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A Phase I study to evaluate safety and tolerability of DTaP-IPV + Hib vaccine in healthy adult volunteers in India

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ABSTRACT

Background: To assess safety and tolerability of a diphtheria and tetanus toxoid, acellular pertussis, inactivated poliovirus and *Haemophilus influenza type B* conjugate adsorbed vaccine (DTaP-IPV + Hib), manufactured by Serum Institute of India Pvt. Ltd. (SIIPL)'s, the current first-in-human Phase 1 study was conducted in healthy adults.

Methods: Vaccine was administered as a single 0.5 mL dose intramuscularly into deltoid muscle of 24 healthy adults aged 18–45 years, who were then followed prospectively for one month for safety outcomes.

Results: All 24 participants completed the study in compliance with protocol. Four solicited adverse events were reported in three participants during the study; all adverse events were mild and recovered completely. No deaths, unsolicited adverse events, or serious adverse events were reported.

Conclusion: SIIPL DTaP-IPV + Hib vaccine was well tolerated and safe in study subjects. Further clinical development will be conducted to assess safety and immunogenicity in young children, the target population.

Clinical Trial Registration: CTRI/2017/07/009034.

Introduction

Vaccines protecting children against diphtheria, tetanus, pertussis (whopping cough), poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib) infection are recommended by the World Health Organization (WHO) and for this, the expanded programs on immunization (EPI) are well implemented in most countries globally. The routine use of these EPI vaccines has had an enormous impact, preventing previously common life-threatening childhood infectious diseases [1]. Because the addition of multiple individual vaccines to immunization programs can increase the complexity of vaccine supply, logistics, and vaccination execution, the number of required health facility visits, and the overall cost; combination vaccines have been formulated and introduced to minimize these barriers [2]. Combining multiple antigens in a single injection can facilitate vaccine delivery and administration, result in improved immunization coverage, and increase patient adherence to vaccination schedules [3,4]. Combination vaccines thus can reduce the direct and indirect costs of vaccination.

Serum Institute of India Pvt. Ltd. (SIIPL) has developed and manufactured a combination pentavalent vaccine that includes a liquid diphtheria (D) and tetanus (T) toxoids, acellular pertussis (aP), inactivated poliovirus (IPV) vaccine i.e. DTaP-IPV which is reconstituted with lyophilized Hib capsular polysaccharide conjugate vaccine (PRP-T) at the time of injection (DTaP-IPV + Hib vaccine). Post completion of pre-clinical animal toxicological studies in accordance with Good Laboratory Practices(data on file), we undertook a first-in-human Phase 1 clinical trial to assess the safety of SIIPL's DTaP-IPV + Hib vaccine in healthy adults in India.

Materials and methods

Study design

With the objective to evaluate the safety and tolerability of SIIPL's DTaP-IPV + Hib vaccine following a single dose in 24 healthy Indian male and female adult volunteers, this Phase 1 open-label

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clinical trial was conducted at Phase-I, Pharmacology Unit of Lambda Therapeutic Research Ltd., Ahmedabad, India from July to November 2017. Approvals were sought and received from the Drugs Controller General of India and the Ethics Committee of Care Institute of Medical Sciences, Ahmedabad. The trial was registered prospectively in the Clinical Trials Registry- India (CTRI/2017/07/009034), and was conducted in accordance with the International Council for Harmonization Good Clinical Practice (ICH-GCP) guideline and 'Schedule Y' (amended version 2013) guidelines [5] of Drugs and Cosmetic Act passed by Government of India.

Study vaccine

DTaP-IPV + Hib vaccine (batch number 297U6002) was manufactured and supplied by SIIPL to the Phase-I study site as a powder (1 vial of *H. influenzae* type b conjugate vaccine [Freeze Dried]) to be reconstituted with 1 vial of DTaP-Salk IPV suspension for injection. Each 0.5 mL dose of reconstituted vaccine contains $\geq$ 25 Lf / 30 IU of diphtheria toxoid (DT), $\geq$10 Lf / 40 IU of tetanus toxoid (TT), $\geq$ 25 mcg of pertussis toxoid (PT), $\geq$ 25 mcg of filamentous haemagglutinin (FHA), 40 DU, 8 DU and 32 DU of inactivated poliovirus (Salk IPV) type 1, type 2 and type 3 respectively and 10 μg of polysaccharide of Hib conjugated to the tetanus protein.

Enrolled participants received a single 0.5 mL dose of SIIPL's DTaP-IPV + Hib vaccine intramuscularly into the deltoid muscle of the non-dominant arm using a 25 gauge, (1 or 11/2 in. in length) needle. Required temperature range of + 2 °C to + 8 °C was maintained during transportation and storage of the vaccine at the site of the study.

