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## **POST-MARKETING SURVEILLANCE OF A LIVE-ATTENUATED VARICELLA (OKA-STRAIN) VACCINE IN THE PHILIPPINES**

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### **KEYWORDS**

Varicella, varicella vaccine, oka strain

### **ABSTRACT**

#### **ABSTRACT**

Post-marketing surveillance (PMS) of live-attenuated Oka-strain varicella vaccine (*Varilrix*<sup>TM</sup>) was conducted in Filipino population aged less than nine months. Three thousand four hundred ninety six subjects aged  $\geq$  nine months who received *Varilrix*<sup>TM</sup> as part of routine vaccination were enrolled in this study spanning over a three-year period. Subjects aged  $<13$  years (Group 1) received a single dose of the vaccine and those aged  $\geq 13$  years (Group 2) received two doses with an interval of six-to-ten weeks between doses. Solicited symptoms were collected 30 minutes following vaccination or when subjects returned for the next visit. Unsolicited symptoms were recorded during the 43-day post-vaccination follow-up period. Serious adverse events were recorded throughout the study period. Pain and fever were the most frequently reported and solicited local and general symptoms. Unsolicited symptoms causally related to vaccination were reported in 3.2% (Group 1) and 4.3% (Group 2) of subjects. No serious adverse effects were reported. *Varilrix*<sup>TM</sup> is well-tolerated and has an acceptable safety profile.

#### **INTRODUCTION**

Varicella infection is a contagious childhood ailment caused by varicella zoster virus (VZV).<sup>1</sup> The disease is characterized by fever, malaise and a generalized vesicular rash. Although varicella is believed to cause a mild and benign disease in children, it can lead to complications in older children and adults.<sup>2</sup>

In tropical regions like Southeast Asia, varicella infections are acquired by the older age groups, resulting in greater susceptibility to the disease among adults.<sup>2,3,4,5</sup> In the Philippines (1990s), the seropositivity rate in terms of anti-VZV antibodies was 74% in the 21-to-25 year old age group, but has increased to 85% to 90% by age 40.<sup>6</sup> Considering the potential negative impact of VZV on the health of people, there is a significant implication of such vaccine on the vaccination programs.<sup>7</sup>

Oka-strain varicella vaccine (*Varilrix*<sup>TM</sup>, GlaxoSmithKline [GSK] Biologicals) has been licensed in 92 countries for the immunization of healthy children aged  $\geq$  nine months without a prior history of varicella.<sup>8</sup> Children aged  $<13$  years are recommended to receive one dose of the vaccine and those aged  $\geq 13$  years are recommended to receive two vaccine doses with a six-week interval between doses.<sup>9,10</sup>

Post-marketing surveillance (PMS) studies are mandatory in the Philippines for newly registered biological products.<sup>11</sup> The results from a PMS study conducted to assess the safety and reactogenicity of *Varilrix*<sup>TM</sup> as used in routine clinical practice in accordance with the recommendations in the Prescribing Information (PI) in Filipino subjects are presented here.

## **MATERIALS AND METHODS**

Live-attenuated Oka-strain of Varicella-zoster virus (*Varilrix*<sup>™</sup>, GSK Biologicals) was obtained by the propagation of the virus in the MRC5 human diploid cell culture. Each dose (0.5 mL) of the lyophilized vaccine reconstituted with the diluent, contained live-attenuated Oka-strain not less than  $10^{3.3}$  pfu/dose.

This PMS study was conducted in the Philippines between December 1995 and March 1999 according to Good Clinical Practice, the 1996 version of Declaration of Helsinki. The study protocol was approved by the Department of Health (DOH), Philippines and written informed consent was obtained from the study participants before performance of any study-specific procedures.

Participating physicians enrolled healthy subjects (N=3496) aged nine months onwards for whom they had prescribed *Varilrix*<sup>™</sup> in the course of the normal immunization practice. Since age-related data was not available for 135 subjects, analysis was performed on 3361 subjects. Subjects aged <13 years received subcutaneous injection of one dose of the vaccine and those aged ≥13 years received two doses (6–10 weeks apart). Healthy subjects without a history of varicella infection, acute febrile illness, not allergic to the vaccine strain and not having received immunoglobulins three months prior to receiving the study vaccine were enrolled. All symptoms were reported retrospectively by the subjects at the end of the 43-day post-vaccination follow-up period (at Visit 2 for subjects who received one dose of the vaccine; at Visit 2 and 3 for subjects who received two doses of the vaccine). The adverse events either observed by the investigator or spontaneously reported by the subjects were assessed by the investigator and noted in the medical history/or adverse event section of the subject's case report form.

Subjects were observed for 30 minutes after vaccination for any anaphylactic reactions. Solicited local (redness, swelling and pain at

injection site) and general (fever and rash) symptoms were recorded 30 minutes following vaccination or when subjects returned for the next visit (43-days after vaccination). Unsolicited symptoms reported during the 43-day post-vaccination follow-up period were recorded retrospectively. The intensity of adverse events were graded from 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Fever was defined as axillary temperature ≥37.5°C. Serious adverse events (SAE) were recorded throughout the study period.

