

**PUBLIC ASSESSMENT REPORT
Scientific Discussion**

**PANENZA
Pandemic influenza vaccine (H1N1)
(split virion, inactivated)**

FR/H/447/01-02/DC

Applicant: Sanofi Pasteur

Date of the PAR: November 2009

Information about the initial procedure:

Application/Legal Basis	Full Application/Art. 8(3)
Active substance	Split influenza virus, inactivated containing antigen equivalent to: A/California/7/2009 (H1N1)v – like strain (NYMC X – 179A) 15 micrograms HA
Pharmaceutical form	Suspension for injection
Applicant	Sanofi Pasteur
EU-Procedure number	FR/H/447/01-02/DC
End of procedure	13 November 2009

1. INTRODUCTION

The applicant Sanofi Pasteur submitted on 12 October 2009 a marketing authorisation application for PANENZA through decentralised procedure with France acting as the Reference Member State and Belgium, Germany, Italy, Luxembourg and Spain as Concerned Member States.

The legal basis for this application refers to Article 8(3) of Directive 2001/83/EC (New active substance).

Based on the review of the quality, safety and efficacy data, the French Agency – AFSSAPS – has granted on 16 November 2009 a marketing authorisation for PANENZA in the prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

A comprehensive description of indications and doses is given in the SmPC.

During the procedure, no potential serious risk to public health concerns was raised by the Member States involved in the procedure. The procedure was ended positively on 13 November 2009.

2. QUALITY ASPECTS

Introduction

PANENZA is a non-adjuvanted A/H1N1 pandemic influenza vaccine.

The vaccine consists of a sterile suspension of the split inactivated monovalent bulk formulated in a Phosphate Buffered Saline (PBS) solution, including thiomersal as a preservative for the multidose presentation. The vaccine is presented either in multidose container or in pre-filled syringe.

Active substance

A master and working seed lots were prepared from the reference viral strain which was received from CDC (Centers for Disease Control and Prevention). The manufacturing process for the monovalent bulk is similar to the one used for the licensed VAXIGRIP (Sanofi Pasteur seasonal influenza vaccine) and can be divided into four main parts:

- Propagation of the working seed in fertilised hen's eggs, harvesting and pooling of infected allantoic fluid,
- Purification of the whole virus bulk through zonal centrifugation in sucrose gradient,
- Splitting of viral particles by octoxynol-9,
- Inactivation of the split virion by a formaldehyde treatment, followed by a 0.2 µm membrane filtration.

The critical manufacturing steps are derived from the Vaxigrip process and have been validated for the H1N1 strain.

The specifications applied for the control of the active substance comply with the Ph. Eur. monograph 158 (Influenza vaccine (split virion, inactivated)).

Stability studies at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and $+25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ are ongoing on three monovalent bulk batches. Considering the Applicant has committed to report without delay any out of specification result or trend and based on the current shelf-life for the seasonal vaccine, a 2-year shelf-life is accepted for the Active Substance when stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Medicinal product

The finished product manufacturing process is based on Sanofi Pasteur experience on seasonal influenza vaccine.

Each 0.5 ml dose of vaccine has the following composition:

Active Substance:

Split influenza virus, inactivated containing antigen equivalent to:
A/California/7/2009 (H1N1)_v – like strain (NYMC X – 179A) 15 micrograms HA

Other Ingredients:

Thiomersal
Sodium chloride
Potassium chloride
Disodium phosphate dihydrate
Potassium dihydrogen phosphate
Water for injections

The finished product is presented in pre-filled syringes and multidose vials. Thiomersal is included in multidose vials only.

Batch analysis results of one batch of Panenza in both presentations (pre-filled syringe and multidose vial) were provided and comply with the proposed specifications.

Stability studies are ongoing for batches of filled product in both presentations (one batch of pre-filled syringe at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and $+25^{\circ}\text{C} \pm 2^{\circ}\text{C}$, five batches of multidose vial at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$). Considering the Applicant has committed to report without delay any out of specification result or trend and based on the current shelf-life for the seasonal vaccine, a 1-year shelf-life is accepted for the finished product when stored at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

3. NON-CLINICAL ASPECTS

The non clinical data were limited to data from animal model. No toxicological studies were performed for this non adjuvanted vaccine. Data in animals from inactivated non-adjuvanted seasonal multidose vaccines revealed no special hazard for humans based on conventional local tolerance and repeat dose toxicity studies (please refer to the discussion on the use of the vaccine in pregnant women in the clinical part).

The protective efficacy of the vaccine was studied in a ferret disease model.

When considering the lung viral load after challenge, the non adjuvanted vaccine was shown to achieve a marked decrease in viral load. The applicant explored the correlation between HI Antibody titers and viral load. However, the data were too limited to enable any reliable interpretation. The question of the correlation between immunogenicity and efficacy is a critical question that will have to be addressed in clinic in post-approval to investigate further the relevance of the immunogenicity criteria.

4. CLINICAL ASPECTS

Pharmacokinetics:

In accordance with the note for guidance on clinical evaluation of new vaccines (CPMP/EWP/463/97), no pharmacokinetic studies were performed.

Pharmacodynamics:

In relation to vaccines, pharmacodynamic studies are essentially related to the immunogenicity studies that characterise the immune response to vaccines in humans.

The criteria for these studies are laid down in the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03. With no other criteria to suggest at present, this vaccine should be able to elicit sufficient immunological response to meet all three of the current standards set for existing vaccines in adults or older adults laid down in CPMP/BWP/214/96.

The detailed characterisation of the immunological response is discussed below.

Clinical efficacy:

The clinical dossier consists of three European clinical studies conducted with the current vaccine:

- **GPF07**: a phase II, multicenter, randomized, open label trial in healthy adults aged 18 to 60 years and elderly subjects aged >60 years.
- **GPF 08**: a phase II, multicenter, randomized, open label trial in healthy subjects aged 3 to 17 years.
- **GPF 09** is a phase II, multicenter, randomized, open label trial in healthy children aged 6 to 35 months

In addition, the applicant submitted the results of two US studies conducted with an H1N1 vaccine manufactured in the US, as supportive data:

- **FUF14**: a phase II, multicenter, randomized, observer-blinded, placebo-controlled trial in healthy subjects aged ≥ 18 years
- **FUF15**: a phase II, multicenter, randomized, observer-blinded, placebo-controlled trial in healthy subjects aged 6 months to 9 years

All EU and US clinical trials are ongoing.

Of note, half the adult dose (i.e. 0.25 ml) was investigated in the 6 to 35 months age strata in both the EU and US studies.

In all these studies the vaccine was to be administered in a two-dose schedule 21 days apart.

Pregnant women and patients with immunosuppression were excluded from the studies.

The design of the EU and US studies is described below:

	GPF07	GPF08	GPF09
Design	Phase II, multicenter, randomized, open	Phase II, multicenter, randomized, open	Phase II, multicenter, randomized, open
Countries and No of study sites	France (12 centers)	Finland (15 centers)	Finland (15 centers)
Trial Period	18 August 2009 to 12 September 2009 (First vaccination period D0-D21) Interim report available	18 August 2009 to 15 August 2009 (First vaccination period D0-D21) Interim report available	September 2009 to October 2010
Sample size and study posology	450 subjects aged 18 years or over divided in 3 vaccine groups 300 adults aged 18 to 60 years 15 μ g HA, N = 100 7.5 μ g HA+AF03, N = 100 3.8 μ g HA+AF03, N = 100 150 subjects aged over 60 years 15 μ g HA, N = 50 7.5 μ g HA+AF03, N = 50 3.8 μ g HA+AF03, N = 50	303 subjects aged 3 to 17 years divided in 3 vaccine groups 152 aged 3 to 8 years 15 μ g HA, N = 52 7.5 μ g HA+AF03, N = 50 3.8 μ g HA+AF03, N = 50 151 subjects aged 9 to 17 years 15 μ g HA, N = 52 7.5 μ g HA+AF03, N = 50 3.8 μ g HA+AF03, N = 49	400 subjects aged 6 to 35 months 200 children aged 6-11 months 7.5 μ g HA, N = 50 1.9 μ g HA+ half AF03, N = 50 3.8 μ g HA+half AF03, N = 50 3.8 μ g HA+full AF03, N = 50 200 children aged 12-35 months 7.5 μ g HA, N = 50 1.9 μ g HA+ half AF03, N = 50 3.8 μ g HA+half AF03, N = 50 3.8 μ g HA+full AF03, N = 50

