Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A randomized, open label trial to evaluate and compare the immunogenicity and safety of a novel liquid hexavalent DTwP-Hib/Hep B-IPV (EasySix™) to licensed combination vaccines in healthy infants

Lalitendu Mohanty *, Sunil Sharma, Beauty Behera, Sachin Panwar, Charu Paliwal, Anu Gupta, Deepak Chandra Chilkoti, Anit Singh

Clinical Research Department, Panacea Biotec Ltd., G-3, B-1 Extn/Mohan Co-op, Industrial Estate, Mathura Road, New Delhi, Delhi 110044, India

ARTICLE INFO

Article history:
Received 27 March 2017
Received in revised form 7 September 2017
Accepted 8 September 2017
Available online xxxx

Keywords:
DTwP-HepB-Hib-IPV
Combination vaccines
Hexavalent
Immunogenicity
Infants

ABSTRACT

Immunogenicity and safety of a newly developed liquid DTwP-Hib/HepB-IPV hexavalent vaccine (EasySix™) was evaluated and compared with administration of commercially licensed Pentavac SD® (DTwP-HepB/Hib) and Imovax Polio® vaccine in an open-label, randomized multi-centric trial. 284 participants, aged 6–10 weeks, randomized in a 1:1 allocation, received three doses of test or comparator vaccines, administered 4 weeks apart. Immunogenicity of the vaccines was determined by measuring the baseline and post-vaccination antibody responses and comparing the proportions of subjects achieving seroprotection against the vaccine antigens; safety was evaluated in terms of solicited (local and systemic) and unsolicited incidences in the follow up phase. Post-vaccination, seroprotection was achieved against all six vaccine antigens in both vaccine groups. The seroresponse rate as well as geometric mean titers of antibody for all vaccine components were comparable between EasySix™ and Pentavac SD®-Imovax Polio® group. Both vaccines had similar reactogenicity profiles and were well tolerated; all adverse events resolved completely without any sequelae. Only one serious adverse event was reported that completely resolved; it was regarded unconnected to the vaccine administered. This study demonstrated that immunogenicity and safety profiles of EasySix™ vaccine, manufactured by Panacea Biotec Ltd, are non-inferior to the commercially available vaccines.

Clinical trial registration: CTRI/2015/02/005578.

1. Introduction

Over the years, progressive use of vaccines has led to the prevention of multiple diseases [1]. However, continuous inclusion of new antigens to routine vaccination has added complexity to an existing congested childhood immunization program. American Academy of Pediatrics (AAP) and US Advisory Committee on Immunization Practices (ACIP) recommends vaccination against 14 diseases through the first 2 years of childhood, achieved by 17–20 injections administered during multiple health care visits; this adds burden on both the health care provider and patients [2]. Combination vaccines- composite of vaccines targeting different diseases are being preferred over monovalent vaccines because they are relatively economical, convenient to use, require fewer injections, and thereby have improved compliance [3–6].

Since the first trivalent DTP (Diphtheria, Tetanus, Pertussis) vaccine licensed in US in 1949 [1,7], several DTP combination vaccine have been introduced in vaccination programs globally [8]. Similar immunization schedules facilitated consolidation of vaccines against *Haemophilus influenza* type b (Hib), hepatitis B (Hep B) and polio virus with DTP using different combination strategies [9–20].

Hexavalent combination (DTaP-HepB/Hib-IPV) combining six vaccines targeting diphtheria, tetanus, acellular pertussis (aP), IPV, Hib and Hep B have been developed, tested and licensed (Infanrix®, Hexaxim®) for vaccination in several countries, including India [19,21–29]. However, WHO has hypothesized that substitution of whole cell pertussis (wP) by less responsive acellular pertussis (aP) in DTP combinations [4,30–32] may be related to decrease in protection [33,34]. Currently, DTwP based hexavalent vaccine are commercially unavailable.

* Corresponding author.
E-mail addresses: lalitendumohanty@panaceabiotec.com (L. Mohanty), sharmasunil@panaceabiotec.com (S. Sharma), beautybehera@panaceabiotec.com (B. Behera), sachinpanwar@panaceabiotec.com (S. Panwar), charuplaiwal@panaceabiotec.com (C. Paliwal), anugupta@panaceabiotec.com (A. Gupta), deepakchilkoti@panaceabiotec.com (D.C. Chilkoti), anitsingh@panaceabiotec.com (A. Singh).

https://doi.org/10.1016/j.vaccine.2017.09.029
0264-410X/

The objective of the present study is to assesses the immune response (primary outcome) and safety profile (secondary outcome) of a completely liquid, novel DTwP based hexavalent combination vaccine, EasySix™ (DTwP-Hib/Hep B-IPV) and compared to co-administration of two commercially available licensed products (DTwP-Hib/Hep B-Pentavac SD®; IPV-Imovax Polio®) comprising of same vaccine antigens.

2. Methods

A randomized, open label trial was conducted at four independent centers across India, to assess non-inferiority of a wholly liquid hexavalent DTwP-Hib/HepB-IPV vaccine (EasySix™; Panacea Biotec Ltd.) to immunization with same vaccine antigens using commercially licensed vaccines. Protocols and related pertinent documents were pre-approved by Indian regulatory and Independent Ethics Committees. The study was conducted as per guidelines laid in Declaration of Helsinki, GCP (Central Drug Standard Control Organization) and Ethical Guidelines for Biomedical Research on Human Subjects (Indian Council of Medical Research). Signed informed consent from parents or legally acceptable representatives (LAR) was prerequisite.

