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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** GPF11 **Study Identifier:** NCT01032980 **WHO Universal Trial Number:** U1111-1112-2748
Proprietary Vaccine Name:	PANENZA	

Title of the Study: Post Authorization Safety Study of the Intramuscular Inactivated, Split Virion Pandemic A/H1N1 Influenza Vaccines in Children Aged over 2 Months and in Adult Populations

Study centre: This multicenter study was conducted in France

Publications: None at the time of report writing.

Study period: Date of First enrollment: 05 November 2009
Date of Last visit (contact): 24 January 2011

Development phase: Post Authorization Safety Study

Methodology / Trial Design:

Multicenter, observational, prospective cohort study.

Approximately 5000 subjects aged above 2 months were planned to be enrolled through vaccination centers defined by governmental decision. Vaccination centers involved in the study were located in five cities and their surrounding areas (Paris, Marseille, Lyon, Bordeaux and Lille). Subject distribution was planned as follows:

PANENZA group (planned N = 5000)

Age class	2-23 months	2-60 years*
N	1000	4000

** target: 1000 pregnant women, 1000 immunocompromised subjects, and 2000 subjects <61 years old with risk factors dependent on enrollment rate and vaccination campaign strategy*

Given the timing of the study and the uncertainty of government policy/advice concerning the H1N1 pandemic at the time the study started, several groups such as children, immunocompromised individuals, pregnant women or others had already been vaccinated or were not eligible for vaccination and therefore not eligible to participate in this study when recruitment started.

Following consultation with the "Agence Française de Securité Sanitaires des Produits de Santé" (AFSSAPS), the inclusion of subjects in the PANENZA group was adapted during the course of the study: all subjects vaccinated with PANENZA, regardless of age and presence or not of risk factors, were proposed to be included in GPF11. In addition, all subjects who came to vaccination centers to receive a second injection of PANENZA after having received a first injection outside of the study were proposed to be included in the study and to be followed up for safety after the second vaccination. For these subjects, safety data following the first dose were collected retrospectively.

This study aimed to include any group of the population including subjects at increased risk of H1N1-related complications, such as pregnant women, individuals undergoing immunosuppressive treatment, individuals with cardiovascular disorders, individuals with diabetes and individuals with chronic neurological disorders. Health care workers (HCWs) were also included due to their exposure risk. Included subjects were in line with the target groups defined by the European Medicines Agency (EMA) guidance.

Asthmatic children and elderly people with chronic obstructive pulmonary disease (COPD) were also expected to be among the enrolled subjects.

Subjects were vaccinated with PANENZA according to the recommendations provided in the product leaflet and local recommendations at the time of study start.

Collection of serious adverse events (SAEs) and adverse events of special interest (AESIs) occurred as shown in the table below. Non-serious cutaneous allergic reactions (NSCAR) were collected up to Day 21. Active surveillance occurred on a weekly, fortnightly then monthly basis by telephone for subjects receiving two vaccinations, as follows:

	V01	**Phone call**		**V02**	**Active surveillance (telephone)**										
					Up to 1M PLD				**Up to 2M PLD**		**Up to min. 6M PLD**				
Study Timelines	0	7	14	21	D28		D42	D49	D63	D77	M4	M5	M6	M7	>M7
Contact intervals	-	V01+ D7	V01+ D14	-	V02+ 7D	V02+ 14D	V02+ 21D	V02+ 28D	V02+ 42D	V02+ 56D	V02+ M3	V02+ M4	V02+ M5	V02+ M6	V02+ >M6

*V: Vaccination; D: Days; M: Months; PLD: Post Last Dose; *: Pregnant women*

Note: All subjects receiving the second vaccination of PANENZA after 20 May 2010 were not followed up after the second vaccination.

Active surveillance occurred on a weekly, fortnightly and then monthly basis by telephone for subjects receiving one vaccination, as follows:

		Active surveillance (telephone)										
	V01	**Up to 1M PD**				**Up to 2M PD**		**Up to min. 6M PD**				
Study Timelines	D0	D7	D14	D21	D28	D42	D56	M3	M4	M5	M6	>M6
Contact intervals	-	V01+ 7D	V01+ 14D	V01+ 21D	V01+ 28D	V01+ 42D	V01+ 56D	V01+ M3	V01+ M4	V01+ M5	V01+ M6	V01+ >M6

*V: Vaccination; D: Days; M: Months; PD: Post Dose; *: Pregnant women*

Medical confirmation for suspected or confirmed SAEs and AESIs was sought each time one was identified, by contacting the subject's referral or treating physician.

Objectives:

Primary objective:

- To describe the incidence of SAEs and AESIs after PANENZA administration throughout the study in different age groups

Note: The following AESIs were reported: anaphylaxis, Guillain-Barré Syndrome (GBS), encephalitis, Bell's palsy, neuritis, convulsions, vasculitis, demyelinating disorders and laboratory-confirmed vaccination failure

Primary endpoint:

- Occurrence of SAEs after PANENZA administration throughout the study

Among all potential SAEs, i.e. all AEs (including symptoms) reported during a study visit/phone call that motivated a medical visit, the SAEs were defined as medically confirmed SAEs or any other non-medically confirmed fatal AE.