Study Objectives	Description of safety and immunogenicity of different A(H1N1) formulations 21 days after each vaccination by hemagglutination inhibition (HAI) and seroneutralization (SN) methods in healthy adults and elderly subjects.	Description of safety and immunogenicity of different A(H1N1) formulations 21 days after each vaccination by hemagglutination inhibition (HAI) and seroneutralization (SN) methods in healthy subjects aged 3 to 17 years.	Description of safety and immunogenicity of each candidate vaccine A(H1N1) 21 days after each vaccination by hemagglutination inhibition (HAI) and seroneutralization (SN) methods in children aged 6 to 35 months
Immune Response Assessments	<u>All subjects:</u> anti-HA antibodies by HAI; neutralizing antibodies by SN	<u>All subjects:</u> anti-HA antibodies by HAI; neutralizing antibodies by SN	<u>All subjects:</u> anti-HA antibodies by HAI; neutralizing antibodies by SN
Study duration Follow-up Duration	Immunogenicity : 42 days Safety follow-up 12 months after the last vaccine administration	Immunogenicity : 42 days Safety follow-up 12 months after the last vaccine administration	Immunogenicity : 42 days Safety follow-up 6 and 12 months after the last vaccine administration

US STUDIES	FUF14	FUF15
Design	Phase II, multicenter, randomized, observer-blinded, placebo-controlled	Phase II, multicenter, randomized, observer-blinded, placebo-controlled
Countries and No of study sites Trial Period	USA (15 sites) 06 August 2009 to 31 August 2009 (First vaccination period D0-D21) Interim report available	USA (15 sites) 06 August 2009 to 04 September 2009 (First vaccination period D0-D21) Interim report available
Sample size and study posology	850 subjects aged 18 years or over 500 adults aged 18 to 64 years Group 1: 7.5µg HA, N =150 Group 2: 15µg HA, N = 150 Group 3: 30 µg HA, N = 150 Group 4: Placebo, N=50 350 subjects aged over 65 years Group 1: 7.5µg HA, N =100 Group 2: 15µg HA, N = 100 Group 3: 30 µg HA, N = 100 Group 4: Placebo, N=50	450 subjects aged 6 months to 9 years 225 subjects aged 3 to 9 years Group 1: 7.5µg HA, N =100 Group 2: 15µg HA, N = 100 Group 3: Placebo, N=25 225 subjects aged 6 to 35 months Group 1: 7.5µg HA, N =100 Group 2: 15µg HA, N = 100 Group 3: Placebo, N=25
Study Objectives	Description of safety and immunogenicity of different A(H1N1) formulations 21 days after each vaccination by hemagglutination inhibition (HAI) and seroneutralization (SN) methods in healthy adults and elderly subjects.	Description of safety and immunogenicity of different A(H1N1) formulations 21 days after each vaccination by hemagglutination inhibition (HAI) and seroneutralization (SN) methods in children aged 6 months to 9 years.
Immune Response Assessments	<u>All subjects:</u> anti-HA antibodies by HAI; neutralizing antibodies by SN	<u>All subjects:</u> anti-HA antibodies by HAI; neutralizing antibodies by SN
Study duration Follow-up Duration	Immunogenicity : 42 days Safety follow-up 6 months after the last vaccine administration	Immunogenicity : 42 days Safety follow-up 6 months after the last vaccine administration

Clinical trials on protective efficacy for this new pandemic vaccine have not been performed yet. Therefore the assessment of the potential protective efficacy of Panenza has been based on a detailed characterisation of the immunological response to the vaccine.

Haemagglutination inhibition (HI) assay

Anti-haemagglutinin antibody titres were measured using the method described by the World Health Organization Collaborating Centre for Influenza, Centres for Disease Control, Atlanta, USA (1991).

The following immunological parameters were assessed according to the EMEA recommendations for pandemic vaccines:

Parameters of the Note for Guidance (CPMP/BWP/214/96)

	18 to 60 years	> 60 years
Seroconversion*or significant increase [†] rate of titer (SCR)	>40%	>30%
Geometric mean titre ratio [‡] (GMTR)	>2.5	>2.0
Proportion of subjects with a titer ≥ 40 (1/dil) [§] subjects (SPR)	>70%	>60%

* For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥ 40 (1/dil) (HAI methods).

† For subjects with a pre-vaccination titer ≥ 10 (1/dil) proportion of subjects with a \geq four-fold increase from pre-to post vaccination (HAI methods).

‡ Geometric mean of individual ratios (post-/pre-vaccination titers)

§ Proportion of subjects achieving a post-vaccination titer ≥ 40 (1/dil)

The applicant also submitted the immunological results performed on virus neutralisation that was determined in a seroneutralisation (SN) assay for the European studies. For the supportive US studies, the SN results will be provided as a post marketing approval commitment.

No data on the influenza-specific cellular responses have been provided.

Supportive data:

The manufacturing process of the vaccine Panenza is the same that used for manufacturing the European trivalent flu seasonal vaccine of the same manufacturer. The manufacturing process of the US H1N1 vaccine is the same that used for manufacturing the US trivalent flu seasonal vaccine (Fluzone®).

Although the manufacturing process for the EU pandemic vaccine and the one used for the US pandemic vaccine are not strictly identical, the processes and the final products display major similarities, e.g. both egg-based, same history passage level for the strain, same splitting agent (octoxynol-9) and same inactivation agent (formaldehyde). They also have the same components: 15 µg/0.5 ml dose of HA content, no adjuvant, thiomersal content for the multidose presentation and phosphate buffer, differing only by gelatine content for US vaccine.

Moreover, a comparison has been performed by EU-SRD method on the HA content for both pandemic EU/US batches that were used in the clinical trials: For batch UD12415 used in the US clinical trials (FUF14 and FUF15), the HA content measured by the EU SRD test is of 16.1 µg/dose for a target SRID HA content of 15 µg/dose, which is in line with the batch used for the European clinical trials.

Consequently, based on the same HA content and the other similarities, the efficacy and safety data obtained with the US H1N1 vaccine have been considered as supportive for the European dossier.

Immunogenicity results:

• **Prevaccination serostatus**

As observed with the other pandemic H1N1 vaccines, a large proportion of the adult population exhibited a certain level of pre-existing immunity.

This general finding is currently under investigation at the CHMP level for all the European pandemic vaccines, including Panenza.

BASELINE SEROPOSITIVITY (HAI or SN $\geq 1:10$)

	N	% (95%CI)	N	% (95%CI)
EU STUDIES				
GPF07	Adult 18-60 y		Elderly > 60y	
	101	HI: 40.6 (30.9; 50.8) SN: 47.0 (36.9; 57.2)	45	HI: 45.5 (30.4; 61.2) SN: 57.8 (42.2; 72.3)
GPF08	Children 3-8 y		Children 9-17 y	
	52	HI: 0 (0; 6.8) SN: 3.8 (0.5; 13.2)	52	HI: 11.5 (4.4; 23.4) SN: 17.3 (8.2; 30.3)
GPF09	Children 6-35 mths			
	101	HI: 0 (0; 3.6) SN: 0 (0; 3.6)		
US STUDIES				
FUF14	Adult 18-64 y		Elderly > 65y	
	128	HI: 54.7 (45.7; 63.5)	87	HI: 62.1 (51.0; 72.3)

FUF15	Children 3-9 y (15µg HA)	Children 6-35 mths (7.5 µg HA)
	91 HI:4.4 (1.2;10.9)	92 HI:5.4 (1.8;12.2)

BASELINE SEROPROTECTION (HAI ≥1: 40, SN ≥ 1:80)

	N	% (95%CI)	N	% (95%CI)
EU STUDIES				
GPF07	Adult 18-60 y		Elderly > 60y	
	101	HI: 14.9 (8.6; 23.3) SN:17.0 (10.2; 25.8)	45	HI: 9.1 (2.5; 21.7) SN: 17.8 (8.0; 32.1)
GPF08	Children 3-8 y		Children 9-17 y	
	52	HI: 0 (0; 6.8) SN: 0.0 (0.0; 6.8)	52	HI: 7.7 (2.1; 18.5) SN: 7.7 (2.1; 18.5)
GPF09	Children 6-35 mths			
	101	HI: 0 (0; 3.6) SN: 0 (0; 3.6)		
US STUDIES				
FUF14	Adult 18-64 y		Elderly > 65y	
	128	HI:28.9 (21.2;37.6)	87	HI:24.1 (15.6;34.5)
FUF15	Children 3-9 y		Children 6-35 mths	
	91	HI:3.3 (0.7;9.3)	92	HI:5.4 (1.8;12.2)

• **Immunogenicity results at Day 21 post-dose 1:**

All three CHMP criteria were reached after one dose of Panenza (with 15 µg) for adult and children above 9 years..

