency room visit for any cause in elderly adults vaccinated with Flu vaccine, during the influenza season*. • To evaluate the incidence of pneumonia, ischemic heart disease (unstable angina or myocardial infarction), congestive heart failure, acute cerebrovascular disease and COPD exacerbation in subjects vaccinated with Flu vaccine, during the influenza season*. • To evaluate the incidence of hospitalization or emergency room visit due to pneumonia, ischemic heart disease (unstable angina or MI), congestive heart failure, acute cerebrovascular disease and COPD exacerbation in subjects vaccinated with Flu vaccine, during the influenza season*. • To evaluate the mortality due to laboratory confirmed influenza infection. • To evaluate the overall mortality. <p>* Influenza season was determined for each site based on Government-sponsored influenza surveillance data for 2006, or if unavailable, on historical data relevant to the locale.</p> <p><i>Functional status</i></p> <ul style="list-style-type: none"> • To measure changes in functional status after ILI-episode and at the end of the study. <p><i>Safety</i></p> <ul style="list-style-type: none"> • To evaluate the safety of one dose of Flu vaccine in terms of occurrence of serious adverse

events (SAEs) during the influenza season following the intramuscular administration in elderly.

Immunogenicity

- To evaluate the immune response after vaccination with Flu vaccine in a subset of subjects.

Primary Outcome/Efficacy Variable:

Epidemiology

- Incidence of ILI in subjects having received Flu vaccination prior to influenza season.
- Incidence of laboratory confirmed influenza A and/or B infection in subjects having received Flu vaccination prior to influenza season (viral culture and/or RT-PCR).
- Incidence of any hospitalization or emergency room visit, hospitalization or emergency room visit due to ILI, hospitalization or emergency room visit with laboratory confirmed influenza infection, and hospitalization or emergency room visit due to pneumonia, ischemic HD (unstable angina or MI), congestive heart failure, acute cerebrovascular disease, and COPD exacerbation.
- Incidence of pneumonia, ischemic HD (unstable angina or MI), congestive heart failure, acute cerebrovascular disease, and COPD exacerbation, in subjects having received Flu vaccination prior to influenza season.
- Number of deaths due to laboratory confirmed influenza infection during surveillance period.
- Number of deaths during surveillance period.

Functional Status

- Questionnaire measures related to general health status.

Safety

- Occurrence of serious adverse events in all subjects during the entire study.

Immunogenicity in a subset of subjects

- For each vaccine strain, seroconversion rate with 95% confidence interval (CI) at Day 21 defined as the proportion of subjects with either a pre-vaccination Haemagglutination-inhibition (HI) titre < 1:10 and a post-vaccination titre \geq 1:40, or a pre-vaccination titre \geq 1:10 and a minimum four-fold increase in post-vaccination titre.
- For each vaccine strain, seroprotection rate with 95% CI at Day 0 and Day 21 defined as the proportion of vaccines with a serum HI titre \geq 1:40.
- For each vaccine strain, geometric mean titre (GMT) of serum HI antibodies with 95% CI pre- and post-vaccination.

Secondary Outcome/Efficacy Variable(s):

Not applicable.

Statistical Methods:

All analyses were performed for all subjects from both countries together but also per country. The Total Vaccinated Cohort included all subjects with one vaccine administration documented, for whom data were available.

From this population of vaccinated subjects, the following cohorts were derived:

- ILI episodes cohort: this cohort included all ILI episodes experienced by vaccinated subjects during the influenza season.
- Illness episodes cohort: this cohort included all pneumonia, unstable angina, myocardial infarction, congestive heart failure, stroke, transient ischemic attack and COPD exacerbation episodes experienced by vaccinated subjects during the influenza season.
- No ILI cohort: this cohort included all vaccinated subjects who did not report any ILI episode during the influenza season.
- FLU cohort: this cohort included all vaccinated subjects reporting at least one laboratory-confirmed influenza episode during the influenza season.
- ILI no FLU cohort: this cohort included all vaccinated subjects reporting ILI episodes during the influenza season that were not laboratory-confirmed.

The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity measures were available.

Epidemiology analyses

The analyses were performed on the Total Vaccinated Cohort, the ILI episodes cohort and the Illness episodes cohort.

The following criteria were computed for each country and overall for all subjects having received Flu vaccination prior to influenza season:

- Proportion of subjects with ILI and exact 95% CI.
- Proportion of subjects with culture and/or RT-PCR confirmed influenza A and/or B infection during the influenza season with exact 95% CI.
- Proportion of ILI episodes with culture and/or RT-PCR confirmed influenza A and/or B infection during the influenza season with exact 95% CI.
- Proportion of subjects with any hospitalization or emergency room visit, hospitalization or emergency room visit due to ILI, hospitalization or emergency room visit with laboratory confirmed influenza infection, hospitalization or emergency room visit due to pneumonia, ischemic HD (unstable angina or MI), congestive heart failure, acute cerebrovascular disease, or COPD exacerbation and, hospitalization or emergency room visit due to other reason during the influenza season and with exact 95% CI.
- Proportion of subjects with pneumonia, ischemic HD (unstable angina or MI), congestive heart failure, acute cerebrovascular disease, or COPD exacerbation during the influenza season and with exact 95% CI.
- Proportion of deaths due to laboratory confirmed influenza infection during surveillance period with exact 95% CI.
- Proportion of deaths during the influenza season with exact 95% CI.

