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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** RAB28 **Study Identifier:** NCT00260351
Proprietary Vaccine Name:	PVRV (Purified Vero cell Rabies Vaccine)	

Title of the Study: Immunogenicity and safety of Purified Vero cell Rabies Vaccine (PVRV, Verorab™) administered for rabies post-exposure treatment. Comparison of Essen-IM, Zagreb-IM, and Thai Red Cross (TRC)-ID regimens in the Indian population.

Study centres: 3 sites in India

Publications: None at the time of report writing.

Study period: Date of First enrollment: 15 December 2004
Date of Last visit (contact): 18 July 2006

Development phase: Phase III

Methodology / Trial Design:

This was a randomized, multicenter, open, controlled trial with **three groups** according to the vaccine regimen:

- Group 1 (TRC-ID or test group 1), PVRV administered according to the TRC intradermal (ID) post-exposure prophylaxis (PEP) regimen
  - V01 on day 0 (D0), V02 on D3, V03 on D7, V04 on D14, V06 on D28, V07 on D90, and V08 on D180
- Group 2 (Zagreb-IM or test group 2), PVRV administered according to the Zagreb intramuscular (IM) PEP regimen
  - V01 on D0, V03 on D7, V04 on D14, V05 on D21, V06 on D28, V07 on D90, and V08 on D180
- Group 3 (Essen-IM or reference group), PVRV administered according to the Essen IM PEP regimen
  - V01 on D0, V02 on D3, V03 on D7, V04 on D14, V06 on D28, V07 on D90, and V08 on D180

According to the World Health Organization (WHO) recommendations, subjects with category III exposure received purified equine rabies immunoglobulin (pERIG) on D0 (V01).

Objectives:

Primary objective: (7 visits)

- To demonstrate that PVRV administered according to the TRC-ID regimen (2-2-2-0-0-1-1) was not inferior to PVRV administered according to the Essen-IM regimen (1-1-1-1-0-1-0) in terms of geometric mean titers (GMTs) of virus neutralizing antibody (VNA) on D28, in subjects with a WHO category III exposure.

or

- To demonstrate that PVRV administered according to the Zagreb-IM regimen (2-0-1-0-1-0-0) was not inferior to PVRV administered according to the Essen-IM regimen (1-1-1-1-0-1-0) in terms of GMTs of VNA on D28, in subjects with a WHO category III exposure.

The tested null hypothesis (H_0) for each objective was that the ratio of GMTs ($GMT_{reference}/GMT_{test}$) was ≥ 1.5.

Secondary objectives:

Immunogenicity: To describe the immunogenicity profile of each regimen in terms of GMTs on D0, D7, D14, D90, D180 and seroprotection rate (threshold of 0.5 IU/mL) on D0, D7, D14, D28, D90, D180.

Safety: To assess the safety of the vaccine in each group

Secondary objectives involved only descriptive assessments. Therefore, no clinical hypotheses were formulated.

Endpoints:

***Primary endpoint*:**

- Level of individual VNA on D28 for subjects with a WHO category III exposure.
  GMTs on D28 were calculated and compared in the three regimen groups.

***Secondary endpoints*:**

Immunogenicity:

- Level of VNA and seroprotection rate on D0, D7, D14, D28, D90 and D180 (in accordance with the WHO recommendations, the serological correlate of protection is 0.5 IU/mL). GMTs and seroprotection rates and their corresponding 95% confidence intervals (CIs) were calculated.

Safety:

- Occurrence of any local and systemic immediate reaction (within 30 minutes after each injection);
- Occurrence of any solicited delayed local reaction (the day of injection up to 3 days after);
- Occurrence of any solicited delayed systemic reaction (the day of injection up to 3 days after);
- Occurrence of any unsolicited delayed local and systemic event (the day of injection up to 3 days after);
- Occurrence of any serious adverse event (SAE) any time during the trial.

The numbers and percentages of subjects presenting each one of the criteria listed above and their corresponding 95% CI were calculated. Results were presented after each vaccine injection for each type of reaction/adverse event (AE) according to its severity, duration, and time of onset. AEs were also described by nature (Primary System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA) and relationship to vaccination (for solicited and unsolicited systemic AEs).

