Safety of a second dose of varicella vaccine administered at 4 to 6 years of age in healthy children in Argentina

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Varicela Biken [Live varicella Biken vaccine (strain Oka)] is an effective and safe vaccine for the prevention of varicella infection. Although the recommended schedule in all age groups (children, adolescents and adults) is a single dose, physicians in some countries follow the 2007 recommendation of the US Advisory Committee on Immunization Practices (ACIP) which recommends "implementation of a routine 2-dose varicella vaccination program for children, with the first dose administered at age 12–15 months and the second dose at age 4–6 years."¹ Therefore, cases can arise when two doses of Varicela Biken are given even though the ACIP guidelines are a response to the US epidemiological situation and for US licensed products based on the Oka/Merck and the Oka-RIT strains (Varicela Biken is not registered in US). The aim of this study is to ascertain the safety of a second dose of Varicela Biken in children who have been previously vaccinated with the same vaccine.

In this study, children, 4–6 years of age who had been previously vaccinated with Varicela Biken, received a single 0.5 mL dose of live attenuated varicella virus vaccine containing at least 1,000 Plaque Forming Units (PFU) attenuated live Varicella-zoster virus (Oka strain). Participants were monitored for 30 minutes after vaccination. Predefined injection site and systemic reactions were solicited during the subsequent seven days. Unsolicited injection site reactions and unsolicited systemic events were collected throughout the study. Any serious adverse events occurring throughout the study were reported to the sponsor's pharmacovigilance department.

One hundred and twenty two children were recruited and all provided safety data. There were no immediate adverse events or injection site reactions. Forty three percent of participants reported injection site reactions and 22.1% reported systemic reactions on solicitation during the seven days after vaccination. During the 30 day monitoring period, 43 participants reported a total of 66 adverse events. Seven participants reported a total of eight unsolicited events that were assessed as related to the vaccine or where the relationship to vaccination was unknown. Five of these eight events were injection site reactions and all were mild, systemic reactions included mild rash (1 case) and fever (2 cases). There was a single serious adverse event that was not related to the study medication (subject was a passenger in a motor vehicle accident). A second dose of Varicela Biken was well tolerated and showed no significant safety issues in this population of previously vaccinated children.

Introduction

Varicella virus infection is a highly contagious illness. Although it is generally self-limiting, potentially serious complications (such as bacterial super-infections, pneumonia and encephalitis) can develop in 2–6% of cases, whilst longer-lasting, though rare, sequelae can include severe scarring, ataxia/coordination disorder, epilepsy and cerebral nerve paralysis.² Complications can develop in healthy adults and children, as well as risk-prone subpopulations, and the infection confers a substantial economic burden.³ In the absence of curative treatment, vaccination represents the best option for preventing infection and its consequences⁴ and has a clear economic benefit.^{5–7}

Vaccination is recommended by the World Health Organization in countries where varicella is a significant problem

and where vaccination can be effective and can be afforded.⁸ Consequently, many countries have incorporated the vaccine into childhood vaccination programs.⁹ In the US, an effective immunisation program introduced in 1995¹⁰ resulted in national coverage of 88% among children aged 19–35 months¹¹ which resulted in a reduction of hospital admissions due to varicella by 88% compared with pre-vaccination levels.¹² However, despite this success, outbreaks of varicella continued to be reported, to an increasingly large extent among well-vaccinated populations and some investigators proposed a second vaccination.^{13,14} In response, US authorities recommended a second vaccination, firstly in the context of varicella outbreaks¹⁵ but subsequently more widely.¹⁶

Varicela Biken [Live varicella Biken vaccine (strain Oka), also commercialized as OKAVAX®] is a safe and effective vaccine.¹⁷ Although the recommended schedule for Varicela Biken vaccination

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Table 1. Baseline characteristics

N included	122
Gender	
Male n(%)	56 (45.9)
Female n(%)	66 (54.1)
Male/Female ratio	0.85
Age (Year)	
Mean (SD)	5.3 (0.8)
Median	5.2
Range	4.0–7.0
First quartile; Third quartile	4.6; 5.9

Table 2. Safety summary (N = 122)

