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A phase-I, open label clinical trial to assess the safety & tolerability of qHPV vaccine manufactured by Serum Institute of India Pvt. Ltd. in adults

Hitt Sharma [a,*], K. Anil [b], Sameer Parekh [a], Pramod Pujari [a], Sunil Shewale [a], Shivani Desai [a], R.L. Madhusudhan [b], Jaya Patel [b], Anand Eswaraiah [b], Harish Rao [a], Sunil Gairola [a], Umesh Shaligram [a]

[a] Serum Institute of India Pvt. Ltd., Pune, India
[b] Syngene International Limited, Bangalore, India

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ABSTRACT

Background: This first in human study was designed as an open label clinical trial to assess safety and tolerability of Serum Institute of India Pvt. Ltd. (SIIPL) quadrivalent HPV (qHPV) vaccine.
Methods: A total of 48 healthy male and female (24 each) adult volunteers were administered a 0.5 ml single dose of SIIPL qHPV vaccine intramuscularly, and were followed for one month for safety outcomes viz., immediate, solicited, unsolicited and serious adverse events.
Results: 47 subjects completed the study in compliance with protocol. One subject had pain immediately after immunization which was recovered without treatment. None of the participants experienced any other local or systemic solicited AEs and serious AE.
Conclusion: qHPV vaccine manufactured by SIIPL was found to be safe and well tolerable in adults. Further clinical development should continue to assess safety and immunogenicity, in the target population following recommended 2 and 3-dose schedule.
Clinical Trial Registration – CTRI/2017/02/007785.

Introduction

Human papilloma virus (HPV) is the most common viral infection of the reproductive tract globally. HPV is associated with a range clinical conditions in both men and women, including pre-cancerous lesions to cancer [1]. More than 200 types of HPV have been identified and are classified into low- and high-risk types based on their potential to cause malignancy. The high-risk (carcinogenic) types include HPV 16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70 that are associated with cervical cancers [2,3]. HPV types 16 and 18 are the most carcinogenic and are responsible for approximately 70% of the cervical malignancies. Low risk types, HPV 6 and 11 are the most common strains associated with genital warts and are responsible for approximately 90% of these lesions, causing psychological distress in young men and women [3].

There were an estimated 604,127 new cases and 341,831 deaths from cervical cancer worldwide in 2020 [4]. Major burden of cases is felt in the low- and middle-income countries (LMICs) which are resource-constrained to effectively implement and sustain cervical cancer screening programs [5]. Persistent infection with one of the high-risk types of HPV is a necessary cause of cervical cancer, indicating that the infection is crucial to initiate the process of carcinogenesis. This has led to an optimal strategy of primary prevention using vaccination against HPV. The quadrivalent HPV vaccine has the potential to prevent a significant proportion of cervical cancers (greater than70%) with inclusion of types 16 and 18, and inclusion of types 6 and 11 can help prevent a significant portion (~90%) of anogenital warts, and potential subsequent anogenital cancers [5]. Clinical efficacy of HPV vaccines has been established in young adult women and men. Cost-effectiveness analysis suggests that vaccinating pre-adolescent girls is usually cost-effective, provided the vaccines are affordable to low and middle income countries (LMICs) [1,6].

Serum Institute of India Pvt. Ltd. (SIIPL) has developed a quadrivalent (types 6, 11, 16 and 18) HPV vaccine indigenously and plans to make it available at an affordable price. This new vaccine was tested in a Phase I clinical study after successful completion of the Good Laboratory Practises (GLP) compliant animal toxicological and reproductive studies (Data on file). Here, we report the

* Corresponding author at: Additional Medical Director, Serum Institute of India Pvt. Ltd., Hadapsar, Pune 411028, India.
E-mail address: drhjs@seruminstitute.com (H. Sharma).

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results of the first clinical trial designed to evaluate the safety of SIIPL's qHPV vaccine in healthy adults.

