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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** VBK12 **Study Identifier:** NCT00830648
Proprietary Vaccine Name:	Live Attenuated Varicella Virus Vaccine Biken (Varicela Biken)	

Title of the Study: Safety of a Second Dose of Biken's Varicella Vaccine Administered at 4 to 6 Years of Age in Healthy Children in Argentina

Study centre: 1 site in Argentina

Publications: None at the time of report writing.

Study period: Date of First enrollment: 23 January 2009
Date of Last visit (contact): 04 December 2009

Development phase: Phase IV

Methodology / Trial Design:

Open, monocenter, one-arm phase IV study in children.

Children were allocated to a single study group, and 122 out of a planned 150 subjects received a second dose of Varicella vaccine (Varicela Biken) by subcutaneous (SC) administration into the right upper arm at 4 to 6 years of age.

Objectives:

To describe the safety after a second dose of the study vaccine.

Endpoints:

The endpoints for the safety evaluation were:

- The occurrence, intensity and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination.
- The occurrence, time to onset, number of days of occurrence and intensity of solicited (terms pre-listed in the Case Report Form [CRF]) injection site and systemic reactions occurring between D0 and D7 after injection.
- The occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration, intensity and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs from vaccination day to next study visit (from V01 to V02).
- The occurrence, nature (MedDRA preferred term), relationship to vaccination, outcome and seriousness of any serious AE (SAE) occurring throughout the trial (from V01 to V02).

Assessment methods:

Solicited reactions were collected within 7 days after vaccination. The number and percentage of subjects reporting any solicited injection site reactions or any solicited systemic reactions were summarized by intensity (grade 1, 2, and 3), number of days of occurrence (1 to 3 days, 4 to 7 days, and ≥8 days), and time period of onset (Days 0 to 3, Days 4 to 7, and Days 0 to 7 after vaccination) for each reaction term.

Unsolicited injection site reactions and unsolicited systemic events were collected from Visit 1 (V01) up to V02. They were coded by MedDRA (version 11.1) preferred term and System Organ Class (SOC). The number and percentage of subjects reporting any of these AEs and the number and percentage of subjects reporting any immediate unsolicited systemic AEs (within 30 minutes of vaccination) were summarized by intensity for each preferred term and SOC that had at least one report. The number and percentage of subjects reporting unsolicited systemic events (whether immediate or not) were also summarized by relationship to study vaccine.

SAEs were collected up to V02. The number and percentage of subjects reporting any SAEs were summarized for each preferred term and SOC that had at least one report, as well as by seriousness criterion and outcome.

Sample size (Number of Subjects):

Number planned	150
Number included	122
Number completed	122
Safety Analysis Set	122

Schedules of Vaccination and Specimen Collection:

Two visits (V) were performed in all children.

All subjects received a second dose of Varicella vaccine (Varicela Biken) at 4 to 6 years of age.

Duration of Participation in the Trial:

The expected total duration of follow-up (first visit to last visit) for each subject was 28 to 35 days.

Product Under Investigation:

Live Attenuated Varicella Virus Vaccine (Varicela Biken) manufactured by Biken in Japan.

Form/Dose/Route:

Lyophilized virus suspension reconstituted with distilled water for injection/0.5 mL/Subcutaneous (SC) into the right upper arm.

Batch number:

CP068E and CP080D

Control Product: Not applicable

Other Product(s): Not applicable

Statistical methods

Analysis of safety

The analysis was descriptive.

For each endpoint, the percentage of subjects with the endpoint (i.e. with a given symptom) was computed with its 95% confidence interval (CI).

Unsolicited systemic AEs reported in the 30 minutes after vaccination were summarized by intensity and relationship to vaccination.

Solicited injection site and systemic adverse reactions (ARs) occurring within 8 days post-vaccination (D0 to D7) were described by intensity, number of days of occurrence, and time to onset for each reaction term.

Unsolicited injection site and systemic events were analyzed by nature (MedDRA SOC and preferred term), by intensity and relationship to vaccination.

SAEs were summarized by nature (MedDRA preferred term and SOC), as well as by seriousness criterion and outcome.