Sample size (Number of Subjects):

	Group 1	**Group 2**	**Group 3**	**Total**
N Planned	135	135	135	405
N Included	136	135	134	405
N Completed	128	128	130	386
N Discontinued	8	7	4	19
Voluntary withdrawal	*1*	*0*	*1*	*2*
Lost to follow-up	*7*	*7*	*3*	*17*
N Full Analysis Set (FAS)	136	135	134	405
N Per Protocol Analysis (PP) Set	121	122	122	365
N Safety Analysis Set	136	135	134	405

Schedules of Vaccination and Specimen Collection:

Vaccination:

- Group 1, TRC-ID regimen: 2 intradermal (ID) injections on D0, 2 ID injections on D3, 2 ID injections on D7, 1 ID injection on D28, and 1 ID injection on D90 (i.e. 2-2-2-0-0-1-1)
- Group 2, Zagreb-IM regimen: 2 intramuscular (IM) injections on D0, 1 IM injection on D7, and 1 IM injection on D21 (i.e. 2-0-1-0-1-0-0)
- Group 3, Essen-IM regimen: 1 IM injection on D0, 1 IM injection on D3, 1 IM injection on D7, 1 IM injection on D14, and 1 IM injection on D28 (i.e. 1-1-1-1-0-1-0)

Blood collection:

Six blood samples were drawn from each subject on D0, D7, D14, D28, D90, and D180.

Duration of Participation in the Trial:

The trial lasted 180 days (6 months) for each subject.

Product Under Investigation:

Purified Vero cell Rabies Vaccine (PVRV, Verorab™)

Form/Dose:

Freeze-dried inactivated purified rabies virus reconstituted with diluent/0.5 mL

Route

- Group 1: ID injection; 0.1 mL per injection (≥0.5 IU/injection)
- Group 2: IM injection; 0.5 mL per injection (≥2.5 IU/injection)
- Group 3: IM injection; 0.5 mL per injection (≥2.5 IU/injection)

Batch number:

X0292-2 (expiry date: 28 February 2006)

Control Product: Not applicable

Associated Product:

Purified equine rabies immune globulin (pERIG, Favirab™)

Form/Dose/Route:

Solution for injection/vial of 5 mL/ Infiltration around and into the wound and/or single IM injection into the thigh and/or the gluteal region at the total dose of 40 IU/kg body weight

Batch number: Y5012-1 (expiry date: 31 December 2005)

Statistical methods

Primary criteria analyses

A non-inferiority testing approach was used to compare GMTs on D28 of the TRC-ID and Zagreb-IM regimens against the Essen-IM regimen. The following hypotheses were tested:

(1) H_{01}: $GMT_{Essen}/GMT_{TRC} \geq 1.5$ versus H_{11}: $GMT_{Essen}/GMT_{TRC} < 1.5$

(2) H_{02}: $GMT_{Essen}/GMT_{Zagreb} \geq 1.5$ versus H_{12}: $GMT_{Essen}/GMT_{Zagreb} < 1.5$

with GMT_{Essen} = GMT in the Essen-IM regimen group;

GMT_{TRC} = GMT in the TRC-ID regimen group,

GMT_{Zagreb} = GMT in the Zagreb-IM regimen group; and

1.5 = maximum GMT ratio clinically acceptable to conclude to non-inferiority.

These hypotheses were equivalent to the following ones after Log_{10} transformation:

(1) H_{01}: $Log_{10}(GMT_{Essen}) - Log_{10}(GMT_{TRC}) \geq Log_{10}(1.5) \approx 0.176$ versus
H_{11}: $Log_{10}(GMT_{Essen}) - Log_{10}(GMT_{TRC}) < Log_{10}(1.5) \approx 0.176$

(2) H_{02}: $Log_{10}(GMT_{Essen}) - Log_{10}(GMT_{Zagreb}) \geq Log_{10}(1.5) \approx 0.176$ versus
H_{12}: $Log_{10}(GMT_{Essen}) - Log_{10}(GMT_{Zagreb}) < Log_{10}(1.5) \approx 0.176$

If the H_{01} was rejected, it could be concluded that PVRV given in TRC-ID regimen was not inferior to PVRV given in Essen-IM regimen in terms of GMT on D28. If H_{02} was rejected, it could be concluded that PVRV given in Zagreb-IM regimen was not inferior to PVRV given in Essen-IM regimen in terms of GMT on D28.