Participants experiencing at least one:	N	%	95% CI
Immediate unsolicited adverse event	0	0	0.0; 3.0
Immediate unsolicited adverse reaction	0	0	0.0; 3.0
Solicited reaction	63	51.6	42.4; 60.8
Solicited injection site reaction	53	43.3	34.5; 52.7
Solicited systemic reaction	27	22.1	15.1; 30.5
Unsolicited adverse event	43	35.2	26.8; 44.4
Unsolicited adverse reaction	7	5.7	2.3; 11.5
Unsolicited non-serious adverse event	42	34.4	26.1; 43.6
Unsolicited non-serious adverse reaction	7	5.7	2.3; 11.5
Unsolicited non-serious injection site adverse reaction	4	3.3	0.9; 8.2
Unsolicited non-serious systemic adverse event	40	32.8	24.6; 41.9
Unsolicited non-serious systemic adverse reaction	3	2.5	0.5; 7.0
Adverse event leading to study discontinuation	0	0	0.0; 3.0
Serious adverse event	1	0.8	0.0; 4.5
Death	0	0	0.0; 3.0

Immediate unsolicited reactions and events were recorded during the 30 mins following vaccination. Solicited reactions were recorded from day 0 to day 7. Unsolicited adverse events and reactions were recorded until the final visit.

is a single dose in children (or any age group), anecdotal evidence suggests that clinicians in some countries, perhaps following recommendations from the ACIP in US where Varicela Biken is not registered, or other similar national recommendations, administer a second dose. Varicela Biken is licensed as a single dose vaccine and therefore its use in a two-dose schedule is not currently recommended. However, given the possibility of children receiving a second dose of varicella vaccines in some territories, a study of such use of Varicela Biken is warranted to ascertain its safety in this context.

Results

Patient disposition. 122 participants were included, all of whom attended both visits and all completed the study. The baseline

demographic characteristics are shown in **Table 1**. Twenty participants (24.6%) attended for their second visit outside the prescribed window (28–35 days after the vaccination) but they were not excluded from the safety analysis.

Overall safety. The overall safety results are summarized in **Table 2**. Solicited reactions were elicited from 63 (51.6% of the participants), the majority (84%) of which were injection site reactions. Unsolicited adverse events were reported by 43 participants (35.2%). Seven participants (5.7%) experienced a total of eight unsolicited reactions that were considered related to study medication.

Immediate adverse events. No unsolicited adverse events or injection site reactions were reported during the 30 minutes after vaccination.

Solicited adverse reactions between day 0 and day 7. Solicited adverse reactions are summarized in **Table 3**. Solicited injection site reactions were reported by 53 (43.4%) of participants. There were no grade 3 solicited injection site reactions. Twenty-seven participants (22.1%) reported systemic reactions upon solicitation. One solicited grade 3 systemic reaction (malaise) was reported. Two thirds of the cases of solicited fever were reported before day 4. All episodes lasted less than three days and all resolved within seven days. Most (66.7%) were of moderate (grade 2) severity and none were severe (grade 3, temperature $\geq 39^{\circ}\text{C}$). Headache also tended to occur soon after treatment (two thirds before day 4), to be of mild severity (73.3%, grade 1) and short duration (93.3% lasted less than three days), and all resolved within seven days. Two thirds of the episodes of malaise occurred before day 3, 86.7% lasted less than three days and all resolved within eight days, with 73.3% of the episodes being of mild intensity. 75% of myalgia episodes occurred soon after vaccination (before day 4); most episodes (83.3%) lasted less than three days, were of mild severity (grade 1) and all resolved within seven days.

A single severe (grade 3) episode of malaise occurred on the day after vaccination and lasted three days. No intervention was required and the investigator assessed the episode as being not related to the study vaccination.

Unsolicited adverse events between vaccination and visit 2. Unsolicited adverse events between vaccination and the second visit (planned between day 28 and 35) are summarized in **Table 4** and elaborated by the Medical Dictionary for Regulatory Activities terminology (MedDRA®) preferred term in **Table 5**. Forty-three participants (35.2%) reported a total of 66 events during the study period. Seven participants (5.7%) reported a total of eight unsolicited events assessed as either related to the study vaccination (or the relationship was not recorded), none of which were rated as severe. Five of these eight events were injection site reactions, all were of mild severity and no action was required. Systemic reactions in three participants included mild rash in one and two episodes of fever (one with axillary temperature of 38.9°C starting on Day 16 after vaccination and lasting 3 days, the second with axillary temperature 39.9°C starting on Day 16 after vaccination and lasting 2 days) medication was prescribed for both. The most frequent unsolicited adverse events (>2 participants) were cough, pharyngitis, fever, vomiting, diarrhoea and acute otitis media.