Study population and procedures

Before initiation of any study-related procedures written informed consent was obtained from volunteers. Male or female participants aged 18–45 years with a normal body mass index and healthy as established by medical history, clinical examination, laboratory investigation were included. Participants with history of acute illness or fever in the past 7 days were excluded. Other exclusion criteria were known hypersensitivity to any components of the vaccine, serious reaction following any prior vaccine administration, any condition associated with suppression of immune response or on any drug that suppresses immunity, any major systemic disorder, positive serology for Human Immunodeficiency Virus, hepatitis B or hepatitis C, abnormal electrocardiogram or chest X-ray. Female participants who were pregnant or planning pregnancy or lactating during trial participation were also excluded. A total of 24 participants (12 males and 12 females) were enrolled in the study and received a single injection of SIIPL's DTaP-IPV + Hib vaccine.

Safety assessment

Post-vaccination, participants were monitored at the study site for a minimum of 4 h for any reactogenicity and immediate unsolicited adverse events (AEs). Subsequently, active follow-up of each participant was done over a period of 7 days for local and systemic solicited AEs. Unsolicited and serious AEs (SAEs) occurring during 30 days follow-up period were recorded. All participants were provided diary cards on days 0, 4, and 7 to record duration and intensity of AEs. The data from the diary cards were assessed by the investigator for relationship to the study vaccine and assignment of severity grading and then recorded in the case report forms.

The endpoints for the study were incidence of immediate AEs within 4 h of vaccination; incidence of local and systemic solicited AEs during 7 days follow-up post-vaccination; and frequency of unsolicited AEs and SAEs during 30 days follow-up post-vaccination. Additionally, blood samples for hematology (Hb, Complete blood count), biochemistry (Total Protein, Albumin, Globulin, Urea, Creatinine, SGOT (AST), SGPT (ALT), Serum electrolytes, Bilirubin, Random glucose) and urine samples (Specific Gravity, pH, Glucose, Protein, Bilirubin, ketones, Urobilinogen, Erythrocytes, Leucocytes, Nitrite and, if necessary, microscopic examination) were obtained from the participants on days 0, 7 and 30 post-vaccination. Serum pregnancy screening on days 0 and 30 and a urine pregnancy test on day 0 were conducted in female participants. Independent oversight of this study was provided by an independent data and safety monitoring board (DSMB) composed of four members with pertinent experience in the fields of safety of vaccines and statistical analysis who were not associated with SIIPL and had declared no for any conflicts of interest.

No formal sample size estimation was done for this study as it was a Phase I clinical trial for safety evaluation. The statistical software SAS® version 9.3 for Windows [SAS Institute Inc., USA] was used for analyzing the data. For the coding of AEs in to System, Organ and Class (SOC) the Medical Dictionary for Regulatory Activities (MedDRA version 20.0) was used. All the concomitant medications were classified using the December 2016 version of WHO Drug Dictionary. Post-vaccination changes in the laboratory test results as compared to baseline for each parameter were summarized using descriptive statistics. Laboratory values for each parameter were classified as normal or abnormal, and abnormal values were subsequently assessed for their clinical significance, based on the principal investigator's clinical judgment.

Results

Total 60 study participants were screened for eligibility, of which 24 participants, [12 male and 12 female] were enrolled in the study and vaccinated with a single dose of DTaP-IPV + Hib vaccine (Fig. 1, Table 1). All the 24 participants completed the study as per planned in the study protocol.

No immediate hypersensitivity reactions were reported. Four solicited AEs were reported in three participants during the study period (Table 2). After administration of study vaccine on day 0, one participant reported injection site erythema and another participant reported injection site pain. Both these AEs resolved with treatment. Yet another participant reported injection site pain and one episode of vomiting on day 0 after administration of study vaccine and these events resolved spontaneously. All reported AEs were mild (Grade 1) in severity and assessed to be related to the study vaccine. All AEs resolved without any sequelae. No unsolicited AEs or SAEs were reported in the study. No clinically significant changes in the laboratory values were observed in any of the study participants. Post-vaccination safety data of all the trial participants, obtained at day 7 and day 30 was analyzed by the DSMB members. They concluded that there were no safety concerns and and recommended that the vaccine can proceed for further clinical development in children involving the assessment of safety and immunogenicity.

