Synopsis

Company:	sanofi pasteur
Investigational Product:	Smallpox vaccine, LISTER strain, produced on chick embryo cells (VV LISTER/CEP)
Active Substance:	Live vaccinia virus (LISTER strain)

Title of the Trial:	A Long-Term Safety and Immunogenicity Follow-up of Healthy Adults Vaccinated with One Dose of Smallpox Vaccine (LISTER Strain)
Development Phase:	Phase II
Coordinating Investigator:	Not Disclosed
Investigators and Trial Centers:	Five centres in France
Publications:	None at the time of report writing
Trial Period:	23 October 2006 to 22 June 2011 (Last Contact Last Subject [LCLS]= 22 July 2011)
Methodology/Trial Design:	The study consisted in five annual visits scheduled for the subjects vaccinated in the Phase II trial entitled "Take Evaluation and Safety of Smallpox Vaccine (LISTER Strain) in Naïve Healthy Adults" and referenced as VVL04. For each participant, the time baseline in this study was the date of his/her vaccination in VVL04. Participation in the first year visit scheduled 12 months post-vaccination was mandatory to be enrolled in the study. From Year 3, subjects may be enrolled in VVL05 at any year of their anniversary date (+/- 45 days) of VVL04 vaccination. One diary card (DC) was given to the subjects every year from Month (M) 12 to M48 and was collected at each visit from M24 up to M60 to record any condition he/she may have presented since the last visit. During the first two years of follow-up, phone calls were performed every six months between two annual visits in order to record long-term safety, i.e. two phone calls planned at M18 and M30, respectively. For the subjects who had experienced smallpox vaccine reactions during or after VVL04 or in the course of the present study, the following applied: • M18 and M30 phone calls were to be replaced by visits. • The long-term evolution of these events was to be recorded and the Investigator was requested to arrange annual visits for the subjects with the corresponding medical specialist, i.e. cardiologist, neurologist, dermatologist, and/or infectious disease specialist. The subjects included in VVL05 were followed-up as an observational cohort without any specific constraints such as for instance, limitation of any drug intake or participation in another clinical trial.
Objectives:	1) To yearly describe the vaccinia antibody (Ab) persistence up to five years post-VVL04 vaccination. 2) To follow-up the long-term safety up to five years post-VVL04 vaccination.

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Endpoints:

Immunogenicity

1) Neutralizing Ab titers at 12, 24, 36, 48, and 60 months post-VVL04 vaccination, i.e. (M12, M24, M36, M48, and M60).
2) Titer ratio: M12/Day 28*, M24/M12, M36/M24, M48/M36, and M60/M48.
3) Persistence of detectable neutralizing Ab titer, i.e. ≥10 (1/dil) at M12, M24, M36, M48, and M60.

(*D28 titers were measured in VVL04 and after M12, annual titers were compared to previous year only)

Safety

1) Evolution of smallpox vaccine reactions experienced by subjects during or after VVL04 and included in VVL05.
2) Occurrence of:

- Any serious adverse event (SAE) related to smallpox vaccination.
- Other specific events such as:
  - cardiac events such as myocarditis, myopericarditis, pericarditis, ischemic heart disease (including angina pectoris and myocardial infarction),
  - neurological events such as encephalitis and seizure,
  - cutaneous events such as degenerescence of the scar at or near the vaccination site.

3) Pregnancy (including outcome).

Sample Size:

	Number of Subjects
Planned sample size*	230
Subjects enrolled at V01	147
Sample size for the analysis at V01	147
Subjects attending V02	110
Sample size for the analysis at V02	110†
Subjects attending V03	121
Sample size for the analysis at V03	121
Subjects attending V04	104
Sample size for the analysis at V04	104
Subjects attending V05	103
Sample size for the analysis at V05	103

*Total number of subjects having participated in VVL04 Study and corresponding to the maximum number that could be enrolled in VVL05

†111 subjects for safety analysis set

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Schedules of Vaccination and Specimen Collection and Duration of Participation in the Trial	No vaccinations were performed during the present trial. A total of five blood samples of 10 mL were taken during the study, one per year up to the end of the trial, i.e. at M12, M24, M36, M48 and M60.
Investigational Product:	Smallpox vaccine LISTER strain produced on chick embryo cells and administered previously in VVL04 study.
Form:	Liquid suspension in multidose vials (0.25 mL per vial).
Composition:	Each dose is a drop of approximately 1 µL of vaccine containing approximately $\geq 10^8$ $CCID_{50}$/mL.
Route:	Percutaneous by multiple punctures in the deltoid area.
Batch Numbers:	Not Disclosed
Control Product:	Not applicable as no control product was administered.
Other Product:	Not applicable as no other product was administered.
Inclusion Criteria:	1) Subject vaccinated and who completed the Phase II VVL04 trial. 2) Informed Consent Form (ICF) signed. 3) Subject able to attend all scheduled visits and to comply with all trial procedures. 4) Subject entitled to national social security.
Exclusion Criteria:	1) Subject deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized without his/her consent.
Statistical Methods:	The statistical analyses were descriptive. For each parameter, the point estimate and the 95% Confidence Interval (CI) were used. Results were analyzed annually as a pooled analysis over the three batches of vaccine used in VVL04 study, as similar results between the batches were observed in VVL04. ***Sample size*** The population of the current trial was based on the population of VVL04. Thus, a maximum of 230 subjects was followed up during VVL05. The population was defined each year on the basis of the subjects attending each annual visit.