Serious adverse events. A single, unrelated serious adverse event was recorded in which a participant was involved in a car accident during the study period and sustained multiple injuries.

Discussion

This study was designed to ascertain the safety of a second dose of Varicela Biken. The results indicate no particular safety issues associated with a second dose of vaccine, even though such second dose is not recommended.

There were no immediate adverse events and 43.4% of participants reported solicited injection reactions (pain, erythema and swelling) that were predominantly of mild intensity, short duration and characteristic of vaccination reactions. Systemic reactions were rare and usually of mild severity, resolving quickly and requiring no intervention. Fever, which was observed in 7.4% of patients, was mostly of moderate severity. Other solicited systemic reactions (myalgia, headache and malaise) were similarly infrequent and systemic reactions as a whole mostly occurred within 4 days of vaccination and resolved within 3 days. Severe solicited adverse reactions were very rare (0.8%), being restricted to a single case of malaise of short duration that resolved without sequelae and no severe ($\geq 39^{\circ}\text{C}$) fever was observed. No immediate unsolicited events were reported and unsolicited events reported between vaccination and the first visit were systemic and likely associated with common childhood diseases (cough, nasopharyngitis, fever, vomiting, diarrhea, acute otitis media, etc.). A single serious adverse event was reported, but this was not associated with the study vaccination.

Despite the current trend towards a 2-dose vaccination schedule for the routine immunization against varicella as recommended by the ACIP for US registered vaccines, a single dose of Varicela Biken was shown to be sufficient where vaccine coverage rates are insufficient to interrupt wild varicella zoster virus circulation. This study shows that when administered as a 2-dose schedule, Varicela Biken was safe in children and no unexpected unsolicited events were observed.

Varicela Biken is a widely used vaccine with which there is considerable experience over many years and in many different countries with different epidemiological situations. It was first licensed in Japan in 1987 and is now registered in over 40 countries across the globe and the safety and efficacy of the recommended 1-dose schedule is well-established.¹⁷ Physicians in some countries have adopted a change of practice that occurred in US following ACIP recommendations in 2005 which recommended a second dose for outbreak control (i), later extended to cover all children aged 4–6 years old in 2006 (xv). However, it must be remembered that these recommendations were drawn up to address the specific US epidemiological situation of high vaccine coverage and for US registered vaccines derived from strains which have undergone more passages in cell culture than the Oka/Biken strain.

All currently marketed Varicella vaccines are live attenuated vaccines derived from the same parental strain, a wild-type Varicella zoster virus originally isolated in 1971 in Japan from a healthy child with varicella named Oka. The wild Oka strain was

Table 3. Injection site and systemic reactions solicited from participants within eight days of vaccination (n = 122)

Participants experiencing at least one:	N	%	95% CI
Solicited injection site reaction	53	43.4	34.5; 52.7
Grade 3	-	-	-
Other			
Pain	35	28.7	20.9; 37.6
Erythema	30	24.6	17.2; 33.2
Swelling	18	14.8	9.0; 22.3
Solicited systemic reaction	27	22.1	15.1; 30.5
Grade 3			
Malaise	1	0.8	0.0; 4.5
Other			
Fever	9	7.4	3.4; 13.5
Headache	15	12.3	7.0; 19.5
Malaise	15	12.3	7.0; 19.5
Myalgia	12	9.8	5.2; 16.6

Table 4. Unsolicited adverse events reported within 30 days of vaccination

Participants experiencing at least one:	N	%	95% CI
Unsolicited adverse event	43	35.2	26.8; 44.4
Unsolicited adverse reaction	7	5.7	2.3; 11.5
Unsolicited non-serious adverse event	42	34.4	26.1; 43.6
Grade 3 unsolicited non-serious adverse event	3	2.5	0.5; 7.0
Unsolicited non-serious adverse reaction	7	5.7	2.3; 11.5
Grade 3 unsolicited non-serious adverse reaction	1	0.8	0.0; 4.5
Unsolicited non-serious injection site adverse reaction	4	3.3	0.9; 8.2
Grade 3 unsolicited non-serious injection site adverse reaction	0	0.0	0.0; 3.0
Unsolicited non-serious systemic adverse event	40	32.8	24.6; 41.9
Grade 3 unsolicited non-serious systemic adverse event	3	2.5	0.5; 7.0
Unsolicited non-serious systemic adverse reaction	3	2.5	0.5; 7.0
Grade 3 unsolicited non-serious systemic adverse reaction	1	0.8	0.0; 4.5
Serious adverse events	1	0	0.0; 4.5