- Occurrence of AESIs after PANENZA administration throughout the study

Statistical methods for primary objective:

SAEs and AESIs reported throughout the study up to 6 months after the last vaccination (for all subjects) and 3 months following delivery (for pregnant women, if delivery occurred more than 3 months after the last vaccination), were summarized in terms of number and percentage of subjects by age group. For the main parameters, 95% confidence intervals (CIs) of percentages were calculated using the exact binomial distribution (Clopper-Pearson method).

Secondary objective:

- To describe the incidence of non-serious cutaneous allergic reactions after PANENZA administration in different age groups up to 21 days after the last vaccination

Secondary endpoint:

- Occurrence of non-serious cutaneous allergic reactions after PANENZA administration up to 21 days after the last vaccination

Sample size (Number of Subjects):

	Planned Sample Size	Subject included in the SafAS		Discontinued subjects
By Age				
Age	**Total**	**Enrolled**	**Total**	**Total**
2-23 months	1000	871	871	28
2-8 years	4000	1959	2567	34
9-17 years		91		3
18-44 years		316		18
45-60 years		201		12
> 61 years	-	496		33
Total	5000	3934		128
By Risk Category*				
Pregnancy	1000	166		12
HCW	-	60		4
Immunocompromised	-	152		5
Cardiovascular disorders	-	457		28
Diabetes	-	93		9
Neurological disorders	-	110		4
Asthma	-	276		14
COPD	1000	148		12

SafAS: safety analysis set

HCW: Health Care Worker

COPD: Chronic Obstructive Pulmonary Disease

** Risk factors dependent on enrolment rate and vaccination campaign strategy*

Duration of Participation in the Trial:

The planned duration of each subject's participation in the study was approximately 7 months for all subjects (this duration was longer for subjects having received a second dose of PANENZA more than 21 days after the first vaccination). Subjects receiving the second injection of PANENZA after 20 May 2010 had a follow-up of 6 months after the first vaccination but not after the second injection, so as to limit the heterogeneity of the follow-up period across subjects. Pregnant women (defined as subjects with a last menstrual period [LMP] until 1 month following vaccination) were followed up for at least 6 months after the last vaccination and 3 months following delivery (if delivery occurred more than 3 months after the last vaccination). In the event of miscarriage, the subject was followed up for 6 months after the last vaccination. Children born from these pregnant women were also followed up during their first 3 months of life.

The duration of each subject's participation was a maximum of 9 months.

Statistical methods

The same statistical method was used for primary and secondary objectives.

SAEs and AESIs reported throughout the study up to 6 months after the last vaccination (or after the first vaccination for subjects having received the last vaccination after 20 May 2010) and 3 months following delivery (for pregnant women, if delivery occurred more than 3 months after the last vaccination), were summarized in terms of number and percentage of subjects by age group. For the main parameters, 95% CIs of percentages were calculated using the exact binomial distribution (Clopper-Pearson method).

NSCARs reported up to 21 days after the last vaccination (for all subjects) were summarized in terms of number and percentage of subjects by age group per vaccine received. For the main parameters, 95% CIs of percentages were calculated using the exact binomial distribution (Clopper-Pearson method).

In total, 5 statistical analyses were performed: 4 interim analyses and 1 final analysis.

Calculation of sample size:

A cohort of 5000 subjects exposed to PANENZA was planned. The following subgroup was targeted dependent on enrollment rate and the vaccination campaign strategy:

- 1000 children 2-23 months old
- 1000 pregnant women
- 1000 immunocompromised subjects
- 2000 subjects < 61 years old with risk factors

The ability to detect an AE is dependent on the expected frequency of the AE in those exposed to the vaccine, and the total number of subjects.

A cohort of at least 5000 subjects would have provided a probability of 0.95 to observe at least one event which occurred with an incidence of 1/1666 (similarly if no event was observed we could reject, with an alpha level of 5%, incidences greater than 1/1667). Additionally, a subgroup of 1000 subjects would provide a probability of 0.95 to observe at least one event which occurred with an incidence of 1/333.

A sample size of 5000 subjects should have allowed for the detection of at least three cases of an AE, with a probability of 0.876, if the event occurred with a frequency of at least one in 1000 subjects (exact calculation using the binomial distribution).

Finally, 3934 subjects were recruited rather than the planned 5000 subjects. The present report provides safety information obtained from all subjects followed up for 6 months after the last vaccination, as well as data from women exposed to vaccination during their pregnancy and from their newborns. With 3934 subjects included, there was a probability of 0.906 to observe at least one event which occurs with an incidence of 1/1666.

Results summary:

Subject disposition and sample size

A total of 3934 subjects were included in the study and received at least one vaccination of PANENZA between November 2009 and April 2010:

- 1742 were included at the time of their first PANENZA vaccination
- 2192 were included at the time of their second PANENZA vaccination
- Among the 3934 subjects, 2701 received the second vaccination

The overall male: female distribution of the subjects was balanced (1936 males [49.2%]: 1998 females [50.8%]) and the majority of subjects were below the age of 8 years (2830 subjects [71.9%]). All the risk factors defined in the protocol were represented in the enrolled population. A total of 128 subjects discontinued the study either for voluntary withdrawal (123 subjects) or due to an AE (5 subjects). Among the 3934 subjects enrolled, a follow-up duration of 6 months after any vaccination was achieved for 2884 subjects (73.3%).