Analysis of the functional status

The analyses of the functional status were performed on the following cohorts: No ILI cohort, ILI no FLU cohort, and FLU cohort.

For subjects with more than one ILI episode, the first ILI episode during the influenza season for subjects without viral culture and/or RT-PCR confirmed influenza and the first laboratory-confirmed influenza episode for subjects with viral culture and/or RT-PCR confirmed influenza were reported.

Functional status assessment was based on 3 different general health status questionnaires: Barthel Index, SF-36® Health Survey (short-form health survey with only 36 questions) and EQ-5D (Euro Quality Of Life) Health questionnaire.

For each questionnaire, descriptive statistics (mean and standard deviation) were computed, for each country and overall.

Immunogenicity analysis

The analysis of immunogenicity was performed on a subset of subjects (approximately 100 per country). Results were presented for the ATP cohort for immunogenicity.

For each vaccine strain, the following parameters (with 95% CI) were tabulated:

- Geometric mean serum HI titre at Day 0 and 21.
- Seroconversion rate at Day 21.
- Seroprotection rate at Day 0 and 21.
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Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.

Safety analysis

The occurrence of SAEs during the entire study period was tabulated on the Total Vaccinated Cohort, according to Medical Dictionary of Regulatory Activities (MedDRA) preferred terms.

Study Population: Males or females aged ≥ 65 years at the time of vaccination and with residence status allowing free mixing with general community were enrolled. Written informed consent obtained from each subject prior to the performance of any study-specific procedures.

Number of subjects	Brazil	Australia	Total
Planned, N	1000	1000	2000
Randomised, N (Total Vaccinated Cohort)	836	688	1524
Completed, n (%)	818 (97.8)	667 (96.9)	1485 (97.4)
Total Number Subjects Withdrawn, n (%)	18 (2.2)	21 (3.1)	39 (2.6)

Withdrawn due to Adverse Events, n (%)	6 (0.7)	5 (0.7)	11 (0.7)		
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable		
Withdrawn for other reasons, n (%)	12 (1.4)	16 (2.3)	28 (1.8)		
Demographics	Brazil	Australia	Total		
N (Total Vaccinated Cohort)	836	688	1524		
Females: Males	576:260	344:344	920:604		
Mean Age, years (SD)	73.8 (6.73)	73.9 (6.50)	73.8 (6.63)		
White - Caucasian / European heritage, n (%)	715 (85.5)	673 (97.8)	1388 (91.1)		
Primary Efficacy Results:					
Proportion of subjects with at least one ILI episode confirmed with viral culture and/or RT-PCR (influenza A and/or B infection) or not confirmed (Total Vaccinated Cohort)					
	Event Type	All subjects N = 1524			
		n	%	95% CI	
				LL	UL
ILI (confirmed or not)	At least 1 ILI episode	466	30.6	28.3	33.0
	1 ILI episode	380	24.9	22.8	27.2
	2 ILI episodes	75	4.9	3.9	6.1
	> 2 ILI episodes	11	0.7	0.4	1.3
Lab confirmed influenza (Viral culture and/or RT-PCR)	Influenza A and/or B	28	1.8	1.2	2.6
	Influenza A only#	17	1.1	0.7	1.8
	Influenza B only#	11	0.7	0.4	1.3
Viral culture confirmed influenza	Influenza A and/or B	19	1.2	0.8	1.9
	Influenza A only#	11	0.7	0.4	1.3
	Influenza B only#	8	0.5	0.2	1.0
RT-PCR confirmed influenza	Influenza A and/or B	28	1.8	1.2	2.6
	Influenza A only#	17	1.1	0.7	1.8
	Influenza B only#	11	0.7	0.4	1.3
Viral culture and RT-PCR confirmed influenza	Influenza A and/or B	19	1.2	0.8	1.9
	Influenza A only#	11	0.7	0.4	1.3
	Influenza B only#	8	0.5	0.2	1.0
# Only the first episode has been taken into account					
N = total number of subjects					
n (%) = number (percentage) of subjects with a specified event type					
95% CI = exact 95% confidence interval - LL = Lower Limit, UL = Upper Limit					
Primary Efficacy Results:					
Proportion of subjects with at least one hospitalization or ER visit due to any reason, due to ILI, due to laboratory confirmed influenza infection and due to pneumonia, ischemic HD, congestive heart failure, acute cerebrovascular disease or COPD exacerbation (Total Vaccinated Cohort)					
Reason of hospitalization or emergency room visit	Number of hospitalizations or ER visits	All subjects N = 1524			
		n	%	95% CI	
				LL	UL
Any reason	At least one	151	9.9	8.5	11.5
	One	125	8.2	6.9	9.7
	Above one	26	1.7	1.1	2.5
ILI	At least one	21	1.4	0.9	2.1
	One	21	1.4	0.9	2.1
	Above one	0	0.0	0.0	0.2
Laboratory confirmed influenza infection	At least one	3	0.2	0.0	0.6
	One	3	0.2	0.0	0.6
	Above one	0	0.0	0.0	0.2