The criteria were not all met for the children of 6-35 months of age for EU and US studies. The same applies for the 3 to 9 years from the US study (*FUF15*). This lower immunogenicity response is not unexpected in this age range and is also known for a flu primo-vaccination, which lead to a vaccination schedule with two doses for priming.

European Studies

	GPF07		GPF08		GPF09
	Adult 18 - 60 y	Elderly > 60 y	Children 3 - 8 y	Children 9 - 17 y	Children 6-35 months
GMTR	N = 101	N = 43	N = 50	N = 52	N = 101
	HI:48.7 (35.6; 66.5) SN:93.7 (67.4; 130)	HI:18.5 (11.7; 29.3) SN:31.2 (17.3; 56.3)	HI:35.0 (24.0; 51.1) SN:123 (79; 192)	HI:125 (81.9; 190) SN:322 (199; 521)	HI:4.54 (3.64; 5.66) SN:14.6 (10.9; 19.5)
SPC	HI:93.0 (86.1; 97.1) SN:96.0 (90.2; 98.9)	HI:83.7 (69.3; 93.2) SN:81.8 (67.3; 91.8)	HI:94.0 (83.5; 98.7) SN:94.0 (83.5; 98.7)	HI:98.1 (89.7; 100) SN:96.2 (86.8; 99.5)	HI:33.3 (24.0; 43.7) SN:53.1 (42.7; 63.4)
SCR	HI:92.0 (84.8; 96.5) SN:96.0 (90.1; 98.9)	HI:81.4 (66.6; 91.6) SN:88.6 (75.4; 96.2)	HI:94.0 (83.5; 98.7) SN:96.0 (86.3; 99.5)	HI:98.1 (89.7; 100) SN:100 (93.2; 100)	HI:33.3 (24.0; 43.7) SN: 81.3 (72.0; 88.5)

US Studies

	FUF14		FUF15	
	Adult 18 - 64 y	Elderly > 65 y	Children 3 - 9 y	Children 6-35 months (7.5 ug)
	N = 128	N = 87	N = 91	N = 92
GMTR	HI:59.6 (46.5;76.5) HI:98.4 (94.5;99.8)	HI:2.1 (16.5;32.2) HI:92.0 (84.1; 96.7)	HI:10.4 (8.02;13.5) HI:74.7 (64.5; 83.3)	HI:3.33 (2.54; 4.35) HI:46.7 (36.3; 57.4)
SPC				
SCR	HI:95.7	HI:88.5	HI:74.7	HI:45.7

	(88.0;99.1)	(79.9;94.3)	(64.5; 83.3)	(35.2; 56.4)
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- **Immunogenicity results at Day 21 post-dose 2:**

In adults and adolescents/children from 9 to 17 years of age, a second dose administered 21 days apart did not increase notably the antibody response in comparison with the immunogenicity levels achieved after the first dose.

For the age strata of children between 3 and 9 years of age, the results of the US study indicated a trend in favor of a second dose for enhancing notably the antibody response.

For children of 6 to 35 months of age, the US data showed that neither the half dose nor the full dose did meet the immunogenicity criteria after one dose but these criteria were achieved after the second dose for both dosages.

EU STUDIES

	GPF07		GPF08	
	Adult 18 - 60 y	Elderly > 60 y	Children 3 - 8 y	Children 9 - 17 y
	N = 101	N = 43	N = 50	N = 52
GMTR (D42/D21)	HI:1.23 (1.06;1.42) SN:1.32 (1.13;1.54)	HI:1.52 (1.16;2.00) SN:1.43 (1.08;1.88)	HI:4.66 (3.69;5.88) SN:3.91 (2.84;5.39)	HI:1.91 (1.45;2.52) SN:1.93 (1.37;2.73)
GMTR (D42/D0)	HI:58.7 (45.0; 76.7) SN:123 (90;168)	HI:28.1 (18.5;42.8) SN:44.5 (24.0;82.6)	HI:163 (119;223) SN:481 (356;650)	HI:238 (179;316) SN:622 (422;915)
SPC	HI:98.0 (93.0;99.8) SN:97.0 (91.6;99.4)	HI:95.3 (84.2;99.4) SN:90.9 (78.3;97.5)	HI:100 (92.9;100) SN:100 (92.9;100)	HI:100 (93.2;100) SN:100 (93.2;100)
SCR	HI:96.0 (90.2;98.9) SN:97.0 (91.5;99.4)	HI:90.7 (77.9;97.4) SN:86.4 (72.6;94.8)	HI:100 (92.9;100) SN:100 (92.9;100)	HI:100 (93.2;100) SN:100 (93.2;100)

US STUDIES

	FUF14		FUF15	
	Adult 18 - 64 y	Elderly > 65 y	Children 3 - 9 y	Children 6-35 months
	N = 128	N = 87	N = 91	N = 92
GMTR (D42/D21)	HI:0.973 (0.877;1.08)	HI:0.984 (0.862;1.12)	HI:5.57 (4.56; 6.81)	HI:9.69 (7.64;12.3)
GMTR (D42/D0)	HI:58.1 (54.8;73.6)	HI:22.7 (17.1;30.1)	HI:55.0 (42.7;70.7)	HI:32.2 (24.1;43.1)
SPC	HI:100 (95.7;100)	HI:95.4 (88.6;98.7)	HI:98.9 (94.0;100)	HI:91.3 (83.6;96.2)
SCR	HI:97.7 (93.3;99.5)	HI:93.1 (85.6;97.4)	HI:98.9 (94.0;100)	HI:90.2 (82.2;95.4)

Additional sub-group analyses:

During the procedure, the applicant has been requested to provide additional sub-groups analyses.

- **SUBGROUP ANALYSES ACCORDING TO THE PRE-EXISTING SEROLOGICAL STATUS BEFORE VACCINATION**

In a context of a pandemic, the applicant was requested to provide subgroup analyses according to the pre-existing serological status during the procedure. The applicant has submitted those data for post-dose 1 and post-dose 2 in subjects aged 18-64 years, and for post dose 1 in subjects above 65 years of age. They are detailed for the EU studies in the following tables:

Immunogenicity Criteria in Adults According to Status at Baseline D0-D21-D42 - HAI Method

parameters	GPF07								
	18-39years			40-60 years			61-64 years		
	All N=41	Sero- negative N=21	Sero- positive N=20	All N=60	Sero- negative N=39	Sero- positive N=21	All N=9	Sero- negative N=4	Sero- positive N=5
GMTR (D21/D0) 95%CI	83.0 54.3;127	108 62.7; 185	64.0 32.3;127	34.1 22.4;52.0	36.2 20.8;63.1	30.5 15.3;60.5	25.4 9.37;68.8	38.1 nc	18.4 nc
GMTR (D42/D0) 95%CI	83.2 56.9;121	132 84.2; 208	51.1 28.8;90.8	46.3 32.2;66.7	57.0 35.9;90.6	31.5 17.2;57.5	34.6 10.8;110	117 nc	13.0 nc
GMTR (D42/D21) 95%CI	1.05 0.849;1.31	1.39 1.00;1.93	0.798 0.623;1.02	1.36 1.12;1.65	1.57 1.19;2.08	1.03 0.877;1.22	1.36 0.492;3.77	3.08 nc	0.707 nc
SPC % (D21) 95%CI	100 91.2 ;100	100 83.2;100	100 83.2;100	88.3 77.4;95.2	84.6 69.5;94.1	95.2 76.2;99.9	100 66.4;100	100 nc	100 nc
SPC % (D42) 95%CI	100 91.4 ;100	100 83.9;100	100 83.2;100	96.7 88.5;99.6	94.9 82.7;99.4	100 83.9;100	100 66.4;100	100 nc	100.0 nc
SCR % (D21) 95%CI	97.5 86.8; 99.9	100 83.2;100	95.0 75.1;100	88.3 77.4;95.2	84.6 69.5;94.1	95.2 76.2;99.9	88.9 51.8;99.7	100 nc	80.0 nc
SCR % (D42) 95%CI	97.6 87.1; 99.9	100 83.9;100	95.0 75.1;100	95.0 86.1;99.0	94.9 82.7;99.4	95.2 76.2;99.9	100 66.4;100	100 nc	100.0 nc

nc: not computed

Immunogenicity Criteria in Adults ≥ 65 years according to serological Status at Baseline D0-D21 – HAI Method

parameters	GPF07					
	65-74 years			>75 years		
	All N=22	Sero- negative N=16	Sero- positive N=6	All N=13	Sero- negative N=4	Sero- positive N=9
GMTR (D21/D0) 95%CI	13.5 7.06;25.6	16.4 7.19;37.2	8.00 2.42;26.4	26.1 8.87;77.0	45.3 nc	19.9 5.54;71.2
SPC % (D21) 95%CI	77.3 54.6;92.2	75.0 47.6;92.7	83.3 35.9;99.6	83.3 51.6;97.9	75.0 nc	87.5 47.3;99.7
SCR % (D21) 95%CI	77.3 54.6;92.2	75.0 47.6;92.7	83.3 35.9;99.6	83.3 51.6;97.9	75.0 nc	87.5 47.3;99.7

nc: not computed

Discussion on the use of the vaccine in pregnant women:

This is an important issue both in terms of efficacy and safety given that:

- The burden of disease and severity during epidemics and pandemics has been consistently shown to be high in pregnant women with an increased risk along the progression of pregnancy term and the presence of co-morbidities. Based on CDC reports, pregnant women appear to be at increased risk for severe complications from the pandemic A(H1N1)v virus infection, as observed in other pandemics.
- The population of pregnant women may represent a particular target for the use of this *non adjuvanted* vaccine considering the long experience of the seasonal vaccine use.