Materials and methods

Study design

This was a Phase-I, open label clinical trial to assess the safety of recombinant qHPV (Type 6, 11, 16, 18) vaccine manufactured by SIIPL in healthy Indian adults. The study was conducted during Feb to Jul 2017 at Phase-I, Human Pharmacology Unit of Syngene International Limited, Bangalore, India. The study was carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 'Guidance on Good Clinical Practice' and 'Schedule Y' guidelines issued under Drugs and Cosmetic Act, Government of India [7]. The study was registered on national clinical trial registry (CTRI/2017/02/007785).

Study objective

The objective of the study was to assess the safety and tolerability of qHPV vaccine following a single intramuscular dose, in healthy male and female adult volunteers.

Subjects and study procedures

Written informed consent was obtained from the volunteers before initiation of any trial related procedures. After consent, thorough screening was conducted to assess eligibility for participation. The inclusion criteria were healthy male subjects aged between 18 and 26 years and female subjects aged between 18 and 45 years with a normal body mass index. Subjects were excluded if they had any acute illness or fever 7 days prior to the vaccination, history of any serious reaction to any prior vaccination or known hypersensitivity to any of the vaccine components, any immunosuppressive condition or on any immunosuppressive therapy, or any major systemic disorder. Subjects were also excluded in case of HIV, Hepatitis B and Hepatitis C seropositivity, abnormal electro-cardiogram (ECG) or chest X-ray. Female participants who were pregnant or breast-feeding, or planning to be pregnant during the trial period were also excluded from the study. A total of 48 participants (24 male and 24 females) were enrolled in the study.

Dosage and administration

The enrolled subjects received a single 0.5 ml dose of SIIPL's qHPV vaccine (batch no. 220H6003) intramuscularly into the deltoid muscle of the non-dominant arm using 25 G, 1 in. needle. The vaccine was transported and stored at the study sites between 2 and 8 °C temperature.

Composition of vaccine

The qHPV vaccine manufactured by SIIPL is a sterile liquid suspension prepared from the highly purified VLPs of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Hansenula polymorpha* (yeast) and self-assembled into VLPs. The VLPs for each type are purified and adsorbed on AlOH adjuvant. The qHPV VLP vaccine was prepared by combining the adsorbed VLPs of each HPV type, the AlOH-containing adjuvant formulation, and a buffer. Each 0.5 ml dose of SIIPL qHPV contains not less than HPV 6L1 Protein 20mcg, HPV 11L1 Protein 40mcg, HPV 16L1 Protein 40mcg and HPV18L1 Protein 20mcg along with other excipients. The antigen concentrations of the active ingredients of SIIPL's qHPV vaccine are similar to those of an established and commercially available qHPV vaccine in India (Gardasil®, marketed by MSD Pharmaceuticals Pvt Ltd) [8].

Assessment of reactogenicity (safety) and follow up

Following vaccination, all participants were observed at the study site for 4 h for any immediate adverse events. Each subject was actively followed up for the vaccine reactogenicity (solicited local and systemic adverse events) over the 7-day period, after vaccination. In addition, unsolicited AEs and SAEs were recorded for a 30-day follow-up period after vaccination. All these subjects were given diary cards to record the adverse events. The diary cards were collected, reviewed and transcribed in the case report forms. In addition to these scheduled visits, the study team also contacted each participant telephonically on days 3, 14 and 21 to know their health status.

The study endpoints included incidence of immediate adverse events within 4 h of vaccination, solicited adverse events within 7 days post vaccination period and incidence of unsolicited AEs and SAEs within 30 days, post vaccination. In addition, haematology (Hb, Complete blood count), biochemistry (Total Protein, Albumin, Globulin, Urea, Creatinine, aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and urine parameters (Specific Gravity, pH, Glucose, Protein, Bilirubin, Ketones, Urobilinogen, Erythrocytes, Leucocytes, Nitrite and, if necessary, microscopic examination) were tested on day 0, 7 and 30 post vaccination, to assess any clinically significant abnormalities. Independent oversight of this study was provided by a Data Safety Monitoring Board (DSMB), a multidisciplinary group with expertise in the field of vaccines, drug safety and statistics who were not affiliated with SIIPL and had no other potential conflicts of interest.

Since this was a Phase I clinical study, no formal sample size calculation was performed.