Sample size:

The sample size was arbitrarily set to 150 subjects so that there was a 95% probability to observe at least one event which occurred with an incidence of 2%. However, as the number of subjects included was reduced to 122 subjects, instead of 150, there was a 95% probability to observe at least one event, which occurred with an incidence of 2.5% and a 92% probability to observe at least one event with an incidence of 2%.

Results summary:

A total of 122 subjects were included in the trial.

No subjects had an early termination. No subjects were voluntarily withdrawn, not for an AE. No subjects were discontinued for non-compliance with the protocol.

Demographic characteristics

The median age at Visit 1 (V01) at the time of the study vaccine injection was 5.2 years (4.0; 7.0, min; max). Two subjects were enrolled 1 day before their 7th birthday (i.e. still within the inclusion criterion of 4 to 6 years), however the statistical calculation followed a formula which rounded off these ages to 7.0 ([date of inclusion (V01) birth date]/365.25). These were not protocol deviations.

There were 56 male (45.9 %) versus 66 (54.1 %) female subjects.

Safety:

Reactogenicity

Injections site reactions:

After vaccination, pain, erythema and swelling reactions were observed in 28.7%, 24.6% and 14.8% of subjects, respectively.

Almost all solicited injection site reactions occurred within 4 days after vaccination and most lasted less than 3 days and were of mild (grade 1) severity.

No solicited injection site reactions were recorded as severe (grade 3).

Systemic reactions:

Any fever (≥37.5°C, axillary) was observed in 7.4% of subjects.

All other solicited systemic reactions were observed in 9.8% (for myalgia) to 12.3% (for headache and malaise) of subjects.

Most of the solicited systemic reactions occurred within 4 days after vaccination, lasted less than 3 days and were of mild severity.

Grade 3 (severe) solicited systemic reactions had a very low incidence after one dose given. Grade 3 (severe) malaise was reported in one subject (0.8%), who experienced grade 3 malaise, occurring on Day 1 after vaccination, with a duration of 3 days. No action was taken and the investigator assessed the episode as not being related to study vaccination.

Grade 3 (severe) fever (≥39.0°C) was not reported in any subject.

Unsolicited AEs/reactions:

Between any vaccine injection and the next visit, from a total of 122 subjects with documented doses of vaccine administration, 43 subjects (35.2%) reported at least one unsolicited AE. Most of the unsolicited AEs were common childhood diseases (cough, nasopharyngitis, pyrexia [fever], vomiting, diarrhoea, acute otitis media etc.)

Seven subjects (5.7%) experienced a total of eight unsolicited reactions (i.e. events regarded as being related to vaccination by the investigator or where the relationship was not recorded and were therefore regarded as being related to vaccination). Four subjects reported 5 cases of unsolicited injection site reactions (2 subjects reported injection site hematoma, 1 subject reported injection site induration and 1 subject reported both injection site induration and injection site warmth). Three subjects reported 3 cases of unsolicited systemic reactions (1 subject reported rash and 2 subjects reported fever). One case of fever in 1 subject was reported as grade 3 (severe).

Serious Adverse Events (SAEs):

Overall, during the study (FVFS to LVLS) 1 subject experienced at least one SAE.

The SAE reported was due to multiple injuries. It was assessed as not being related to vaccination by the investigator and the sponsor. The SAE resolved within 2 days.

No deaths occurred during the study (FVFS to LVLS) and no drop outs were reported due to AEs.

Conclusions:

- A second dose of Biken's Varicella vaccine (Varicela Biken) administered subcutaneously was well tolerated in children when given at 4 to 6 years of age. The most common solicited injection site reactions were pain and erythema but none were grade 3 (severe). The rates for solicited systemic reactions were low, and only one grade 3 (severe) malaise reaction was reported. The unsolicited AEs reported were mostly due to common childhood diseases, and only one of the 8 unsolicited ARs reported (fever) was grade 3 (severe) in intensity.
- The SAE reported was due to multiple injuries. It was assessed as not being related to vaccination by the investigator and the sponsor. The SAE resolved within 2 days.
- No deaths occurred during the study (FVFS to LVLS) and no drop outs were reported due to AEs.

Date of Report: 30 June 2010