There are data published on the immunogenicity efficacy of seasonal vaccines in pregnant women indicating that no differences are expected between pregnant and non pregnant women.

No reprotoxicity study has been judged necessary for this non adjuvanted vaccine. This approach has been accepted considering that the results previously reported with the trivalent seasonal vaccines could be extrapolated for this vaccine, and the admitted fact that no additional reproductive and developmental toxicity study is needed for the annual seasonal strains variations of the flu seasonal vaccines.

The large clinical experience gained with the similarly produced seasonal vaccine is a source of reassurance for the use of this non adjuvanted vaccine in this specific sub-group population.

CLINICAL SAFETY:

Background

The safety data provided by the MAH that were provided are the following:

- Safety data up to 21 days after the second dose for the European studies GPF07 and GPF08
- Safety data collected up to 21 days after the first dose in the European paediatric study (GPF09) in children from 6 month to 35 months of age
- Safety data up to 21 days after the second dose for the US FUF14 and FUF15

Overall, this safety data assessment has been derived from about 2,400 subjects aged 6 months to \geq 65 year who have received either a non adjuvanted H1N1 vaccine (Panenza) or an adjuvanted formulation of the H1N1 vaccine (the adjuvanted formulation of the H1N1 vaccine was only used in the European studies).

Based on similarities in the final composition of the two non adjuvanted H1N1 vaccines used in the European and US studies and similar manufacturing processes, the safety data obtained with the US H1N1 vaccine have been also regarded as supportive.

Data exposure

In the European studies, safety data derived from 1,154 subjects aged from 6 months to more than 60 years who have received a non adjuvanted or adjuvanted formulation of HA H1N1 vaccine. A total of 350 subjects aged from 6 months to more than 60 years received at least one dose of Panenza. Among these 3 studies, GPF09 study included 401 subjects aged 6 to 35 months, GPF08 study included 303 subjects aged 3 to 17 years and, GPF07 study included 450 adults aged 18 to more than 60 years.

In the US studies, safety data derives from 1323 subjects aged from 6 months to more than 65 years who have received one of the 3 different doses of the non adjuvanted H1N1 vaccine (7.5 μ g, 15 μ g or 30 μ g of HA) or a placebo. A total of 462 subjects received 15 μ g of HA H1N1 vaccine, 464 have received 7.5 μ g of HA vaccines, 247 subjects received 30 μ g of HA and 150 have received a placebo (i.e. normal saline). In these 2 studies, FUF15 study included 474 subjects aged 6 months to 9 years and, FUF14 study included 849 adults aged 18 to more than 65 years.

Adverse events

Solicited adverse events (AEs) were monitored for 7 days post dose 1. Other adverse events (unsolicited AEs) were recorded for 21 days Post dose 1.

Globally, all serious adverse events (SAEs) were recorded during the study period for 21 days post last dose and, up to the end of the trial.

Of note, the collection period for any category of adverse events was the same for paediatric and adult subjects. The duration of subjects follow-up is similar for the same category of adverse events.

Individual studies analysis

- **European studies (GPF07, GPF08 and GPF09):**

- **In subjects aged 18 to 60 years:**

18-60 years (GPF07)	N° DOSE	TOTAL N=300;N=299	3.8 μ g+AF03/0.5 ml N=99; N=99	7.5 μ g+AF03/0.5 ml N=100; N=99	15 μ g/0.5 ml N=101; N=101
Subject experiencing at least one:		Time Period	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate reaction	D1	30 mn	None	None	None
	D2		None	None	None
Solicited reaction	D1	D0-D7	70.7%	66.0%	41.6%
	D2		54.5%	51.5%	33.7%

Solicited injection site reaction	D1	D0-D7	64.6%	58.0%	14.9%
	D2		47.5%	40.4%	20.8%
Injection site pain	D1		63.6%	55.0%	12.9%
	D2		44.4%	38.4%	18.8%
Injection site erythema	D1		5.1%	10.0%	1.0%
	D2		3.0%	3.0%	1.0%
Solicited systemic reaction	D1	D0-D7	45.5%	43.0%	35.6%
	D2		30.3%	31.3%	24.8%
Myalgia	D1		33.3%	33.0%	16.8%
	D2		20.2%	19.2%	16.8%
Headache	D1		28.3%	24.0%	25.7%
	D2		16.2%	17.2%	12.9%
Malaise	D1		9.1%	15.0%	7.9%
	D2		7.1%	12.1%	5.9%
Fever	D1		1.0%	1.0%	1.0%
	D2		4.0%	1.0%	1.0%
Unsolicited non serious reaction	D1	D0-D21	8.1%	13.0%	12.9%
	D2		12.1%	16.2%	17.8%
Unsolicited related non serious reaction	D1	D0-D21	1.0%	7.0%	1.0%
	D2		1.0%	1.0%	1.0%
Serious adverse event	D1	D0-D21	None	1.0% (n=1) Gastro-esophageal reflux	None
	D2		1.0% (n=1) Psychotic disorder	None	None
New onset chronic illness	D1	D0-D21	None	None	None
	D2		None	None	None
Death	D1	D0-D21	None	None	None
	D2		None	None	None
Discontinuation due to an AE	D1		None	None	None
	D2		None	None	None

A second dose of active vaccines/placebo was not administered in one subject out of 300.

No AEs leading to study discontinuation were reported for any subject aged 18 to 60 years. Within 21 days post-immunization, the safety profile of the Panenza after the first and the second vaccination was better than that of the adjuvanted vaccine.

Generally, solicited reactions were less frequent after the second dose than after the first one in all study groups. The frequency of non serious unsolicited reactions was similar after each dose of Panenza.

The frequency of fever reactions was low in the non adjuvanted group (1.0%). Fever reaction was more frequent post Dose 2 (4.0% of subjects) than after the first one (1.0%)

Solicited reactions, mostly solicited injection site reactions, were more frequently reported in the adjuvanted vaccine groups than in the non-adjuvanted vaccine group. Solicited systemic reactions were less reported with Panenza than with the adjuvanted vaccine.

In all study groups, the most frequently reported solicited injection site and systemic reactions were injection site pain, headache and, myalgia.

Two subjects reported SAEs assessed as unrelated to the vaccine but, not leading them to study discontinuation:

- One previous case-report of gastro-esophageal reflux after Dose 1 in a subject aged 78 years included in the 7.5µg HA + AF03 vaccine group;
- One subject aged 23 years included in the 3.8µg HA + AF03 vaccine who experienced a brief psychotic disorder judged unrelated to the vaccination, 9 days post Dose 2.