All statistical analyses were performed using SAS® version 9.4 for Windows [SAS Institute Inc., Cary, NC, USA]. All the adverse events were classified according to the Medical Dictionary for Reg-

Table 1
Demographics and Baseline Characteristics (ITT Population).

Parameter	Statistics	qHPV (N = 48)
Gender		
Female	n (%)	24 (50.00%)
Male	n (%)	24 (50.00%)
Age (Males)	N	24
(Years)	Mean ± SD	22.58 ± 1.932
	Median	22.00
	(Min, Max)	(19.00, 25.00)
Age (Females)	N	24
(Years)	Mean ± SD	31.63 ± 6.247
	Median	32.00
	(Min, Max)	(21.00, 42.00)
Height (m)	N	48
	Mean ± SD	1.62 ± 0.099
	Median	1.60
	(Min, Max)	(1.42, 1.82)
Weight (kg)	N	48
	Mean ± SD	59.21 ± 6.919
	Median	57.75
	(Min, Max)	(50.00, 72.50)
Body Mass Index (Kg/m^2)	N	48
	Mean ± SD	22.71 ± 1.919
	Median	23.05
	(Min, Max)	(18.84, 24.89)

Note: SD – Standard Deviation; (Min, Max) – (Minimum, Maximum).
% = (n/N) * 100, N = No. of Subjects Enrolled, n = number of subjects assigned for individual analysis set.