Pneumonia, ischemic HD, congestive heart failure, acute cerebrovascular disease or COPD exacerbation	At least one	47	3.1	2.3	4.1
	One	37	2.4	1.7	3.3
	Above one	10	0.7	0.3	1.2
Other reason	At least one	103	6.8	5.5	8.1
	One	91	6.0	4.8	7.3
	Above one	12	0.8	0.4	1.4

N = total number of subjects
n (%) = number (percentage) of subjects with hospitalization or emergency room visit due to the specified reason
95% CI = exact 95% confidence interval - LL = Lower Limit, UL = Upper Limit
acute cerebrovascular disease = stroke or transient ischemic attack

Primary Efficacy Results:

Proportion of subjects with at least one pneumonia, ischemic HD (unstable angina or MI), congestive heart failure, acute cerebrovascular disease (stroke or transient ischemic attack) or COPD exacerbation (Total Vaccinated Cohort)

Illness	Number of episodes	All subjects N = 1524			
		n	%	95% CI	
				LL	UL
Pneumonia	At least one episode	21	1.4	0.9	2.1
	One episode	21	1.4	0.9	2.1
	Above one episode	0	0.0	0.0	0.2
Ischemic heart disease	At least one episode	12	0.8	0.4	1.4
	One episode	11	0.7	0.4	1.3
	Above one episode	1	0.1	0.0	0.4
Unstable angina	At least one episode	6	0.4	0.1	0.9
	One episode	6	0.4	0.1	0.9
	Above one episode	0	0.0	0.0	0.2
Myocardial infarction	At least one episode	6	0.4	0.1	0.9
	One episode	5	0.3	0.1	0.8
	Above one episode	1	0.1	0.0	0.4
Congestive heart failure	At least one episode	10	0.7	0.3	1.2
	One episode	10	0.7	0.3	1.2
	Above one episode	0	0.0	0.0	0.2
Acute cerebrovascular disease	At least one episode	11	0.7	0.4	1.3
	One episode	9	0.6	0.3	1.1
	Above one episode	2	0.1	0.0	0.5
Stroke	At least one episode	8	0.5	0.2	1.0
	One episode	8	0.5	0.2	1.0
	Above one episode	0	0.0	0.0	0.2
Transient ischemic attack	At least one episode	4	0.3	0.1	0.7
	One episode	3	0.2	0.0	0.6
	Above one episode	1	0.1	0.0	0.4
COPD exacerbation	At least one episode	11	0.7	0.4	1.3
	One episode	7	0.5	0.2	0.9
	Above one episode	4	0.3	0.1	0.7
Any illness	At least one episode	57	3.7	2.8	4.8
	One episode	45	3.0	2.2	3.9
	Two episodes	7	0.5	0.2	0.9
	Above two episodes	5	0.3	0.1	0.8

N = total number of subjects
n (%) = number (percentage) of subjects with a specific number of illness episodes
95% CI = exact 95% confidence interval - LL = Lower Limit, UL = Upper Limit

Primary Efficacy Results:

Number of deaths during the influenza season (Total Vaccinated Cohort)

Cause of death #	All subjects N = 1524			
	n	%	95% CI	
			LL	UL
Laboratory confirmed influenza infection	0	0.0	0.0	0.2
ILI (not laboratory confirmed as influenza)*	1	0.1	0.0	0.4
Other*	9	0.6	0.3	1.1

N = total number of subjects

n (%) = number (percentage) of subjects with a specific event type

95% CI = exact 95% confidence interval: LL = Lower limit, UL = upper limit

= Several causes of death could be counted for the same subject

*For 1 subject, ILI (not laboratory confirmed as influenza) and another cause were reported

Primary Efficacy Results:

Barthel Index at baseline and at the end of the study for subjects who did not report any ILI episode during the influenza season, for each country and overall, in % (No ILI cohort)

Country	Parameter	Baseline (Day 0)	End of study	Change during the study
Brazil	N	587	574	573
	Missing	2	15	16
	Mean	96.0	95.5	-0.7
	SD	11.6	13.1	8.6
Australia	N	467	435	433
	Missing	2	34	36
	Mean	97.7	97.9	0.0
	SD	8.0	5.6	7.5
All	N	1054	1009	1006
	Missing	4	49	52
	Mean	96.8	96.5	-0.4
	SD	10.2	10.6	8.2

N = total number of subjects at each time point by country and overall. For 'Change during the study,' N = total number of subjects with Baseline and End of study information available by country and overall.