- In subjects aged more than 60 years:

> 60 years (GPF07)	N° DOSE	TOTAL N=150; N=148	3.8 µg+AF03/0.5 ml N=54; N=54	7.5 µg+AF03/0.5 ml N=51; N=50	15 µg/0.5 ml N=45; N=44
Subject experiencing at least one:		Time Period	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate reaction	D1	30 mn	None	None	None
	D2		None	None	None
Solicited reaction	D1	D0-D7	27.8%	49.0%	15.6%
	D2		27.8%	39.2%	25.0%
Solicited injection site reaction	D1	D0-D7	20.4%	45.1%	6.7%
	D2		20.4%	39.2%	18.2%
Injection site pain	D1		16.7%	43.1%	4.4%
	D2		18.5%	37.3%	15.9%
Injection site erythema	D1		3.7%	15.7%	2.2%
	D2		1.9%	7.8%	0.0%
Solicited systemic reaction	D1	D0-D7	9.3%	17.6%	13.3%
	D2		13.0%	7.8%	18.2%
Myalgia	D1		3.7%	11.8%	11.1%
	D2		7.4%	5.9%	11.4%
Headache	D1		5.6%	5.9%	8.9%
	D2		11.1%	3.9%	11.4%
Malaise	D1		3.7%	5.9%	8.9%
	D2		1.9%	3.9%	0.0%
Fever	D1		None	3.9%	None
	D2		1.9%	0.0%	0.0%
Unsolicited non serious reaction	D1	D0-D21	7.4%	7.8%	4.4%
	D2		9.3%	11.8%	11.4%
Unsolicited related non serious reaction	D1	D0-D21	1.9%	3.9%	0.0%
	D2		None	None	None
Serious adverse event	D1	D0-D21	None	None	2.2% (n=1) Malaise
	D2		None	1.9% (n=1) Ischemic stroke	None
New onset chronic illness	D1	D0-D21	None	None	None
	D2		None	None	None
Death	D1	D0-D21	None	None	None
	D2		None	None	None
Discontinuation due to an AE	D1		None	None	2.2% (n=1) Malaise
	D2		None	1.9% (n=1) Ischemic stroke	None

A second dose of active vaccines/placebo was not administered in only 2 out of 150 subjects. The reasons of discontinuation were due to SAEs judged unrelated to the vaccine (occurrence of malaise post Dose 1 in subject aged 78 years included in the non adjuvanted vaccine group and, case-report of ischemic stroke complicated by a myocardial infarction post Dose 2 in subject aged 89 years included in the 7.5µg + AF03 vaccine group).

Within 21 days post-immunization, the safety profile of Panenza after the first and the second dose better was better than those of the adjuvanted vaccine.

Generally, solicited reactions and unsolicited events were less frequent after the second dose than after the first one with Panenza.

Solicited reactions, mostly solicited injection site reactions, were less frequently reported in the Panenza group. The frequency of solicited systemic reactions was similar in all study groups after each dose.

In all study groups, the most frequently reported solicited injection site and systemic reactions were injection site pain, headache and myalgia.

– In subjects aged 9 to 17 years:

9-17 years (GPF08)	N° DOSE	TOTAL N=151;N=150	3.8 µg+AF03/0.5 ml N=49; N=49	7.5 µg+AF03/0.5 ml N=50; N=49	15 µg/0.5 ml N=52; N=52
Subject experiencing at least one:		Time Period	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate reaction	D1	30 mn	None	None	None
	D2		None	None	None
Solicited reaction	D1	D0-D7	98.0%	90.0%	75.0%
	D2		79.6%	81.6%	61.5%
Solicited injection site reaction	D1	D0-D7	83.7%	84.0%	63.5%
	D2		69.4%	73.5%	53.8%
Injection site pain	D1		79.6%	76.0%	61.5%
	D2		67.3%	73.5%	53.8%
Injection site erythema	D1		22.4%	18.0%	9.6%
	D2		22.4%	16.3%	5.8%
Solicited systemic reaction	D1	D0-D7	75.5%	58.0%	57.7%
	D2		55.1%	55.1%	34.6
Myalgia	D1		36.7%	30.0%	25.0%
	D2		32.7%	26.5%	19.2%
Headache	D1		57.1%	48.0%	40.4%
	D2		42.9%	42.9%	28.8%
Malaise	D1		36.7%	32.0%	28.8%
	D2		32.7%	30.6%	13.5%
Fever	D1		6.1%	6.0%	1.9%
	D2		6.1%	12.2%	3.8%
Unsolicited non serious reaction	D1	D0-D21	51.0%	44.0%	40.4%
	D2		26.5%	32.7%	28.8%
Unsolicited related non serious reaction	D1	D0-D21	24.5%	22.0%	11.5%
	D2		6.1%	12.2%	3.8%
Serious adverse event	D1	D0-D21	None	None	None
	D2		None	None	None
New onset chronic illness	D1	D0-D21	None	None	None
	D2		None	None	None
Death	D1	D0-D21	None	None	None
	D2		None	None	None
Discontinuation due to an AE	D1		None	None	None
	D2		None	None	None

No AEs leading to study discontinuation were reported. No SAEs and no discontinuations due to an AE were reported in all study groups.

Within 21 days post-immunization, the safety profile of Panenza after the first and the second dose was better than that of the adjuvanted vaccine.

Generally, solicited reactions and unsolicited events were less frequent after the second dose than after the first one in all study groups except for fever reactions. Both solicited injection site reactions and solicited systemic reactions were less reported with Panenza than with the adjuvanted vaccine.

In all study groups, the most frequently reported solicited injection site and systemic reactions were injection site pain, headache, malaise and, myalgia.

– In subjects aged 3 to 8 years:

3-8 years (GPF08)	N° DOSE	TOTAL N=152;N=149	3.8 µg+AF03/0.5 ml N=50; N=50	7.5 µg+AF03/0.5 ml N=51; N=50	15 µg/0.5 ml N=51; N=49
Subject experiencing at least one:		Time Period	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited	D1	30 mn	None	None	None

immediate reaction	D2		None	2.0% (n=1)	None
Solicited reaction	D1	D0-D7	86.0%	86.3%	68.6%
	D2		86.0%	74.0%	59.2%
Solicited injection site reaction	D1	D0-D7	84.0%	74.5%	54.9%
	D2		78.0%	74.0%	51.0%
Injection site pain	D1		80.0%	70.6%	45.1%
	D2		74.0%	60.0%	46.9%
Injection site erythema	D1		36.0%	39.2%	13.7%
	D2		38.0%	52.0%	16.3%
Solicited systemic reaction	D1	D0-D7	54.0%	54.9%	37.3%
	D2		50.0%	40.0%	28.6%
Myalgia	D1		32.0%	17.6%	11.8%
	D2		24.0%	20.0%	8.2%
Headache	D1		20.0%	33.3%	21.6%
	D2		32.0%	24.0%	12.2%
Malaise	D1		20.0%	27.5%	21.6%
	D2		36.0%	22.0%	14.3%
Fever	D1		4.0%	13.7%	2.0%
	D2		20.0%	12.0%	4.1%
Unsolicited non serious reaction	D1	D0-D21	26.0%	45.1%	56.9%
	D2		26.0%	48.0%	44.9%
Unsolicited related non serious reaction	D1	D0-D21	8.0%	21.6%	23.5%
	D2		6.0%	14.0%	10.2%
Serious adverse event	D1	D0-D21	0.0%	1.9% (n=1) Pneumonie	1.9% (n=1) Asthme
	D2		None	None	2.0%
New onset chronic illness	D1	D0-D21	None	None	None
	D2		None	None	None
Death	D1	D0-D21	None	None	None
	D2		None	None	None
Discontinuation due to an AE	D1		0.0%	1.9% (n=1) Pneumonie	None
	D2		None	None	None

A second dose of active vaccines/placebo was not administered in 3 subjects out of 152. The reason of discontinuation of one of them was due to a SAEs judged unrelated to the vaccine (occurrence of pneumonia post Dose 1 in subject aged 5 years included in the 7.5µg HA vaccine group).

Within 21 days post-immunization, the safety profile of panenza after the first and the second vaccination was better than that of the adjuvanted vaccine, with a lower frequency of the AEs after the second dose than after the first one.

Generally, solicited reactions and unsolicited events were less frequent after the second vaccination than after the first one in all study groups except for fever reactions. Both solicited injection site reactions and solicited systemic reactions were less reported with panenza than with the adjuvanted vaccine.

Solicited reactions, mostly solicited injection site reactions, were more frequently reported in the adjuvanted vaccine groups.

In all study group, the most frequently reported solicited injection site and systemic reactions were injection site pain, headache and, malaise.

One related SAE (bronchial asthma) was reported as related by the Sponsor and no AESI was reported up to D42.

- In subjects aged 6 to 35 months:

In the European study GPF09, the safety data derives from 401 subjects aged from 6 to 35 months who have received only one dose of a non adjuvanted or adjuvanted formulations of H1N1 vaccine at the current stage of evaluation. A total of 101 subjects received half a dose of Panenza (7.5 ug of HA).