Discussion

This was a first-in-human Phase 1 clinical trial conducted to assess the safety and tolerability of SIIPL's DTaP-IPV + Hib vaccine. As a general approach, the safety of SIIPL's DTaP-IPV + Hib vaccine was initially evaluated in healthy adults to provide sufficient safety data to allow further clinical development of the vaccine in the intended target population of infants and toddlers [6]. This vaccine is not indicated for adults; therefore, only a single dose of SIIPL's DTaP-IPV + Hib vaccine was administered in this Phase 1 trial in

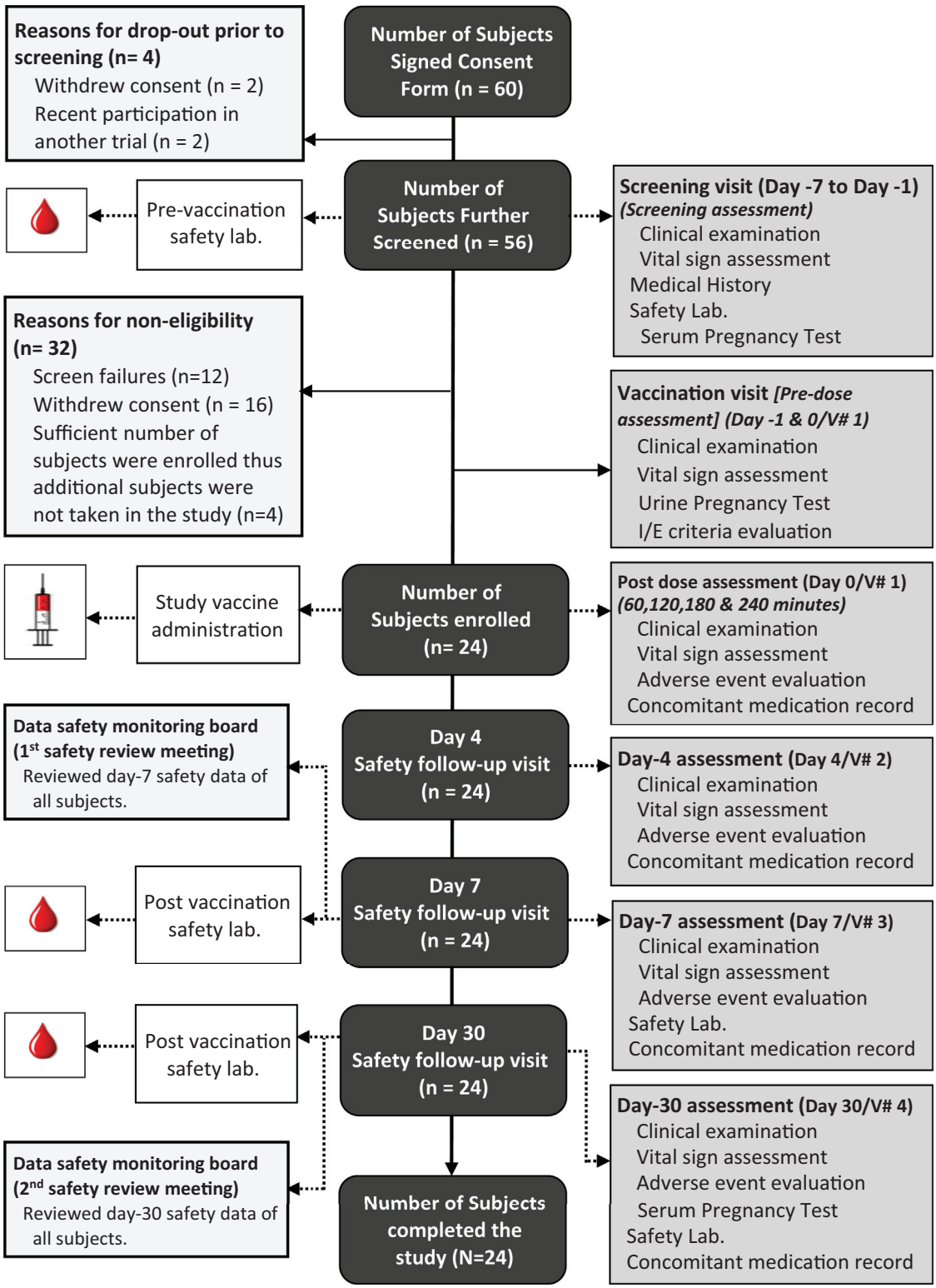

Fig. 1. CONSORT Flow diagram. N = Total sample size.

healthy adults. No immediate post-vaccination reactogenicity or unsolicited AEs were observed during the first 4 h of direct observation. Pain at the site of injection was the most common solicited local AE and was reported in two participants on Day 0. No unsolicited AEs or SAEs occurred in the study population. Overall, no safety concerns were reported following single dose administration of DTaP-IPV + Hib vaccine in healthy Indian adults.