then attenuated through 24 successive passages in cell culture to yield the Oka/Biken strain, found in Varicela Biken, which has been used since 1974 to vaccinate Japanese children. Subsequent attenuation passages led to the development of two additional attenuated VZV strains: the Oka/Merck strain, obtained after 31 passages in tissue culture and the Oka-RIT strain obtained after 35 passages in cell culture.¹⁸ Only vaccines derived from these more attenuated strains are licensed in the US and therefore subject to ACIP recommendations.

Table 5. Unsolicited adverse events between vaccination and final visit by system organ class and MedDRA preferred term

Participants experiencing at least one:	n	%	95% CI	n AEs
Unsolicited Adverse Events	43	35.2	26.8; 44.4	66
Blood and lymphatic system disorders	1	0.8	0.0; 4.5	1
Lymphadenitis	1	0.8	0.0; 4.5	1
Ear disorders	2	1.6	0.2; 5.8	2
Ear pain	2	1.6	0.2; 5.8	2
Gastrointestinal disorders	7	5.7	2.3; 11.5	10
Diarrhea	3	2.5	0.5; 7.0	3
Sore throat	1	0.8	0.0; 4.5	1
Toothache	1	0.8	0.0; 4.5	1
Vomiting	5	4.1	1.3; 9.3	5
General disorders and administration site conditions	12	9.8	5.2; 16.6	13
Influenza like illness	1	0.8	0.0; 4.5	1
Injection site hematoma	1	0.8	0.0; 4.5	1
Injection site swelling	2	1.6	0.2; 5.8	2
Injection site warmth	1	0.8	0.0; 4.5	1
Fever	8	6.6	2.9; 12.5	8
Immune system disorders	2	1.6	0.2; 5.8	2
Allergy to arthropod sting	1	0.8	0.0; 4.5	1
Food allergy	1	0.8	0.0; 4.5	1
Infections and infestations	17	13.9	8.3; 21.4	19
Bronchiolitis	1	0.8	0.0; 4.5	1
Otitis	1	0.8	0.0; 4.5	1
Gastroenteritis	1	0.8	0.0; 4.5	1
Nasopharyngitis	9	7.4	3.4; 13.5	10
Acute otitis media	3	2.5	0.5; 7.0	3
Pharyngitis	1	0.8	0.0; 4.5	1
Rhinitis	1	0.8	0.0; 4.5	1
Sinusitis	1	0.8	0.0; 4.5	1
Injury, poisoning and procedural complications	1	0.8	0.0; 4.5	1
Multiple injuries	1	0.8	0.0; 4.5	1
Nervous system disorders	2	1.6	0.2; 5.8	2
Headache	2	1.6	0.2; 5.8	2
Respiratory, thoracic and mediastinal disorders	11	9.0	4.6; 15.6	11
Cough	9	7.4	3.4; 13.5	9
Sore throat	2	1.6	0.2; 5.8	2
Skin and subcutaneous tissue disorders	3	2.5	0.5; 7.0	3
Dermatitis	1	0.8	0.0; 4.5	1
Petechiae	1	0.8	0.0; 4.5	1
Rash	1	0.8	0.0; 4.5	1
Surgical and medical procedures	1	0.8	0.0; 4.5	1
Tooth extraction	1	0.8	0.0; 4.5	1
Vascular disorders	1	0.8	0.0; 4.5	1
Hematoma	1	0.8	0.0; 4.5	1

There is much evidence to support the efficacy of a single-dose regimen of Varicela Biken vaccine. For example, in countries where routine varicella vaccination is not yet in place, and when vaccine use is restricted to the private market, coverage rates may

not be high enough to interrupt wild virus circulation. Vaccine-induced immunity may then be regularly boosted through natural exposure. In Japan for example, where the Oka/Biken strain (the same used in Varicela Biken) has been used since 1987, a

follow-up study showed that a protective immunity was still detected 20 years after receipt of a single dose.¹⁹ However, the observation that both GMTs and the degree of skin reactions to VZV (indicating humoral and cellular immunity respectively) at 20 years were almost twice those observed at 10 years suggested that asymptomatic reinfection with the wild virus occurred and contributed to the persistence of vaccine-induced immunity.¹⁰