6-11 months (GPF09)	TOTAL N=201	N° Dose	Gpe 1 : 1.9µg+1/2AFO3 N=48	Gpe2 : 3.8µg+1/2AF03 N=50	Gp3: 3.8µg+AF03 N=52	Gp4 : 7.5µg N= 51
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	0.0	0.0
		D2				
Solicited AEs	D0-D7	D1	77.1	76.0	82.7	82.4
		D2				
Solicited local AEs	D0-D7	D1	35.4	42.0	50.0	27.5
		D2				
Local pain/tenderness		D1	18.8	20.4	28.8	9.8
		D2				
Local erythema		D1	10.4	14.0	30.8	13.7
		D2				
Solicited systemic AEs	D0-D7	D1	70.8	64.0	69.2	74.5
		D2				
Irritability		D1	45.8	40.8	42.3	62.7
		D2				
Crying abnormal		D1	39.6	36.0	26.9	41.2
		D2				
Appetite lost		D1	33.3	24.5	26.9	25.5
		D2				
Drowsiness		D1	22.9	22.4	30.8	25.5
		D2				
Fever		D1	8.3	18.0	17.3	7.8
		D2				
Unsolicited Non Serious AEs	D0-D21	D1	64.6	66.0	53.8	64.7
		D2				
Unsolicited Non Serious related AEs	D0-D21	D1	12.5	8.0	7.7	7.8
		D2				
SAEs	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
New onset chronic illness	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
Death	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
Discontinuation due to an AE		D1	0.0	0.0	0.0	0.0
		D2				
12-35 months (GPF09)	TOTAL N=200	N° Dose	Gpe 1 : 1.9µg+1/2AFO3 N=48	Gpe2 : 3.8µg+1/2AF03 N=50	Gp3: 3.8µg+AF03 N=52	Gp4 : 7.5µg N= 50
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	0.0	0.0
		D2				
Solicited AEs	D0-D7	D1	68.8	62.0	67.3	61.2
		D2				
Solicited local AEs	D0-D7	D1	60.4	52.0	59.6	51.0
		D2				
Local pain/tenderness		D1	50.0	36.0	50.0	30.6
		D2				
Local erythema		D1	14.6	14.0	28.8	14.3
		D2				

Solicited systemic AEs	D0-D7	D1	33.3	32.0	42.3	30.6
		D2				
Headache		D1	2.9	0.0	2.8	2.6
		D2				
Malaise		D1	17.6	0.0	5.6	15.4
		D2				
Myalgia		D1	11.8	2.9	16.2	10.3
		D2				
Shivering		D1	5.9	2.9	16.7	2.6
		D2				
Fever		D1	0.0	8.6	8.1	2.6
		D2				
Unsolicited Non Serious AEs	D0-D21	D1	58.3	68.0	55.8	56.0
		D2				
Unsolicited Non Serious related AEs	D0-D21	D1	10.4	14.0	9.6	14.0
		D2				
SAEs	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
New onset chronic illness	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
Death	D0-D21	D1	0.0	0.0	0.0	0.0
		D2				
Discontinuation due to an AE		D1	0.0	0.0	0.0	0.0
		D2				

Within 21 days post-immunization, the safety profile of Panenza and the adjuvanted vaccine after the first vaccination was similar.

Solicited reactions, particularly solicited injection site reactions, were more frequently reported with the adjuvanted vaccine than with Panenza.

In all study groups, the most frequently reported solicited injection site reaction was injection site pain/tenderness. The most frequently reported solicited systemic reactions were malaise and myalgia for subjects aged 12 to 35 months, and irritability and abnormal crying in infants of 6 -11 months of age. Most solicited reactions were of Grade 1 intensity, occurred within 3 days after the administration and resolved within 3 days. No grade 2 and 3 fever reactions were reported with Panenza.

No SAEs and no discontinuations due to an AE were reported in all study groups.

- **US studies (FUF14 and FUF15):**

- **In subjects aged 18 to 64 years:**

18-64 years (FUF14)	TOTAL N=497 N=483	N° Dose	Gpe 1 : 7.5µg N=150 N=144	Gpe2 : 15µg N=151 N=147	Gp3 : 30µg N= 148 N=145	Gp4 : Placebo N= 48 N=47
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	0.0	0.0
		D2	0.0	0.0	0.0	0.0
Solicited AEs	D0-D7	D1	58.9	50.7	57.2	44.7
		D2	44.3	39.3	53.1	36.2
Solicited local AEs	D0-D7	D1	36.8	28.1	33.1	17.0
		D2	28.6	29.7	39.9	8.5
Local pain		D1	37.1	29.3	32.7	16.3
		D2	27.9	29.0	39.2	8.5
Local swelling		D1	0.7	1.4	1.4	0.0
		D2	0.0	1.4	1.4	0.0
Solicited systemic AEs	D0-D7	D1	48.6	43.9	42.1	40.4
		D2	32.1	24.1	34.3	36.2
Myalgia		D1	30.1	20.4	22.4	22.4

		D2	15.7	11.0	18.3	10.6
Headache		D1	33.6	32.7	27.2	32.7
		D2	25.7	14.5	21.8	23.4
Malaise		D1	23.8	15.6	18.4	18.4
		D2	15.7	10.3	17.6	12.8
Fever		D1	0.7	0.7	1.4	2.0
		D2	0.7	0.0	0.7	0.0
Unsolicited Non Serious AEs	D0-D21	D1	22.1	19.7	20.1	22.4
		D2	15.3	17.7	15.9	21.3
Unsolicited Non Serious related AEs	D0-D21	D1	1.3	4.6	4.7	8.2
		D2	0.0	0.0	1.4	0.0
SAEs	D0-D21	D1	0.0	0.0	0.0	2.1 (n=1) Diabetes
		D2	0.0	0.6(n=1) Viral gastroenteritis	0.6 (n=1) Gastroenteritis	2.1 (n=1) Right pleural effusion
New onset chronic illness	D0-D21	D1	0.0	0.0	0.7 (n=1) Hypercholesterolaemia	4.2 (n=2) Hypercholesterolaemia HTA , ↗ Cholest, Diabetes
		D2	0.0	0.7 (n=1) Depression	0.0	0.0
Death	D0-D21	D1	0.0	0.0	0.0	0.0
		D2	0.0	0.0	0.0	0.0
Discontinuation due to an AE		D1	0.7% (n=1) Herpes Zoster/Shingles	0.0	0.0	0.0
		D2	0.0	0.0	0.0	0.0

A second dose of active vaccines/placebo was not administered in 14 subjects. The reason for discontinuation in one of them was due to an AE judged unrelated to the vaccine (occurrence of Herpes Zoster post Dose 1 in subject aged 59 years having received 7.5µg HA vaccine).

Within 21 days post-immunization, the safety profile of all study groups after the first and the second vaccination were similar, with a decrease of the frequency of the AEs after the second vaccination compared to the first one.

The most frequently reported solicited injection site reaction was injection site pain. The most frequently reported solicited systemic reactions were headache, myalgia and malaise.

Four SAEs (viral gastroenteritis, Gastroenteritis, Right pleural effusion and diabetes) were reported as unrelated by the Sponsor up to D42.

Four New onset chronic illnesses (NOCIs) were reported as unrelated by the sponsor up to D42. Hypercholesterolaemia was most frequently reported.

– In subjects aged ≥ 65 years:

≥ 65 years (FUF14)	TOTAL N=352 N=339	N° Dose	Gpe 1 : 7.5µg N=99 N=95	Gpe2 : 15µg N=103 N=99	Gp3 : 30µg N= 99 N=97	Gp4 : Placebo N= 51 N=48
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	1.0	0.0
		D2	0.0	0.0	0.0	0.0
Solicited AEs	DO-D7	D1	23.7	23.8	37.8	13.7
		D2	24.5	22.2	25.0	22.9
Solicited local AEs	D0-D7	D1	12.4	12.9	18.4	0.0

		D2	10.6	14.1	19.8	4.2
Local pain		D1	10.3	12.0	16.2	0.0
		D2	10.6	14.1	16.7	4.2
Local ecchymosis		D1	2.1	0.0	2.0	0.0
		D2	0.0	1.0	0.0	2.1
Solicited systemic AEs	D0-D7	D1	16.5	16.8	26.5	13.7
		D2	18.1	15.2	13.5	20.8
Myalgia		D1	7.2	9.0	11.1	4.0
		D2	5.3	10.1	8.3	10.4
Headache		D1	11.3	10.0	16.2	12.0
		D2	9.6	7.1	8.3	18.8
Malaise		D1	4.1	7.0	15.2	8.0
		D2	11.7	4.0	7.3	10.4
Fever		D1	0.0	0.0	1.0	2.0
		D2	0.0	0.0	0.0	2.1
Unsolicited Non Serious AEs	D0-D21	D1	17.2	9.8	17.2	22.0
		D2	14.7	14.1	18.6	14.6
Unsolicited Non Serious related AEs	D0-D21	D1	2.0	1.0	1.0	2.0
		D2	0.0	2.0	4.1	2.1
SAEs	D0-D21	D1	1.0 (n=1) Myasthenia gravis	0.0	0.0	0.0
		D2	0.0	1.0 (n=1) Diverticulitis	2.1(n=2) Left arm laceration Angina	0.0
New onset chronic illness	D0-D21	D1	0.0	0.0	0.0	0.0
		D2	0.0	0.0	0.0	0.0
Death	D0-D21	D1	0.0	0.0	0.0	0.0
		D2	0.0	0.0	0.0	0.0
Discontinuation due to an AE		D1	1.0 (n=1) Macular rash	0.0	0.0	1.9 (n=1) Inf.tractus urinaire
		D2	0.0	0.0	1.0 (n=1) Nausea,dizziness	2.1 (n=1) Rash

A second dose of active vaccines/placebo was not administered in 13 subjects. The reason for discontinuation in 4 of them was due to the occurrence of an AE. Only one of them was judged as related to the vaccine (rash on arms, upper back, and chest in a subject aged 70 years but included in the placebo group).