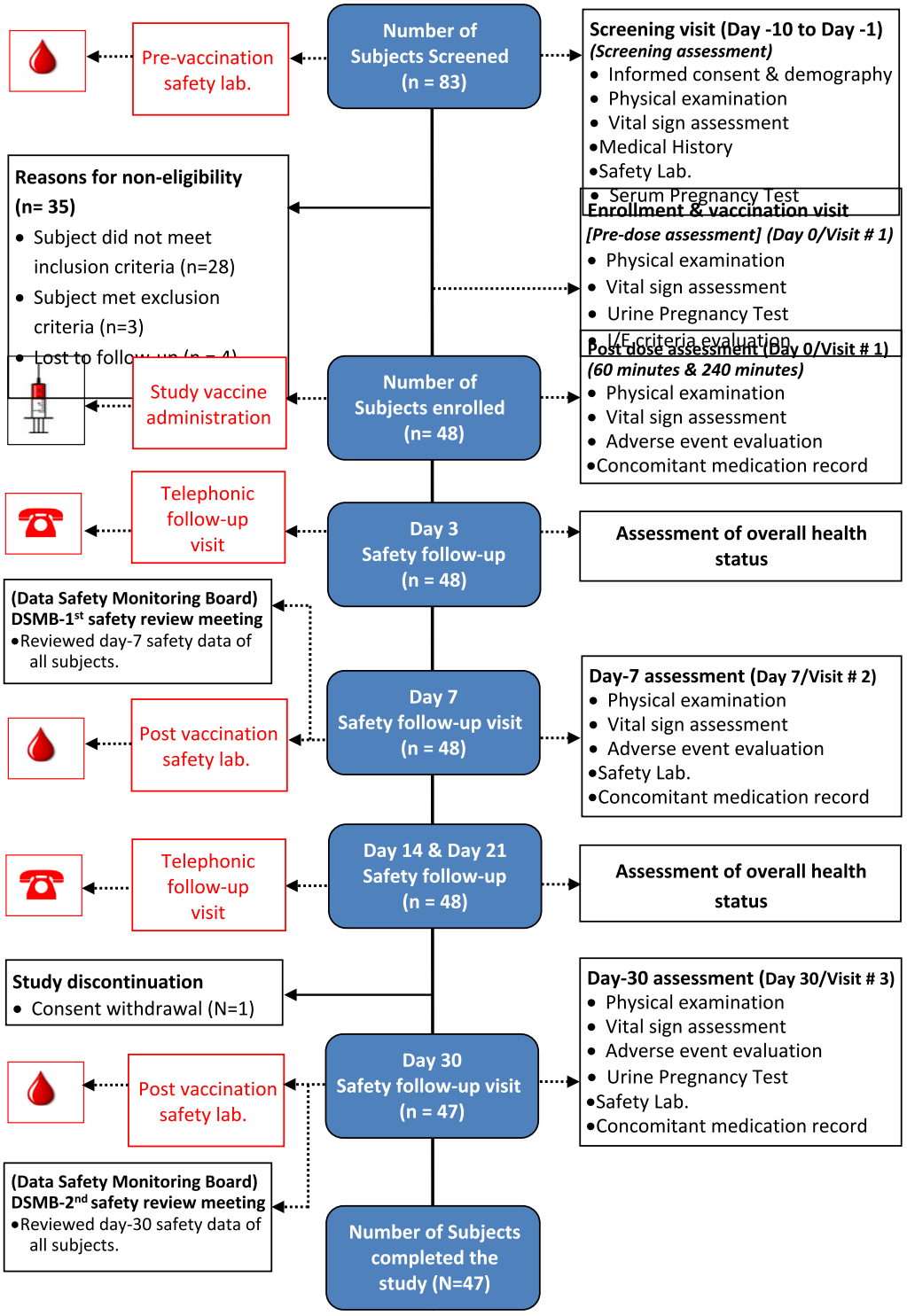

Fig. 1. Subject Disposition.

ulatory Activities (MedDRA version 18.1) System, Organ and Class (SOC). Any medication received concomitantly was coded using WHO Drug Dictionary. Descriptive statistics was used for each laboratory test result. Change from baseline to post vaccination was also summarized. Laboratory results were categorized as normal and abnormal. Abnormal results were further classified as clinically significant and clinically non-significant, based on Investigator's clinical judgment.

The study was conducted after approval from the Drugs Controller General of India and the Institutional Review Board. The study procedures complied with the Indian regulatory guidelines, the declaration of Helsinki and the good clinical practices guidelines. All the participants were enrolled after their written informed consent was obtained. As per prevailing regulations, the consent process was recorded audio-visually.

Results

A total of 83 subjects were screened out of which 48 [24 Male and 24 female] healthy volunteers were enrolled and vaccinated.

The mean age (±SD) of study participants was 22.58± (1.932) years in males and mean age (±SD) of 31.63± (6.247) years in females. Demographics and baseline characteristics are provided in Table 1. Twenty eight of 83 subjects screened didn't meet the inclusion criteria, three subjects were meeting the exclusion criteria and four subjects lost to follow-up, before enrollment in the study. Out of 48 subjects enrolled, one subject withdrew her consent, prior to the last (day 30) follow up visit. Finally, 47 subjects completed the study in compliance with the study protocol. Subject disposition is summarized in Fig. 1.

There were no immediate hypersensitivity reactions observed within 4 h of vaccination. One subject had pain at injection site immediately after immunization and recovered without any treatment. The event was assessed to be of mild (Grade 1) severity and related to study vaccine. No other local or systemic solicited AE or serious AE was reported by any participant during the 30 day follow up period. There were mild to moderate abnormalities reported in the laboratory results of 6 subjects, which were documented as unsolicited adverse events. Two subjects had increased value of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at Visit 3 (day 30). However, repeat tests showed AST and ALT values were within normal limit. These adverse events were assessed to be Grade 2-moderate in severity and not related to study vaccine. Increased fasting blood sugar was observed in two subjects but it was found to be normal at the time of subsequent visit or after repeat test. It was assessed to be Grade1, mild in severity and not related to study vaccine. Additionally, one subject was positive for increased Leucocytes, Leucocyte esterase and bacteria in urine on day 30 visit, which was possibly due to urinary tract infection. The subject was requested for a repeat test which he refused and hence outcome of the event could not be assessed. Two female subjects reported presence of blood in urine which was related to ongoing menstruation. All these findings of abnormal urinary parameters were assessed to be grade 1, mild in severity, not related to study vaccine and recovered without any medical intervention. No significant changes were seen in the vital parameters during the entire course of the study. No abnormal findings were observed during the post-study physical examination. The DSMB members reviewed the post-vaccination Day 7 and day 30 safety data of all the subjects and concluded that the study has met the primary endpoints of safety. They recommended that the vaccine should be further assessed for immunogenicity and safety in the next phase of clinical trials.