SD = standard deviation

Primary Efficacy Results:

Barthel Index at each time point* for subjects who reported ILI episodes during the influenza season that were not confirmed by viral culture or RT-PCR, for each country and overall, in % (ILI no FLU cohort)

Country	Parameter	Baseline (Day 0)	Onset of ILI (1)	Follow-up of ILI (2)	Change during surveillance period of ILI (2-1)	End of study	Change during the study
Brazil	N	224	49	50	47	221	221
	Missing	0	175	174	177	3	3
	Mean	96.8	95.1	94.1	-1.1	95.7	-1.2
	SD	8.8	16.6	16.5	4.8	11.1	8.2
Australia	N	213	NC	NC	NC	198	197
	Missing	1	NC	NC	NC	16	17
	Mean	97.3	NC	NC	NC	97.3	0.0
	SD	7.4	NC	NC	NC	6.4	7.6

All	N	437	NC	NC	NC	419	418
	Missing	1	NC	NC	NC	19	20
	Mean	97.0	NC	NC	NC	96.4	-0.6
	SD	8.1	NC	NC	NC	9.2	8.0

N = total number of subjects at each time point by country and overall. For Change during the study, N = total number of subjects with Baseline and End of study information available by country and overall.

NC = information not collected or not computed

Onset of ILI = Only the first episode of ILI with Barthel Index was recorded

Follow-up of ILI = Only the first episode of ILI with Barthel Index was recorded

SD = standard deviation

* time point = baseline, onset of ILI, follow up of ILI and end of study

Primary Efficacy Results:

Barthel Index at each time point* for subjects reporting at least one lab-confirmed influenza episode during the influenza season, for each country and overall, in % (FLU cohort)

Country	Parameter	Baseline (Day 0)	Onset of ILI (1)	Follow-up of ILI (2)	Change during surveillance period of ILI (2-1)	End of study	Change during the study
Brazil	N	23	4	5	4	23	23
	Missing	0	19	18	19	0	0
	Mean	99.3	96.3	98.0	-2.5	98.0	-1.3
	SD	1.7	7.5	2.7	5.0	4.5	5.0
Australia	N	5	NC	NC	NC	5	5
	Missing	0	NC	NC	NC	0	0
	Mean	99.0	NC	NC	NC	99.0	0.0
	SD	2.2	NC	NC	NC	2.2	3.5
All	N	28	NC	NC	NC	28	28
	Missing	0	NC	NC	NC	0	0
	Mean	99.3	NC	NC	NC	98.2	-1.1
	SD	1.8	NC	NC	NC	4.1	4.8

N = total number of subjects at each time point by country and overall. For Change during the study, N = total number of subjects with Baseline and End of study information available by country and overall.

NC = information not collected or not computed

SD = standard deviation

* time point = baseline, onset of ILI, follow up of ILI and end of study

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who did not report any ILI episode during the influenza season, for both countries, in % (No ILI cohort)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	978	957	899
	Missing	80	101	159
	Mean	74.3	74.4	0.4
	SD	18.2	18.1	15.5
Mental	N	1039	962	949
	Missing	19	96	109
	Mean	79.1	79.1	-0.3
	SD	16.5	15.3	14.9
Global	N	975	944	884
	Missing	83	114	174
	Mean	77.9	78.4	0.7
	SD	16.9	16.3	14.8

N = total number of subjects at each time point. For Change during the study, N = total number of subjects with Baseline and End of study information available.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who did not report any ILI episode during the influenza season, for Brazil, in % (No ILI cohort for Brazil)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	588	574	574
	Missing	1	15	15
	Mean	75.9	78.0	1.7
	SD	17.7	15.7	16.2
Mental	N	588	573	573
	Missing	1	16	16
	Mean	79.9	80.8	0.5
	SD	17.1	13.8	16.0
Global	N	588	573	573
	Missing	1	16	16
	Mean	78.6	81.1	2.1
	SD	17.1	14.1	15.7

N = total number of subjects at each time point in Brazil. For Change during the study, N = total number of subjects with Baseline and End of study information available in Brazil.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who did not report any ILI episode during the influenza season, for Australia, in % (No ILI cohort for Australia)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	390	383	325
	Missing	79	86	144
	Mean	71.8	68.9	-2.0
	SD	18.7	20.0	13.9
Mental	N	451	389	376
	Missing	18	80	93
	Mean	78.1	76.7	-1.5
	SD	15.5	17.1	12.8
Global	N	387	371	311
	Missing	82	98	158
	Mean	76.8	74.4	-1.9
	SD	16.7	18.4	12.8