The statistical methodology was based on the use of the 95% two-sided CIs of the difference of the decimal log-transformed GMTs. If the upper limit of the CI was smaller than 0.176, the regimen was considered as clinically non-inferior to the Essen- IM regimen in terms of GMT on D28.

Secondary criteria analyses

All secondary criteria were described by group, using usual descriptive statistics.

Sample size

The sample size calculation was performed with the Software Nquery.

Considering the clinically acceptable limit for non-inferiority set at 0.176, an expected standard deviation (SD) equal to 0.41, a global type I error of 5%, and a power of 90%, 116 subjects per group were necessary to test the null hypothesis. Anticipating about 15% of non-evaluable subjects, 135 subjects were included in each regimen group.

Interim analysis

An interim analysis was planned to be performed but not carried out due to the delay in the serological analyses.

Results summary:

Participants were male (80.2%) and female (19.8%) subjects whose ages ranged from 6 to 65 years (mean age was 30.6 ± 11.8 years). The proportion of males and females and the age of the participants were similar in the three groups.

Immunogenicity

Primary objective

In the PP Set, geometric mean rabies VNA titers on D28 were 3.5 ± 3.7 IU/mL in the TRC-ID group, 4.4 ± 3.2 IU/mL in the Zagreb-IM group, and 3.3 ± 2.8 IU/mL in the Essen-IM group. The differences in log_{10}-transformed GMTs between the TRC-ID or the Zagreb-IM and the Essen-IM groups were -0.03 (95% CI: -0.18; 0.12) and -0.12 (95% CI: -0.26; 0.01), respectively. The upper limits of the 95% CI of the difference in log_{10}-transformed GMTs (0.12 and 0.01, respectively) were <0.176, indicating that both the TRC-ID and Zagreb-IM regimens could be considered as clinically non-inferior to the Essen-IM regimen in terms of GMT on D28.

In the FAS, geometric mean VNA titers on D28 were 3.4 ± 3.7 IU/mL in the TRC-ID group, 4.3 ± 3.2 IU/mL in the Zagreb-IM group and 3.4 ± 2.9 IU/mL in the Essen-IM group. The differences in log_{10}-transformed GMTs between the TRC-ID or the Zagreb-IM and the Essen-IM groups were 0.00 (95% CI: -0.14; 0.15) and -0.10 (-0.24; 0.04), respectively. The upper limits of the 95% CI of the difference in log_{10}-transformed GMTs (0.15 and 0.04, respectively) were <0.176, indicating that both the TRC-ID and Zagreb-IM regimens could be considered as clinically non-inferior to the Essen-IM regimen in terms of GMT on D28.

Secondary immunogenicity objectives

At baseline, in the PP Set, VNA titers were low (nearly all the VNA titers were <0.5 IU/mL) and similar in the three groups. They increased in all groups after the vaccine injections to reach their maximum on D28 in the Zagreb-IM group (4.4 ± 3.2 IU/mL) and on D180 in the TRC-ID group (5.6 ± 3.5 IU/mL) and the Essen-IM group (3.8 ± 4.4 IU/mL). Similar results were found in the FAS.

At baseline, in the PP Set, all the subjects except 4 in the TRC-ID group, 2 in the Zagreb-IM group, and 6 in the Essen-IM group had VNA titers <0.5 IU/mL. In all groups, the percentage of subjects with VNA titers ≥0.5 IU/mL increased after the vaccine injections to reach their maximum on D28 in the Zagreb-IM group (99.2%) and on D180 in the TRC-ID and the Essen-IM groups (100%). On D28, 99.2% of the subjects from the TRC-ID group, 99.2% of the subjects from the Zagreb-IM group, and 98.4% of the subjects from the Essen-IM group had VNA ≥0.5 IU/mL. Similar results were found in the FAS.

Safety:

No deaths, no SAEs, and no AEs leading to premature withdrawal were reported during the study.

In the TRC-ID group

No immediate systemic reaction was reported. Overall, 22 subjects (16.4%), all from center 2, experienced 371 immediate local reactions (i.e. erythema, pain, and induration). All these immediate local reactions were of mild intensity and spontaneously resolved within 9 days.