Within 21 days post-immunization, the safety profile after the first and the second vaccination were similar, with a comparable frequency of the AEs after the second vaccination compared to the first one.

The most frequently reported solicited injection site reaction was injection site pain. The most frequently reported solicited systemic reactions were headache, myalgia and malaise.

Four SAEs (myasthenia gravis, diverticulitis, left arm laceration and angina) were reported as unrelated by the Sponsor up to D42.

– In subjects aged 3 to 9 years:

3-9 years (FUF15)	TOTAL N=245 N=238	N° Dos e	Gpe 1 : 7.5µg N=110 N=111	Gpe2 : 15µg N=110 N=102	Gp3 : Placebo N= 25 N=25
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	4.0
		D2	0.9	0.0	0.0
Solicited AEs	DO-D7	D1	80.0	66.3	88.0
		D2	44.1	45.5	48.0
Solicited local AEs	D0-D7	D1	48.7	47.1	56.0
		D2	35.1	34.7	36.0
Local pain		D1	42.5	40.4	48.0
		D2	30.6	30.7	32.0

Local erythema		D1	12.4	13.5	8.0
		D2	9.0	5.0	8.0
Solicited systemic AEs	D0-D7	D1	28.9	23.1	32.0
		D2	26.1	21.8	28.0
Myalgia		D1	16.8	8.7	4.0
		D2	12.6	10.9	12.0
Headache		D1	13.3	10.6	20.0
		D2	11.7	9.9	12.0
Malaise		D1	15.9	11.5	28.0
		D2	14.4	13.9	20.0
Fever		D1	1.8	1.0	4.0
		D2	3.6	5.0	4.0
Unsolicited Non Serious AEs	D0-D21	D1	31.6	24.5	32.0
		D2	23.4	28.4	28.0
Unsolicited Non Serious related AEs	D0-D21	D1	2.6	2.8	0.0
		D2	1.8	0.0	0.0
SAEs	D0-D21	D1	0.0	0.0	4.0 (n=1) Humerus fracture
		D2	0.0	0.0	0.0
New onset chronic illness	D0-D21	D1	0.0	0.0	0.0
		D2	0.09% (n=1) Seasonal allergies	0.0	0.0
Death	D0-D21	D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0
Discontinuation due to an AE		D1	0.8% (n=2)		
		D2	0.0	0.0	0.0

A second dose of active vaccines/placebo was not administered in 7/245 subjects. According to the MAH, two subjects reported an AE occurring within 21 days of vaccination which led to study discontinuation after Dose 1.

Within 21 days post-immunization, the safety profile of all study groups after the first and the second dose were similar, with a decrease of the frequency of the AEs after the second vaccination compared to the first one.

The most frequently reported solicited injection site reaction was injection site pain. The most frequently reported solicited systemic reactions were headache, malaise and myalgia.

Similar rates and types of non serious unsolicited AEs and ARs within 21 days each injection were reported. Most solicited reactions were of Grade 1 intensity, occurred within 3 days after the administration and resolved within 3 days. Very few Grade 3 solicited reactions were observed following a single or two doses of vaccine. No unsolicited ARs were reported in the 15µg HA vaccine group.

One SAE (humerus fracture) was reported as unrelated by the Sponsor up to D42. No SAEs were reported post Dose 2.

– In subjects aged 6 to 35 months:

6-23 months (FUF15)	TOTAL N=135 N=131	N° Dos e	Gpe 1 : 7.5µg N=61 N=59	Gpe2 : 15µg N=56 N=54	Gp3 : Placebo N= 18 N=18
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	1.8	0.0
		D2	0.0	0.0	0.0
Solicited AEs	D0-D7	D1	59.0	56.4	61.1
		D2	57.6	51.9	55.6
Solicited local AEs	D0-D7	D1	45.9	29.1	38.9
		D2	44.1	29.6	44.4
Local tenderness		D1	39.3	25.5	27.8
		D2	32.2	20.4	38.9
Local erythema		D1	21.3	7.3	5.6
		D2	20.3	9.3	11.1
Solicited systemic AEs	D0-D7	D1	42.6	49.1	44.4
		D2	28.8	42.6	38.9

Irritability		D1	37.7	40.0	38.9
		D2	23.7	31.5	33.3
Crying abnormal		D1	27.9	21.8	27.8
		D2	13.6	16.7	22.2
Appetite lost		D1	13.1	21.8	16.7
		D2	8.5	16.7	16.7
Drowsiness		D1	13.1	20.0	16.7
		D2	13.6	13.0	11.1
Fever		D1	9.8	3.6	0.0
		D2	0.0	9.3	5.6
Unsolicited Non Serious AEs	D0-D21	D1	Unknown	Unknown	Unknown
		D2	27.1	38.9	22.2
Unsolicited Non Serious related AEs	D0-D21	D1	Unknown	Unknown	Unknown
		D2	1.7	3.7	0.0
SAEs	D0-D21	D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0
New onset chronic illness	D0-D21	D1			
		D2	0.0	0.0	0.0
Death	D0-D21	D1			
		D2	0.0	0.0	0.0
Discontinuation due to an AE		D1			
		D2	0.0	0.0	0.0

24-35 months (FUF15)	TOTAL N=94 N=94	N° Dos e	Gpe 1 : 7.5µg N=44 N=42	Gpe2 : 15µg N=42 N=41	Gp3 : Placebo N= 8 N=8
Subject experiencing at least one	Time Period		Nb case-report (%)	Nb case-report (%)	Nb case-report (%)
Unsolicited immediate AEs	30 mn	D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0
Solicited AEs	D0-D7	D1	42.9	40.5	75.0
		D2	39.0	45.0	37.5
Solicited local AEs	D0-D7	D1	31.8	33.3	62.5
		D2	29.3	42.5	37.5
Local pain		D1	28.6	29.3	37.5
		D2	24.4	41.0	25.0
Local erythema		D1	11.9	16.7	37.5
		D2	7.3	22.5	12.5
Solicited systemic AEs	D0-D7	D1	23.8	21.4	37.5
		D2	14.6	22.5	25.0
Myalgia		D1	9.5	7.3	25.0
		D2	0.0	5.1	25.0
Headache		D1	2.4	2.4	12.5
		D2	0.0	2.6	12.5
Malaise		D1	16.7	14.6	37.5
		D2	12.2	15.4	25.0
Fever		D1	2.4	2.4	12.5
		D2	7.3	2.5	0.0
Unsolicited Non Serious AEs	D0-D21	D1	Unknown	Unknown	Unknown
		D2	31.0	29.3	25.0
Unsolicited Non Serious related AEs	D0-D21	D1	Unknown	Unknown	Unknown
		D2	11.9	0.0	12.5
SAEs	D0-D21	D1	2.3% (n=1) (Boil on the right buttock)	0.0	0.0
		D2	0.0	0.0	0.0
New onset chronic illness	D0-D21	D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0
Death	D0-D21	D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0
Discontinuation due to an AE		D1	0.0	0.0	0.0
		D2	0.0	0.0	0.0

A second dose of active vaccines/placebo was not administered in 7/229 subjects. No AEs leading to study discontinuation were reported for any subject aged 6 to 35 months.

The safety profile after the first and the second dose were similar for all study groups, with a decrease of the frequency of the AEs after the second dose compared to the first one.

In all study groups, the most frequently reported solicited injection site reaction was injection site pain/tenderness. The most frequently reported solicited systemic reactions were malaise and myalgia for subjects aged 24 to 35 months, and irritability and abnormal crying in the 6 to 23 months age group. Most solicited reactions were of Grade 1 intensity, occurred within 3 days after the administration and resolved within 3 days. Very few Grade 3 solicited reactions were observed following a single or two doses of vaccine.