Discussion

The main burden of HPV-related disease is due to cervical cancer. Availability of affordable vaccines is a key to scale up HPV vaccination and maintain equity in access to HPV vaccines to reduce burden of cervical cancer [9,10].

This is a first in human study conducted to assess the safety and tolerability of SIIPL's qHPV vaccine following a single intramuscular dose in healthy adult volunteers. One subject reported pain at injection site immediately post-vaccination. No other solicited adverse events were observed during 7 day follow up period. There were mild to moderate abnormalities reported in the laboratory results which were not clinically significant and assessed to be not related to study vaccine.

These findings are consistent with Phase I studies conducted for HPV 16 and bivalent HPV (types 16 and 18) L1 VLP vaccine. In a randomised double-blind Phase I study, Harro et al assessed safety and immunogenicity of two different doses (10 mcg or 50 mcg) of (HPV16) L1 VLP vaccine in healthy adults [11]. The most commonly reported side effect was pain at the site of injection which was mild and short-lived. More pain was observed in that study but this may be due to different adjuvants and a three dose schedule. They reported microscopic hematuria in one subject and asymptomatic SGPT elevation 1 month after receiving the second vaccine dose, which resolved during the subsequent month in another subject. In another open-label Phase I study, Hu et al [12] assessed safety of *E.coli*-expressed recombinant bivalent HPV (types 16 and 18) vaccine in 38 healthy women from 18 to 55 y of age. In that study, pain at the site of injection was the most common solicited AE and was of short duration and resolved spontaneously. Similar to our findings, the changes in blood parameters after each vaccination were random, mild, and not clinically significant.

Strengths of this study are rigorous follow-up of all the subjects to collect safety data and assessment of a wide range of safety laboratory parameters tested before and after vaccination. Although, a 3-dose schedule (at 0, 1–2 and 6 months) is recommended for HPV vaccine in this age group we assessed safety of single dose with 30 day follow-up. This may be considered as potential limitation of this study, however this met the minimum regulatory requirement to fast-track the clinical development. Safety of this vaccine was also assessed in subsequent Phase II/III study in 9–14 years (2-dose schedule at 0, 6 months) and 15–26 years (3-dose schedule at 0, 2 and 6 months) age cohorts in both genders and the safety analysis has not shown any concerns.[Clinical Trial Registration Number: CTRI/2018/06/014601]. We plan to report outcomes of that trial in a separate publication. As this was primarily a Phase I safety study, the immunogenicity of the SIIPL qHPV vaccine was not evaluated in this study which will be done in further planned studies.

From the safety results, it was concluded that the qHPV vaccine manufactured by SIIPL was found to be safe and well tolerated in healthy men and women. These results paved the way for further assessment of safety and immunogenicity of this vaccine in subsequent phases of clinical development.

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CRediT authorship contribution statement

Hitt Sharma: Conceptualization, Writing – review & editing. **K. Anil:** Methodology, Investigation. **Sameer Parekh:** Conceptualization, Writing – original draft. **Pramod Pujari:** Conceptualization, Writing – original draft. **Sunil Shewale:** Conceptualization, Writing – original draft. **Shivani Desai:** Writing – review & editing. **R.L. Madhusudhan:** Methodology, Investigation. **Jaya Patel:** Methodology, Investigation. **Anand Eswaraiah:** Methodology, Investigation. **Harish Rao:** Writing – review & editing. **Sunil Gairola:** Writing – review & editing. **Umesh Shaligram:** Project administration.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors HS, SP, PP, SS, SD, HR, SG and US are employees of Serum Institute of India Pvt. Ltd., Pune, India. AK, RLM, JP, AE are employees of Syngene International Ltd., Bangalore.

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Data Availability Statement

Data are available upon reasonable request, from the corresponding author. Request will be reviewed and approved by the sponsor. Once the request has been approved, data can be transferred after signing a confidentiality agreement.

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