Within the 3 days following the D0, D3, D7, D28 and D90 injections, 13 subjects (9.7%), 10 from center 2 and 3 from center 3, experienced 174 delayed local reactions. All these delayed local reactions were solicited local reactions (i.e. erythema and induration, followed by pain and pruritus) of mild intensity that commonly occurred within 1 day after vaccine injection and either lasted ≤1 day or between 4 and 7 days.

Within the 3 days following the D0, D3, D7, D28 and D90 injections, 7 subjects (5.2%), 4 from center 1 and 3 from center 3, experienced 10 delayed systemic AEs. All these delayed systemic AEs were of mild intensity, and nearly all were solicited systemic AEs (i.e. arthralgia, dizziness, fever, headache, myalgia, and urticaria rash). The vast majority of delayed systemic AEs occurred within the day after vaccine injections and lasted ≤3 days. Among the 7 subjects with delayed systemic AEs, 2 experienced delayed systemic reactions: one subject experienced fever (38°C) after D3 injections and one subject experienced body pain (unsolicited reaction) after D28 injection.

In the Zagreb-IM group

No immediate systemic reaction was reported, and no subject experienced immediate local reactions.

Within the 3 days following the D0, D7 and D21 injections, 3 subjects (2.3%), all from center 3, experienced 9 delayed local reactions All these delayed local reactions were solicited local reactions (i.e. pain and pruritus) of mild intensity that occurred within 1 day after vaccine injection and lasted ≤3 days.

Within the 3 days following the D0, D7 and D21 injections, 4 subjects (3.0%), 1 from center 1 and 3 from center 3, experienced 6 delayed systemic AEs. All these delayed systemic AEs were of mild intensity, and nearly all were solicited systemic AEs (i.e. arthralgia, headache, and myalgia). Delayed systemic AEs commonly occurred within the day after vaccine injections and always lasted ≤3 days. Among the 4 subjects with delayed systemic AEs, 3 experienced delayed systemic reactions: one subject experienced headache after D0 injections, one subject experienced arthralgia and myalgia after D7 injection, and one subject experienced headache after D7 injection.

In the Essen-IM group

No immediate systemic reaction was reported, and no subject experienced immediate local reactions.

Within the 3 days following the D0, D3, D7, D14 and D28 injections, 6 subjects (4.5%), 5 from center 3 and 1 from center 1, experienced 17 delayed local reactions. All these delayed local reactions were solicited local reactions (i.e. pain and pruritus) of mild intensity that occurred within 1 day after vaccine injection and commonly lasted between 2 and 3 days.

Within the 3 days following the D0, D3, D7, D14 and D28 injections, 6 subjects (4.5%), 3 from center 1 and 3 from center 3, experienced 19 delayed systemic AEs. All delayed systemic AEs except one (a case of drowsiness of moderate intensity) were of mild intensity. The vast majority of delayed systemic AEs were solicited systemic AEs (i.e. arthralgia, dizziness, dyspnea, fever, general pruritus, headache, nausea, and urticaria rash). Delayed systemic AEs commonly occurred within the day after injections and lasted ≤3 days. Amongst the 6 subjects with delayed systemic AEs, 4 experienced delayed systemic reactions: one subject experienced nausea after D0 injection, and dyspnea and nausea after D3 injection; one subject experienced headache after D3 injection; one subject experienced dizziness, nausea, dyspnea, and general pruritus after D7 injection, and dizziness, headache, and urticaria rash after D14 injection; and one subject experienced drowsiness after D14 injection (this event required health care contact).

Conclusions:

This study showed that:

- PVRV administered according to the TRC-ID regimen was not inferior to PVRV administered according to the Essen-IM regimen in terms of GMTs on D28, in subjects with a WHO category III exposure
- PVRV administered according to the Zagreb-IM regimen was not inferior to PVRV administered according to the Essen-IM regimen in terms of GMTs on D28, in subjects with a WHO category III exposure
- The immunogenicity profile of the three rabies post-exposure prophylaxis regimen differed in terms of GMTs and seroprotection rates on D0, D7, D14, D28, D90, and D180. The maximum GMTs and seroprotection rates were observed on D28 for the Zagreb-IM regimen and on D180 for the TRC-ID and Essen-IM regimens.
- The three regimens were safe and well tolerated in subjects with a WHO category III exposure, although the TRC-ID regimen induced a higher number of immediate local reactions than the IM regimens.

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