Analysis was performed on all subjects who had received at least one dose of the vaccine and for whom age-related data was available (total study cohort). The percentage of doses followed by any symptom (solicited/unsolicited) reported during the 43-day follow-up period was tabulated along with 95% Confidence Interval (CI). All statistical analyses were performed using SAS version 8.2.

## **RESULTS**

The study cohort consisted of 3361 subjects, who can be evaluated— 3266 subjects aged <13 years (Group 1) and 95 subjects aged ≥13 years (Group 2). The mean age (±SD) of the subjects was 2.77 (± 2.6) years in Group 1 and 20.80 (± 9.9) years in Group 2. The ratio of male and female subjects was similar in both groups.

Documentation on post-vaccination adverse events was available for 2903 subjects (2811 and 92 subjects in Group 1 and Group 2, respectively) of the 3361 subjects who received the vaccine. Overall incidence of any symptoms was reported following 8% (Group 1) and 4% (Group 2) of doses (Figure 1). Pain at the injection site (following ≤2% of doses) was the most frequently reported, solicited, local symptom while fever (following ≤3.5% of doses) was the most frequently reported, solicited, general symptom in both groups during the 43-day post-vaccination follow-up period (Figure 2).

Percentage of subjects reporting unsolicited adverse events classified by WHO preferred

term during 43 days after vaccination was 5.1% (Group 1) and 5.4% (Group 2). Non-serious adverse events causally related to vaccination were reported by 3.2% of subjects in Group 1 and 4.3% of subjects in Group 2. Injection site reaction was the most frequently reported non-serious adverse event (2.1% and 3.3% of subjects in Group 1 and Group 2, respectively). One subject in Group 1 reported Grade 3 fever during the post-vaccination follow-up period. No unsolicited symptoms were reported post-dose 2 in Group 2. No SAE was reported during the entire study period.

### **DISCUSSION**

Before the introduction of routine varicella vaccines in developing Southeast Asian countries, certain factors like the epidemiology of varicella and the socioeconomic impact of varicella compared to other health concerns competing for the limited resources have to be taken into consideration. In most developing countries, vaccine-preventable diseases with higher mortality rates are of high priority than routine varicella mass vaccination. Routine varicella vaccination is being considered in developing countries only if there is sufficient evidence of high incidence. Varicella disease incidence rate in the Philippines is 47.8/100,000, leading to 35,700 hospitalizations annually, and a case-fatality rate of 0.082/100,000 population.<sup>12</sup> Due to this disease burden and its effect on morbidity and mortality rates, WHO has recommended the introduction of routine varicella vaccination of healthy children in this region.<sup>2,13</sup>

This study showed that the overall reactogenicity of the vaccine to be low with < 8% of subjects reporting any symptoms, which is in line with the results of a previous prospective study with *Varilrix*<sup>TM</sup> in the Philippines.<sup>2</sup> Pain at the injection site (following  $\leq 2\%$  of doses) and fever (following  $\leq 3.5\%$  of doses) were the most frequently reported solicited local and general symptom in both groups, respectively. Unsolicited symptoms were reported by <6% of subjects in both groups. No subjects experienced any SAE and

no mortalities were reported during the entire study period of 3 years.

Safety and reactogenicity of the vaccine were assessed by recording of symptoms noted by the physician or as reported by the subjects spontaneously at the end of the 43-day post-vaccination follow-up period. Due to the time lag between the occurrence of symptoms and in reporting the same, there were chances of under-reporting of the adverse events, which was considered as one of the main drawbacks of this PMS study. However, unlike the pre-licensure studies which are conducted in a controlled manner, the PMS studies help to detect rare adverse events that were not observed in the pre-licensure studies. Thus, a more complete safety profile of a vaccine can be determined in a post-marketing study, when the vaccine is given to a large number of people in an uncontrolled setting.<sup>14</sup>

Based on the results of this study and the data from other previous studies conducted using *Varilrix*<sup>TM</sup>, it can be concluded that *Varilrix*<sup>TM</sup> was well-tolerated with an acceptable reactogenicity profile in the Filipino children, adolescents and young adults aged >9 months after either one or two doses of the vaccine. Hence, the DOH of the Philippines can now consider the introduction of mass varicella vaccination program for healthy Filipino population.

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**Declaration of Conflict of interest:** Dr Jose Salazar does not have any conflict of interest. Dr Salvacion Gatchalian, and Dr Hans L Bock were employees of GlaxoSmithKline Biologicals during the time of study conduct and/or data analysis/interpretation and manuscript preparation. In addition, Dr Gatchalian owns GlaxoSmithKline shares.

**Trademark statement:** *Varilrix* is a trademark of the GlaxoSmithKline group of companies.

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