Methods

Study design. This open, single center, phase IV clinical trial was conducted at a specialised unit undertaking vaccination of individuals referred by their general practitioner or pediatrician in Argentina. The protocol was approved by two independent ethics committees; Comité de Ética FUNCEI-Helios Salud and the Comité Independiente de Ética para Ensayos en Farmacología Clínica (Fundación de Estudios Farmacológicos y de Medicamentos—FEFyM). The study was conducted in accordance with the Edinburgh revision of the Declaration of Helsinki, Good Clinical Practice and International Conference on Harmonisation guidelines as well as relevant local and national requirements and was registered at ClinicalTrials.gov on 27 January 2009 (identifier NCT00830648). Parents or legal guardians of all participants gave written informed consent.

Participants. Children who had been referred to the institution by paediatricians for a second dose of varicella vaccine were eligible to participate in the study. Pediatricians who had previously referred children to the vaccination centre for varicella biken vaccinations were contacted and asked to participate in the study. Participating pediatricians sent lists of eligible patients to the vaccination centre and their parents were solicited for inclusion in the study. To be included, children were required to be aged 4–6 years with a documented first vaccination with Varicella Biken vaccine at least three months before inclusion. Those with known or suspected immunodeficiency, immunosuppressive therapy during the past six months, long-term systemic corticosteroid treatment, chronic illness which could interfere with the study, receipt of any vaccine during the preceding four weeks, history of seizures, seropositivity for HIV, hepatitis B or hepatitis C, history of varicella infection, previous vaccination with varicella vaccine other than Varicella Biken or febrile illness on the day of vaccination were excluded.

Treatment. Participants received a single dose of 0.5 mL Live Attenuated Varicella Virus Vaccine Biken (Varicella Biken) by subcutaneous injection into the upper arm. The injectable vaccine suspension contained at least 1,000 Plaque Forming Units (PFU) attenuated live Varicella-zoster virus (Oka strain).

Study schedule. Eligible participants were evaluated on day 0. Parents or legal guardians of those included gave written informed consent and the children were vaccinated immediately, monitored for 30 minutes following administration and

were discharged from the vaccination unit. A follow-up phone call to the participant's parents or legal guardian was made 2–4 days after vaccination. In addition, parents or guardians recorded solicited reactions and other adverse events on diary cards during the seven days after vaccination. Participants made a final visit around day 30 (between 28–35 days) following vaccination.

Endpoints. Four study endpoints were identified: (1) Occurrence, intensity and relationship to vaccination of unsolicited immediate adverse events (during 30 minutes following vaccination). (2) Occurrence, time to onset, duration and intensity of solicited injection site reactions (pain, erythema, swelling) and systemic adverse reactions (fever, headache, malaise, myalgia) between day 0 and day 7 after vaccination. (3) Occurrence, nature (MedRA preferred term), time to onset, duration, intensity and relationship to vaccination of spontaneously reported adverse events between vaccination and the final visit. (4) Occurrence, nature, relationship to vaccination, outcome and seriousness of any serious adverse event occurring between vaccination and the final visit. Adverse events where the relationship to treatment was not recorded were considered to be related to the study vaccination. The severity of solicited adverse events was graded 1–3 (grade 1, noticeable but does not interfere with daily activities; grade 2, interferes with daily activities; grade 3, prevents daily activities). Fever was also graded (grade 1 $\geq 37.5^{\circ}\text{C}$ to $\leq 38.0^{\circ}\text{C}$; grade 2: $> 38.0^{\circ}\text{C}$ to $\leq 39.0^{\circ}\text{C}$; grade 3: $> 39.0^{\circ}\text{C}$).

Parents were provided with diary cards for recording headache, malaise and muscle aches and pains along with instruction on how to grade severity according to the scales described above.

Statistical methods. A sample size of 122 gave 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%. Data analysis was descriptive.

Disclosure of Potential Conflicts of Interest

DS is a paid consultant of sanofi pasteur and has received honoraria for lecture tours and participation in clinical trials. DF has received honoraria for participation in clinical trials. AM has received honoraria for participation in clinical trials. JA is an employee of sanofi pasteur.

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