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Demography:

Among the 230 subjects vaccinated in VVL04 study (mean age ± standard deviation = 22.2 ± 2.1 year), a total of 147 was included at V01 while 83 declined their participation in the study. The mean age ± standard deviation of all subjects included in VVL05 was 23.2 ± 2.1 year.

On D28 post-vaccination in VVL04 study, the antibody titers were similar in subjects who took part in VVL05 and those who did not, which confirms that no bias was introduced

Immunogenicity:

Antibody measurement was performed using the same methodology.

Anti-Vaccinia Ab Titers (SN-1/dil): Descriptive Results at D28, M12, M24, M36, M48 and M60– Immunogenicity Analysis Set

	D28* (N= 147)	**M12 (N= 147)**	**M24 (N= 111)**	**M36 (N= 121)**	**M48 (N= 104)**	**M60 (N= 103)**
GMT	80.07	11.73	9.90	12.43	18.37	13.11
(95% CI)	(70.96; 90.36)	(10.16; 13.54)	(8.58; 11.44)	(10.65; 14.50)	(15.55; 21.69)	(11.03; 15.59)
Anti-vaccinia Ab levels ≥10 1/dil						
%(n)	99.32 (146)	53.74 (79)	50 (55)	59.5 (72)	77.88 (81)	62.14 (64)
(95% CI)	(96.27; 99.98)	(45.34; 61.99)	(40.32; 59.68)	(50.20; 68.33)	(68.69; 85.43)	(52.04; 71.51)

*Analysis performed on the subset of subjects who were vaccinated during VVL04 study and were included in VVL05.

One year after vaccination, the geometric mean titer (GMT) of the 147 subjects included at V01 was 11.73 (1/dil), compared to 80.07 on D28. The geometric mean of individual titers ratio (GMTR) [M12/D28] was 0.15 (1/dil). Around 53% of subjects showed positive titers of anti-vaccinia Ab, i.e. equal or greater than 10 (1/dil), compared to more than 99% on D28 in VVL04.

The same decrease of GMT was observed between D28 and M12 regardless of the batch of the vaccine they received and of the VVL04 vaccination center.

Two years after vaccination, the GMT continued slightly to decrease down to 9.90 (1/dil). The GMTR [M24/M12] for the 110 subjects attending V02 was 0.75. Half of the subjects remained with positive titers of anti-vaccinia Ab. Three years after vaccination, the GMT (12.43 [1/dil]) had levels comparable to Year 1 and Year 2 results. At M36, 59.5% of subjects had a positive level of anti-vaccinia Ab. Four years after vaccination, the GMT (18.37 [1/dil]) slightly increased with 77.88% of subjects having a positive level of anti-vaccinia Ab. Five years after vaccination, the GMT (13.11 [1/dil]) had levels comparable again to Year 1 and Year 3 results. Overall, after a high decrease one year after the administration of VVLISTER/CEP, the persistence of anti-vaccinia Ab remained stable from Year 2 to Year 5, with 50-77% of subjects having a positive level of anti-vaccinia Ab.

Safety:

At inclusion, the safety information was reported through the collection of significant medical history since the end of VVL04 study. Among the 147 included subjects at V01, 25 reported a significant medical history between the end of VVL04 and V01 of VVL05. However, none of these events were reported by the Investigator as specific events (cardiac, neurological and cutaneous events) or events related to smallpox vaccination. The six subjects who reported a related SAE during VVL04 study and who participated in VVL05 did not report any more specific events in the medical history at V01.

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SAEs related to smallpox vaccination:

No SAEs related to smallpox vaccination were reported during the 5-year follow-up.

Specific events (cardiac, neurological and cutaneous events):

During the 5-year period, 2 subjects reported one specific event each, both considered by the Investigator as related to the vaccination: one right paraesthesis (occurring on Year 1 follow-up but not reported on time) and one eczema. Both events were mild and follow-up information could not be retrieved at the time of the CSR writing. In addition, 3 specific events considered by the Investigator as not related to the vaccination were reported: mild eczema, mild event of extrasystoles and post-influenza pericarditis.

Pregnancies:

During the 5-year period, five elective termination of pregnancy and 15 pregnancies cases were reported. Except for one case with no follow-up information available at the time of the clinical study report writing, all pregnancies were followed-up until delivery of a normal infant at full term without any congenital anomaly.

Conclusions:

Not Disclosed