Similar rates and types of non serious unsolicited AEs and ARs within 21 days each injection were reported in all age groups in subjects aged 6 to 35 months. Most events were of Grade 1 intensity. Few unsolicited injection site reactions were reported within the studied population (see table above).

One SAE (boil on the right buttock) was reported as unrelated by the Sponsor up to D42.

Discussion on the safety data of Panenza:

No safety concern was identified on the basis on the available data in subjects of all age strata. In all study groups, the most frequently reported solicited injection site reaction was injection site pain/tenderness. The most frequently reported solicited systemic reactions were malaise and myalgia.

No deaths and adverse events of special interest (AESI) case-reports were reported in any of the studies. Analysis of SAEs in any age group did not reveal significant safety concern with the use of the vaccine. Only one case of asthma in a 3-year-old male subject was considered to be related to the vaccine. However, this patient had a history of obstructive bronchitis. Moreover, one week before being enrolled in the study, the subject had finished a 1-month treatment with corticosteroids for obstructive bronchitis, reportedly associated to pet exposure (animal dandruff allergy).

The administration of two doses seem well tolerated, with a similar profile than the one reported with the trivalent flu seasonal vaccine. The frequency of reactions was lower after the second than after the first dose.

RISK MANAGEMENT PLAN

The risk management plan submitted by the applicant is in accordance with the “Guideline on Risk management systems for medicinal products for human use” (EMA/CHMP/96268/2005), with the Risk Management plan template (EMA/192632/2006, published on October 2006) and with the “CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan (RMP) to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine”.

Two pivotal trials (GPF07 and GPF08 studies) are provided in support of the application and aim at testing the immunogenicity and safety of Panenza in the form of a multidose presentation in individuals over 18 and between 3 and 17 years old respectively. Clinical data from another clinical study conducted in children from 6 month to 35 months of age have also been provided. Only 350 subjects have been exposed to Panenza in these trials among them 101 subjects aged 6 months to 35 months received an half dose of Panenza (7.5 ug of HA). Given that the non-adjuvanted vaccine is also available in USA, and that Sanofi Pasteur considers that Panenza and the US vaccine are similar; Sanofi Pasteur committed to add US data in the version 2 of Risk Management Plan to complete the safety database. Furthermore, the applicant committed to complete the safety specification with Vaxigrip data. The applicant committed to put Panenza into perspective with the safety profile of the seasonal vaccine, for important identified risks.

The important identified and potential risks and important missing information are the following:

Important identified risk	Infection site reactions, headache, myalgia and malaise Vaxigrip' important adverse events
Important potential risk	Neuritis, convulsions, anaphylaxis, encephalitis, Guillain-Barré Syndrome, Bell's palsy, demyelinating disorders, vasculitis and vaccination failure

	Contamination, medication errors, overdose, potential risk associated with thiomersal and auto-immune diseases
Important missing information	Pregnant or lactating women
	Immunocompromised patients
	Experience in patients with severe hepatic impairment
	Patients with relevant co-morbidity, sub-populations with genetic polymorphisms or patients of different ethnic origins
	Concomitant use of PANENZA with other vaccines, other medicinal products, food or other substances

The applicant is collaborating with academic teams on investigations of the use of the vaccine in pregnant women and in immunocompromised subjects. Moreover, the applicant will investigate the co-administration with seasonal trivalent inactivated vaccine.

Pharmacovigilance Plan

Furthermore, 2 different systems of adverse drug reaction reporting are planned: mail and phone.

Expedited reporting of AESIs won't be later than 15 calendar days but to report fatal, lifethreatening reactions and AESI as soon as possible, rapid communication between sanofi pasteur and Authorities/Public health services is foreseen.

The applicant will prioritize PV activities focusing on the following adverse events:

- Fatal or life-threatening adverse events;
- Serious unexpected adverse events;
- Adverse events of special interest (AESIs): neuritis, convulsion, anaphylaxis, encephalitis, GBS, demyelinating disorders, Bell's palsy, vasculitis and vaccination failure.

Consumer's reports will not be expedited to regulatory authorities, except in case of medical confirmation, but they will be used for aggregated data reports and signal detection. In the pandemic context, simplified safety reports will be sent monthly to regulatory authorities together with the list of vaccine distribution by batch and country.

All potential safety signals identified from clinical trials or spontaneous sources are planned to be reviewed clinically and evaluated on a bi-weekly or an ad-hoc basis. In parallel, background incidence data are estimated to perform the observed to expected analysis. The applicant has also committed to conduct a disproportional reporting as a complementary method for quantitative signal detection.

The applicant proposes to conduct a post-authorisation prospective cohort study in accordance with the CHMP core RMP for vaccines intended for use in a declared pandemic situation in France. The applicant provided the protocol of this post-authorisation prospective cohort study which is currently under assessment.

The protocol of a planned case-control study planned to monitor Guillain-Barré Syndrome has been provided in the version 2 of the RMP.

In accordance with the CHMP Recommendations for the Pharmacovigilance Plan for Pandemic Influenza Vaccines, the ECDC and vaccine manufacturers are collaborating for implementing epidemiological studies to evaluate the effectiveness of H1N1 pandemic influenza vaccines which will be used in Europe.

Several pharmaco-epidemiological studies are planned to be implemented or ongoing in some concerned member states in special groups of the population such as pregnant women and immunocompromised individuals.

Risk minimisation Plan

The RMS agrees with applicant that routine risk minimization activities are sufficient regarding important risks addressed by the applicant however the assessor considered that activities to minimise the risk of

contamination associated with the use of multi-dose vials and the risk of medication errors should be discussed. As a consequence, the applicant addressed contamination and medication errors in the important missing information section of the RMP version 2.0., considering this also to be important potential risks. The RMP version 2.0 proposes both pharmacovigilance and risk minimization activities to manage and mitigate risks linked to contamination or medication errors.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Discussion on the vaccination schedule by age groups:

The applicant has provided the results of three EU studies together with supportive US studies. The criteria for these studies are laid down in the guideline for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03).

Based on those criteria, the vaccine was shown to elicit a serological response with one dose in healthy adults up to 60 years of age, adolescents and children from 9 years of age onwards. No significant gain in enhancing further the antibody response was observed with a second dose given 21 days apart.

Based on the current knowledge and data available, one cannot formally conclude that a second dose in this age strata would not provide any additional protection. Therefore, a second dose could be given, but its need is not yet established. A second dose may also be necessary to administer later as a “booster”.

Under these circumstances, the applicant has committed to assess the antibody persistence with a one or two immunisation schedule. Moreover, the applicant has committed to investigate the possibility for longer than 21 days interval between two doses.

Given the limited data provided in seronegative subjects older than 60 years of age and especially in subjects older than 80 years, it has been considered more cautious to recommend a two doses immunisation schedule with an interval of 21 days.

Regarding the paediatric population below 9 years of age, the data are in favour of a two dose schedule, which is actually similar to the immunisation schedule recommended for seasonal vaccination, i.e. two half doses for the 6 -35 months and two doses the 3-8 years age strata to be administered 21 days apart.

The risk/benefit of the use of Panenza in infants below 6 months of age has not been established.

Particular commitments from the applicant:

The finding of the unexpectedly high pre-existing immunity for this so-called pandemic strain is under investigation at a European level for all the pandemic vaccines. The applicant is collaborating on this investigation for the Panenza vaccine.

In addition, the correlation between the immunogenicity and the efficacy will have to be addressed by the applicant, to give further reassurance on the degree of protection against this pandemic strain.

In conclusion,

- Panenza is an inactivated and non adjuvanted vaccine whose production reproduces that of the seasonal vaccine Vaxigrip, marketed in EU for several decades. Therefore, a large part of the quality dossier is already known and validated.

- Overall, the safety data derived from the clinical studies submitted did not raise any particular concern. Further reassurance is provided from the large experience gained with the similarly produced seasonal vaccine.

- The population of pregnant women is a critical target population for the vaccination campaign with this non adjuvanted vaccine. The available post-marketing data with the seasonal influenza vaccine support the use of this vaccine in this population.

Based on the quality, efficacy and safety data provided, the benefit/risk assessment of Panenza in the targeted adult and paediatric populations is judged positive. All the Concerned Member States considered that Panenza is approvable.

A risk management plan was submitted in accordance with the CHMP-recommended Core RMP for the pandemic vaccines when intended only for use during an actual pandemic.

The current SmPC, Package Leaflet (PL) and packaging are in the agreed template.