Similar to our study, previous studies do not show any notable AEs with DTaP-based vaccines in adults [7–9]. In a prospective, observational study evaluating the safety of subcutaneously administered pediatric formulation of DTaP vaccine in Japanese adults, the incidence of local AEs was 51.1%, with the majority of these AEs resolving within 7 days [7]. In another study assessing the safety of a reduced dose DTaP-IPV vaccine in healthcare work-

Table 1
Demographics and Baseline Characteristics.

Parameter	Statistics	Total (N = 24)
Age	n	24
	Mean (SD)	33.4 (5.59)
	Median	34.0
	Min, Max	22, 43
Gender		
Male	n (%)	12 (50.00%)
Female	n (%)	12 (50.00%)
Race		
Asian	n (%)	24 (100.00%)
Caucasian	n (%)	0 (0.00%)
Other	n (%)	0 (0.00%)
Height (cms)	n	24
	Mean (SD)	161.0 (9.57)
	Median	160.5
	Min, Max	146.5, 175.5
Weight (kg)	n	24
	Mean (SD)	58.0 (5.09)
	Median	57.7
	Min, Max	50.2, 66.6
BMI (kg/m^2)	n	24
	Mean (SD)	22.5 (1.83)
	Median	23.0
	Min, Max	18.7, 24.7

Abbreviations: SD – Standard deviation, BMI – Body mass index, n – Subject Count, N – Total sample size.

Table 2
Summary of solicited adverse events after vaccination (N = 24).

AE Term	n (%) [E]
Subjects with at least one AE	**3 (12.50%) 4**
Local AE	
Injection site erythema	1 (4.17%) [1]
Injection site pain	2 (8.33%) [2]
Systemic AE	
Vomiting	1 (4.17%) [1]

*n (%), E. where n = Count of Subjects (at least one event i.e. subjects counted only once), % = (Number of subjects with at least one event / Number of subjects) * 100 and E = Count of Events; AE – Adverse Event.*

ers, injection site erythema and pain were observed in 14 of the 41 (34.1%) and 19 (46.3%) participants, respectively [8]. The percentage of reported solicited AEs in our study population of adults was less compared to these other studies with DTaP-based combination vaccines. The same toxoid used in different combination vaccines may alter in the purification and deactivation process. Also, the quantity and nature of adjuvant on which these antigens are adsorbed may vary. Therefore, the reactogenecity profile of different DTP-containing combination vaccines could be impacted by these various factors [10].

Combination vaccines including acellular pertussis antigens have better tolerability as compared to whole cell pertussis based combined vaccines, induce robust humoral response and have been widely adopted worldwide [11]. In addition, as progress towards polio eradication occurs, the Strategic Advisory Group of Experts of WHO have recommended that at least one dose of IPV along with Oral poliovirus vaccine (OPV) be administered to infants in countries presently using OPV [12]. IPV has been included in the national immunization schedule of India and its inclusion has increased the complexity of childhood vaccination in India [13]. To overcome the constraints of multiple required injections, SIIPL's DTaP-IPV + Hib combination vaccine provides five antigens in one vaccine. The antigen concentrations of the active ingredients of SIIPL's DTaP-IPV + Hib vaccine are similar to those of an established and commercially available DTaP–IPV//PRP ~ T combination vaccine (Pentaxim™, Sanofi Pasteur) recommended for primary and booster immunization of children. This will be an affordable and efficient alternative to currently available acellular based combination vaccines which could be manufactured in large capacities for supplies both in developed as well as developing countries. Since the vaccine does not contain hepatitis B surface antigen it allows the use of flexible schedules for hepatitis B vaccine administration [14].

To conclude, SIIPL's DTaP-IPV + Hib vaccine was generally tolerated well and safe in this first-in-human clinical trial in healthy Indian adults. Going further, a Phase II/III pivotal clinical trial of the vaccine is planned to assess safety and immune response in young children with age de-escalation approach viz., toddlers followed by infants, the target population. Ongoing safety analysis of this Phase II/III study has not shown any concerns in infants after three doses.

CRediT authorship contribution statement

Hitt Sharma: Conceptualization, Writing – review & editing. **Kiran Marthak:** Methodology, Investigation. **Sameer Parekh:** Conceptualization, Writing – original draft. **Pramod Pujari:** . **Sunil Shewale:** Conceptualization, Writing – original draft. **Shivani Desai:** Writing – review & editing. **Akash Patel:** 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.

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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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