Safety results

Of the 1659 subjects (42.5%) reporting any potential SAE after any vaccine dose, 1080 subjects (27.7%) experienced a potential SAE which was not medically-confirmed and 786 subjects (20.2%) presented at least one potential SAE which was medically-confirmed as non-serious AE. Medically-confirmed SAEs were recorded for 75 subjects (1.9%).

The risk group for which SAEs were most frequently reported was diabetic group (10.9% of subjects), cardiovascular disorders group (7.6%) and COPD group (6.3%).

More subjects (470 [17.6%]) experienced a potential SAE within 21 days following the second injection than within 21 days following the first injection (363 [9.3%]). The number of subjects experiencing a potential SAE which was not medically-confirmed following the second injection (254 subjects [9.5%]) was also higher than following the first injection (208 subjects [5.3%]). In addition, medically-confirmed non-serious AEs were also reported for more subjects after the second injection (227 [8.5%]) than after the first injection (153 [3.9%]). The percentage of subjects reporting medically confirmed SAEs was exactly the same 21 days after the first and second injections (0.4%). In the subset of subjects included in the study at the time of the first vaccination, the percentages of subjects reporting not medically-confirmed potential SAEs and medically-confirmed non-serious AEs were similar after the first and second vaccinations. In this subset, however, more subjects reported SAEs 21 days after the first vaccination (11 subjects [0.6%]) than 21 days after the second vaccination (1 subject [0.2%]).

The highest proportion of potential SAEs (regardless of medical confirmation, including medically confirmed non-serious AEs) was reported for subjects aged 2-23 months (558 subjects [64.7%]). Non-medically-confirmed potential SAEs and medically-confirmed non-serious AEs after any injection were also recorded for proportionally more subjects in the 2-23 months age group than any other group (383 subjects [44.4%] and 290 subjects [33.6%]).

A total of 84 SAEs were medically-confirmed in 75 subjects. Fifteen subjects (0.4%) experienced at least one medically-confirmed SAE within 21 days of the first injection and 10 subjects (0.4%) experienced at least one medically-confirmed SAE within 21 days of the second injection.

The distribution of medically-confirmed SAEs by age group was mostly in the ≥61 years age group (29 subjects [5.9%] reported a total of 30 SAEs [2 related to the administration of PANENZA]) and in the 45-60 years age group (3.6% of subjects reported a total of 9 SAEs [1 related to the administration of PANENZA]). In the younger age groups, the percentages were lower (1.5% of subjects in the 2-23 months age group reported a total of 18 SAEs [2 related to the administration of PANENZA] and 1.0% of subjects in the 2-8 years age group reported a total of 20 SAEs [4 related to the administration of PANENZA]). No SAEs were reported for the 9-17 years age group.

During the entire study period:

- Four deaths were recorded
- Seven AESIs were reported by 6 subjects

Of the 84 medically-confirmed SAEs reported by 75 subjects, 10 events (reported by 9 subjects – nasopharyngitis, bronchopneumopathy, spontaneous abortion, febrile convulsion [2 events], oral herpes, asthma attack, varicella, pyelonephritis and pulmonary embolism) were considered to be related to the administration of PANENZA. None of the related SAEs was fatal or life-threatening.

Five SAEs led to termination of subject participation in the study (and were considered unrelated to the administration of PANENZA).

Newborns: A total of 149 babies were born to women who were exposed to the vaccine during their pregnancy. Of the 20 newborns (14.9%) reporting any potential SAE, 13 newborns (9.7%) experienced a potential SAE which was not medically-confirmed and 8 newborns (6.0%) presented at least one potential SAE which was medically-confirmed as a non-serious AE. Medically-confirmed SAEs were recorded for 3 newborns (2.2%). Two SAEs (bronchiolitis and gastroenteritis) reported for one newborn were considered as related to PANENZA administration by the referral or treating physician.

NSCAR: Among the 3934 subjects enrolled into the study, 78 subjects (2%) experienced at least 1 NSCAR following any injection. Of these, 13 (0.3%) experienced an allergic reaction at the injection site, 32 (0.8%) at a region of the body other than the injection site and 35 (0.9%) to more than one region of the body. Fifty-one subjects (1.3%) experienced a NSCAR within 21 days of the first administration of PANENZA and twenty-nine subjects (1.1%) experienced a NSCAR following the second administration of PANENZA. The highest proportions of subjects experiencing NSCARs were in the 2-23 months (3.6%) and 45-60 years (3.6%) age groups.

Conclusions:

Based on the results presented in this safety report, no concerns were raised regarding the safety of PANENZA following one or two doses, either in vaccinated subjects or newborns of women who were exposed during pregnancy. The safety profile of PANENZA remains favorable for use as indicated in the prescribing information, including use in all age groups and with underlying health conditions.

Date of Report: 19 August 2011.