N = total number of subjects at each time point in Australia. For Change during the study, N = total number of subjects with Baseline and End of study information available in Australia.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported ILI episodes during the influenza season that were not confirmed by viral culture or RT-PCR, for both countries, in % (ILI no FLU cohort)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	406	388	365
	Missing	32	50	73
	Mean	72.2	70.2	-1.1
	SD	19.2	19.9	17.1

Mental	N	429	399	391
	Missing	9	39	47
	Mean	77.1	76.8	-0.6
	SD	17.3	16.7	16.0
Global	N	404	385	361
	Missing	34	53	77
	Mean	75.7	74.9	-0.1
	SD	18.3	18.1	16.7

N = total number of subjects at each time point. For Change during the study, N = total number of subjects with Baseline and End of study information available.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported ILI episodes during the influenza season that were not confirmed by viral culture or RT-PCR, for Brazil, in % (ILI no FLU cohort for Brazil)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	224	220	220
	Missing	0	4	4
	Mean	73.0	74.5	1.3
	SD	18.4	16.3	18.5
Mental	N	224	221	221
	Missing	0	3	3
	Mean	77.5	79.5	1.9
	SD	17.6	13.6	17.1
Global	N	224	220	220
	Missing	0	4	4
	Mean	75.7	78.3	2.5
	SD	17.9	14.5	18.0

N = total number of subjects at each time point in Brazil. For Change during the study, N = total number of subjects with Baseline and End of study information available in Brazil.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported ILI episodes during the influenza season that were not confirmed by viral culture or RT-PCR, for Australia, in % (ILI no FLU cohort for Australia)

General health scores	Parameter	Baseline (Day 0)	End of study	Change during the study
Physical	N	182	168	145
	Missing	32	46	69
	Mean	71.1	64.6	-4.7
	SD	20.3	22.6	14.0
Mental	N	205	178	170
	Missing	9	36	44
	Mean	76.7	73.4	-3.8
	SD	16.9	19.4	13.8
Global	N	180	165	141
	Missing	34	49	73
	Mean	75.7	70.3	-4.2
	SD	18.8	21.1	13.4

N = total number of subjects at each time point in Australia. For Change during the study, N = total number of subjects with Baseline and End of study information available in Australia.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported at least one ILI episode during the influenza season that was confirmed by viral culture or RT-PCR, for both countries, in % (FLU cohort)

General health scores	Parameter	Baseline (Day 0) [%]	End of study [%]	Change during the study [%]
Physical	N	28	28	28
	Missing	0	0	0
	Mean	78.5	77.7	-0.8
	SD	13.9	13.8	14.3
Mental	N	28	27	27
	Missing	0	1	1
	Mean	80.7	78.0	-2.2
	SD	14.8	12.7	16.3
Global	N	28	27	27
	Missing	0	1	1
	Mean	80.8	79.8	-0.6
	SD	14.1	13.0	15.0

N = total number of subjects at each time point. For Change during the study, N = total number of subjects with Baseline and End of study information available.

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported at least one ILI episode during the influenza season that was confirmed by viral culture or RT-PCR, for Brazil, in % (FLU cohort for Brazil)

General health scores	Parameter	Baseline (Day 0) [%]	End of study [%]	Change during the study [%]
Physical	N	23	23	23
	Missing	0	0	0
	Mean	80.6	78.9	-1.6
	SD	13.1	12.8	13.5
Mental	N	23	23	23
	Missing	0	0	0
	Mean	82.9	79.2	-3.7
	SD	13.9	12.1	15.9
Global	N	23	23	23
	Missing	0	0	0
	Mean	82.7	81.3	-1.4
	SD	12.8	11.6	14.2

N = total number of subjects at each time point in Brazil. For Change during the study, N = total number of subjects with Baseline and End of study information available in Brazil

SD = standard deviation

Primary Efficacy Results:

SF-36 general health scores at baseline and at the end of the study for all subjects who reported at least one ILI episode during the influenza season that was confirmed by viral culture or RT-PCR, for Australia, in % (FLU cohort for Australia)

General health scores	Parameter	Baseline (Day 0) [%]	End of study [%]	Change during the study [%]
Physical	N	5	5	5
	Missing	0	0	0
	Mean	68.9	72.2	3.2
	SD	15.1	18.4	18.8

Mental	N	5	4	4
	Missing	0	1	1
	Mean	70.4	71.4	6.6
	SD	15.7	16.0	17.6
Global	N	5	4	4
	Missing	0	1	1
	Mean	71.7	70.7	4.0
	SD	17.9	18.5	21.1

N = total number of subjects at each time point in Australia. For Change during the study, N = total number of subjects with Baseline and End of study information available in Australia.
SD = standard deviation

Primary Efficacy Results:

EQ-5D global score at baseline and at the end of the study for all subjects who did not report any ILI episode during the influenza season, for each country and overall (No ILI cohort)

Country	Parameter	Baseline (Day 0)	End of study	Change during the study
Brazil	N	588	574	574
	Missing	1	15	15
	Mean	0.83	0.87	0.03
	SD	0.21	0.21	0.22
Australia	N	467	432	430
	Missing	2	37	39
	Mean	0.83	0.83	-0.01
	SD	0.19	0.18	0.16
All	N	1055	1006	1004
	Missing	3	52	54
	Mean	0.83	0.85	0.02
	SD	0.20	0.20	0.20

N = total number of subjects at each time point by country and overall. For Change during the study, N = total number of subjects with Baseline and End of study information available by country and overall.
SD = standard deviation

Primary Efficacy Results:

EQ-5D global score at each time point* for all subjects who reported ILI episodes during the influenza season that were not confirmed by viral culture or RT-PCR, for each country and overall (ILI no FLU cohort)

Country	Parameter	Baseline (Day 0)	Onset of ILI (1)	Follow-up of ILI (2)	Change during surveillance period of ILI (2-1)	End of study	Change during the study
Brazil	N	224	52	218	52	221	221
	Missing	0	172	6	172	3	3
	Mean	0.79	0.74	0.85	0.09	0.85	0.05
	SD	0.23	0.23	0.19	0.19	0.21	0.25
Australia	N	213	NC	196	NC	200	199
	Missing	1	NC	18	NC	14	15
	Mean	0.85	NC	0.87	NC	0.80	-0.05
	SD	0.17	NC	0.16	NC	0.22	0.19
All	N	437	NC	NC	NC	421	420
	Missing	1	NC	NC	NC	17	18
	Mean	0.82	NC	NC	NC	0.82	0.00
	SD	0.21	NC	NC	NC	0.22	0.23

N = total number of subjects at each time point by country and overall. For Change during the study, N = total number of subjects with Baseline and End of study information available by country

and overall.

SD = standard deviation

NC = information not collected or not computed

* time point = baseline, onset of ILI, follow up of ILI and end of study

Primary Efficacy Results:

EQ-5D global score at each time point* for all subjects who reported at least one laboratory-confirmed influenza (Viral culture and/or RT-PCR) episode during the influenza season, for each country and overall (FLU cohort)

Country	Parameter	Baseline (Day 0)	Onset of ILI (1)	Follow-up of ILI (2)	Change during surveillance period of ILI (2-1)	End of study	Change during the study
Brazil	N	23	4	23	4	23	23
	Missing	0	19	0	19	0	0
	Mean	0.85	0.64	0.89	0.09	0.90	0.05
	SD	0.11	0.30	0.17	0.13	0.17	0.17
Australia	N	5	NC	5	NC	5	5
	Missing	0	NC	0	NC	0	0
	Mean	0.84	NC	0.88	NC	0.93	0.09
	SD	0.10	NC	0.11	NC	0.10	0.10
All	N	28	NC	NC	NC	28	28
	Missing	0	NC	NC	NC	0	0
	Mean	0.85	NC	NC	NC	0.91	0.06
	SD	0.11	NC	NC	NC	0.15	0.16

N = total number of subjects at each time point by country and overall. For Change during the study, N = total number of subjects with Baseline and End of study information available by country and overall.

SD = standard deviation

NC = information not collected or not computed

* time point = baseline, onset of ILI, follow up of ILI and end of study

Primary Efficacy Results:

Seropositivity rates and GMTs for HI antibody titres at Day 0 and Day 21 (ATP cohort for immunogenicity)

Vaccine strain	Timing	N	≥ 1:10				GMT		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
A/New Caledonia	PRE	189	179	94.7	90.5	97.4	39.2	33.7	45.7
	PI(D21)	190	189	99.5	97.1	100	114.4	96.1	136.0
A/California	PRE	189	174	92.1	87.2	95.5	25.3	22.0	29.1
	PI(D21)	190	187	98.4	95.5	99.7	112.9	94.5	134.9
B/Malaysia	PRE	189	182	96.3	92.5	98.5	59.7	51.0	69.9
	PI(D21)	190	188	98.9	96.2	99.9	203.9	173.9	239.2

N = number of subjects with available results

n (%) = number (percentage) of seropositive subjects (HI titre ≥ 1:10)

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination

PI(D21) = 21 days after vaccination

Primary Efficacy Results:

Seroconversion rate (SCR) for HI antibody titres at Day 21 (ATP cohort for immunogenicity)

Vaccine strain	Timing	N	SCR			
			n	%	95% CI	
					LL	UL
A/New	PI(D21)	189	59	31.2	24.7	38.3

Caledonia						
A/California	PI(D21)	189	105	55.6	48.2	62.8
B/Malaysia	PI(D21)	189	77	40.7	33.7	48.1
<p>N = Number of subjects with available results at Day 0 and at Day 21 n (%) = number (percentage) of subjects who seroconverted at Day 21 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PI(D21) = 21 days after vaccination</p>						
Primary Efficacy Results:						
Seroprotection rates (SPR) for HI antibody titres at Day 0 and Day 21 (ATP cohort for immunogenicity)						
Vaccine strain	Timing	N	SPR			
			n	%	95% CI	
					LL	UL
A/New Caledonia	PRE	189	106	56.1	48.7	63.3
	PI(D21)	190	168	88.4	83.0	92.6
A/California	PRE	189	70	37.0	30.1	44.3
	PI(D21)	190	162	85.3	79.4	90.0
B/Malaysia	PRE	189	135	71.4	64.4	77.8
	PI(D21)	190	185	97.4	94.0	99.1
<p>N = number of subjects with available results n (%) = number (percentage) of seroprotected subjects (HI titre \geq 40 1/DIL) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination PI(D21) = 21 days after vaccination</p>						
Secondary Outcome Variable (s): Not applicable.						
Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort)						
Unsolicited AEs following vaccination were not collected.						
Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) during the entire study period (Total Vaccinated Cohort)						
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]						
All SAEs					All subjects N = 1524	
Subjects with any SAE(s), n (%) [n related]					129 (8.5) [0]	
Pneumonia					13 (0.9) [0]	
Myocardial infarction					8 (0.5) [0]	
Cardiac failure congestive					7 (0.5) [0]	
Cerebrovascular accident					5 (0.3) [0]	
Chronic obstructive pulmonary disease					5 (0.3) [0]	
Breast cancer					4 (0.3) [0]	
Dizziness					4 (0.3) [0]	
Urinary tract infection					4 (0.3) [0]	
Abdominal pain					3 (0.2) [0]	
Angina pectoris					3 (0.2) [0]	
Chest pain					3 (0.2) [0]	
Femur fracture					3 (0.2) [0]	
Gastroenteritis					3 (0.2) [0]	
Infective exacerbation of chronic obstructive airways disease					3 (0.2) [0]	
Transient ischaemic attack					3 (0.2) [0]	
Acute myocardial infarction					2 (0.1) [0]	
Acute respiratory failure					2 (0.1) [0]	

Anaemia	2 (0.1) [0]
Angina unstable	2 (0.1) [0]
Constipation	2 (0.1) [0]
Depression	2 (0.1) [0]
Device related infection	2 (0.1) [0]
Diabetes mellitus	2 (0.1) [0]
Diverticulitis	2 (0.1) [0]
Dyspnoea	2 (0.1) [0]
Hypertensive crisis	2 (0.1) [0]
Intervertebral disc protrusion	2 (0.1) [0]
Lobar pneumonia	2 (0.1) [0]
Renal failure chronic	2 (0.1) [0]
Urinary retention	2 (0.1) [0]
Abscess limb	1 (0.1) [0]
Ankle fracture	1 (0.1) [0]
Anxiety	1 (0.1) [0]
Aortic stenosis	1 (0.1) [0]
Arteriovenous fistula site infection	1 (0.1) [0]
Atrial fibrillation	1 (0.1) [0]
Bacteraemia	1 (0.1) [0]
Bacterial sepsis	1 (0.1) [0]
Bronchitis	1 (0.1) [0]
Bronchopneumonia	1 (0.1) [0]
Cardiac failure	1 (0.1) [0]
Cellulitis	1 (0.1) [0]
Central nervous system infection	1 (0.1) [0]
Cerebral haematoma	1 (0.1) [0]
Cerebral haemorrhage	1 (0.1) [0]
Cerebral ischaemia	1 (0.1) [0]
Circulatory collapse	1 (0.1) [0]
Colon cancer	1 (0.1) [0]
Contusion	1 (0.1) [0]
Coronary artery occlusion	1 (0.1) [0]
Crohn's disease	1 (0.1) [0]
Cystitis	1 (0.1) [0]
Cystitis glandularis	1 (0.1) [0]
Deep vein thrombosis	1 (0.1) [0]
Dehydration	1 (0.1) [0]
Delirium	1 (0.1) [0]
Diarrhoea	1 (0.1) [0]
Duodenal ulcer perforation	1 (0.1) [0]
Fall	1 (0.1) [0]
Femoral neck fracture	1 (0.1) [0]
Gastrointestinal infection	1 (0.1) [0]
Gastrointestinal neoplasm	1 (0.1) [0]
Gout	1 (0.1) [0]
Hand fracture	1 (0.1) [0]
Herpes zoster	1 (0.1) [0]

Incisional hernia	1 (0.1) [0]
Intestinal obstruction	1 (0.1) [0]
Joint dislocation	1 (0.1) [0]
Left ventricular failure	1 (0.1) [0]
Lower limb fracture	1 (0.1) [0]
Lumbar radiculopathy	1 (0.1) [0]
Lumbar vertebral fracture	1 (0.1) [0]
Lung neoplasm	1 (0.1) [0]
Mesothelioma	1 (0.1) [0]
Metabolic acidosis	1 (0.1) [0]
Metastases to lung	1 (0.1) [0]
Metastases to spine	1 (0.1) [0]
Myopathy steroid	1 (0.1) [0]
Non-cardiac chest pain	1 (0.1) [0]
Oropharyngeal cancer stage unspecified	1 (0.1) [0]
Orthostatic hypotension	1 (0.1) [0]
Osteoporosis	1 (0.1) [0]
Ovarian cyst	1 (0.1) [0]
Pancreatic carcinoma	1 (0.1) [0]
Pancreatic carcinoma metastatic	1 (0.1) [0]
Peptic ulcer haemorrhage	1 (0.1) [0]
Polymyalgia rheumatica	1 (0.1) [0]
Post herpetic neuralgia	1 (0.1) [0]
Prostate cancer	1 (0.1) [0]
Pulmonary embolism	1 (0.1) [0]
Radiculopathy	1 (0.1) [0]
Renal failure acute	1 (0.1) [0]
Respiratory failure	1 (0.1) [0]
Retinal detachment	1 (0.1) [0]
Rhabdomyolysis	1 (0.1) [0]
Skin infection	1 (0.1) [0]
Skin laceration	1 (0.1) [0]
Skin lesion	1 (0.1) [0]
Spinal fracture	1 (0.1) [0]
Subdural haematoma	1 (0.1) [0]
Syncope	1 (0.1) [0]
Syncope vasovagal	1 (0.1) [0]
Thoracic vertebral fracture	1 (0.1) [0]
Upper respiratory tract infection	1 (0.1) [0]
Urinary bladder haemorrhage	1 (0.1) [0]
Ventricular fibrillation	1 (0.1) [0]
Vertigo	1 (0.1) [0]
Volvulus	1 (0.1) [0]
Vomiting	1 (0.1) [0]
Fatal SAEs	All subjects
	N = 1524
Subjects with fatal SAE(s), n (%) [n related]	14 (0.9) [0]
Myocardial infarction	2 (0.1) [0]

Pneumonia	2 (0.1) [0]
Acute respiratory failure	1 (0.1) [0]
Aortic stenosis	1 (0.1) [0]
Colon cancer	1 (0.1) [0]
Diabetes mellitus	1 (0.1) [0]
Duodenal ulcer perforation	1 (0.1) [0]
Gastroenteritis	1 (0.1) [0]
Mesothelioma	1 (0.1) [0]
Metastases to lung	1 (0.1) [0]
Oropharyngeal cancer stage unspecified	1 (0.1) [0]
Pancreatic carcinoma metastatic	1 (0.1) [0]
Renal failure acute	1 (0.1) [0]
Respiratory failure	1 (0.1) [0]
Rhabdomyolysis	1 (0.1) [0]
Subdural haematoma	1 (0.1) [0]

Conclusion: At least 1 ILI episode was reported by 466 (30.6%) subjects among which 28 (4.9%) were lab confirmed influenza (viral culture and/or RT-PCR). At least one hospitalization or ER visit was reported by 151 (9.9%) subjects. At least one episode of illness (pneumonia, ischemic heart disease, congestive heart failure, acute cerebrovascular disease or COPD exacerbation) was reported by 57 (3.7%) subjects. A total of 9 subjects died during the influenza season. For all subjects who did not report any ILI episode during the influenza season, the mean Barthel Index was 96.8 and 96.5, the mean SF-36 general health score was 77.9 and 78.4, and the mean EQ-5D global score was 0.83 and 0.85 at baseline and at the end of the study, respectively. For all subjects who did report an ILI episode during the influenza season that was not confirmed by viral culture or RT-PCR, the mean Barthel Index was 97.0 and 96.4, the mean SF-36 general health score was 75.7 and 74.9 and the mean EQ-5D global score was 0.82 and 0.82 at baseline and at the end of the study, respectively. For all subjects who reported at least one laboratory-confirmed influenza episode during the influenza season, the mean Barthel Index was 99.3 and 98.2, the mean SF-36 general health score was 80.8 and 79.8, and the mean EQ-5D global score was 0.85 and 0.91 at baseline and at the end of the study, respectively. At 21 days after Flu vaccination, 168 (88.4%), 162 (85.3%) and 185 (97.4%) subjects had seroprotection rates for HI (antibody titres \geq 1:40) against A/New Caledonia, A/California and B/Malaysia, respectively. A total of 129 (8.5%) SAEs and 14 (0.9%) fatal SAEs were reported during the study. None of these SAEs were considered by the investigator to be related to the study vaccination.

Publications: None.

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