2.1. Subjects

Healthy, full term (>36 weeks gestation period) infants of either sex, aged 6–10 weeks, weighing >3.3 kg, whose parents/Legally acceptable Representative (LAR) gave prior consent, and who complied with all trial procedures, were considered eligible. Exclusion criteria included known HBsAg positivity in mother; immunizations apart from the study vaccine (except zero polio, BCG and birth dose of HBV); history of infection (potentially related to pathogens targeted by the DTwP-Hib/Hep B-IPV vaccine); presence of neurological disorder; history of seizures before trial; temperature >38 °C in last 3 days; indication of acute illness/infection within past 7 days; surgery during the study, known or suspected immune dysfunction (congenital or hereditary); record of anaphylaxis or allergy to vaccine components; evidence of bleeding disorder, any clinically significant chronic disease (such as cardiac, pulmonary, renal, gastrointestinal, hepatic, endocrine, cancer, skin or autoimmune) or basic congenital defects; post-natal administration of immunoglobulin, blood products, cytotoxic agents or radiotherapy and use of any trial or unlisted drug before the commencement or during the trial.

2.2. Study vaccines

A block randomization method was used to randomly allocate 284 eligible subjects in a 1:1 ratio to receive 3-doses primary vaccination series of either EasySix™ or PentavacSD® co-administered with Imovax Polio® (Sanofi Pasteur India Pvt. Ltd.). Treatment groups were assigned to eligible subjects by investigators at their respective site as per the randomization list prepared by the biostatisticians at Panacea Biotec Ltd. using computerized codes (generated by Sealed Envelope Ltd. 2014). To prevent biasness, details of block size and randomization codes were not disclosed to investigators until intervention allocation.

Vaccines were administered to subjects at approximate age of 6, 10 and 14 weeks via intramuscular route. A single injection (0.5 ml) of EasySix™ comprised of diphtheria toxoid (≥30 IU), tetanus toxoid (≥60 IU), inactivated whole cell pertussis (≥4 IU), *H. influenzae* type b conjugated (PRP-TT) (10 μg), recombinant hepatitis B surface antigen (HBsAg) (≥10 μg), inactivated Salk Polio Virus (Type 1 = 40DU, Type 2 = 8DU, Type 3 = 32DU); aluminum phosphate gel (≤1.25 mg) and 2-phenoxyethanol (3.3 mg),or of Pentavac SD® that comprised of HepB/Hib vaccine Pentavac SD® (Serum Institute of India Ltd.) diphtheria Toxoid (≥20 Lf to ≤30 Lf), tetanus Toxoid (≥2.5 Lf to ≤10 Lf), inactivated whole Cell Pertussis (≥4 IU), H. Influenza type b Conjugated (PRP-TT) (10 μg), rec-hepatitis B surface antigen (≥10 μg) and of Imovax Polio® comprised of inactivated Salk Polio Virus (Type 1 = 40 DU, Type 2 = 8 DU, Type 3 = 32 DU); aluminum phosphate gel (≤1.25 mg) and thiomersal (0.005%).

2.3. Serological analysis

For immunogenicity analysis, blood samples (4 ml) were collected before first dose and 4 weeks after conclusion of three dose immunization schedule. The trial sera, stored at −20 °C until analysis, were labeled with a unique 5-digit subject enrollment ID (along with protocol number, parent/LAR initial and sample collection date) that permitted to conduct all serological assays at Drug Discovery Lab, Mohali in a blinded fashion. Immunogenicity was evaluated by measuring antibodies specific for diphtheria and tetanus toxoids, pertussis (Anti PT and Pertussis IgG), Hib (PRP) and Hepatitis B (Anti HBsAg) by specific Enzyme Linked Immunosorbent Assay (ELISA) kits (Demeditec Diagnostics GmbH, Germany). The cut off value for sero-protection against Diphtheria & Tetanus was ≥0.1 IU/ml, for Hib was ≥0.15 μg/ml for short term protection and ≥1 μg/ml for long term protection. For Pertussis, no serological correlate of protection is recognized. The range of testing with upper and lower limits of detection with the use of ELISA kits have been indicated below:

For Diphtheria, range of testing is 0.01–1 IU/ml with limit of detection as 0.01 IU/ml. Whereas, for Tetanus, range of testing is 0.01–5 IU/ml with limit of detection as 0.01 IU/ml. Pertussis IgG, can be quantified in the range of 1–150 U/ml with limit of detection as 1 U/ml. In case of Pertussis PT range of testing is 0.01–200 IU/ml with limit of detection as 0.01 IU/ml. Range of testing for HIB 0.1–10 μg/ml with limit of detection as 0.1 μg/ml. While, Hepatitis can be analyzed from 10 to 1000 mIU/ml and detection limit is 10 mIU/ml. 5 calibrators have been used for all antigens except for Pertussis IgG in which 4 Calibrators have been used.

Neutralizing antibodies against all polio virus types were quantified using seroneutralization assay; the results were computed as the reciprocal of dilution. Defined correlates of seroprotection [35,36] have been established for diphtheria, tetanus, poliovirus, Hib, and Hep B (Table 2). Seroconversion against polio is defined as change in post-vaccination concentration of detectable poliovirus type-specific antibodies from baseline (≥8 reciprocal titer). In absence of universally acceptable correlate of seroprotection for pertussis, seroconversion rate was predefined as a ≥4-fold increase in post vaccination antibody level, in subjects that were initially seropositive for pertussis antigen. In case of subjects that were seronegative to begin with, the response was evaluated as per instruction manual of the Kit (Pertussis IgG ≥ 18 U/ml; anti-PT ≥ 100 μg/ml). Proportion of subjects achieving seroprotection and, antibody geometric mean titers (GMTs) against all six vaccine antigens were evaluated.

2.4. Safety assessment

Subjects were monitored for minimum of 30 min to identify and resolve any adverse response to vaccination. Parents or LAR recorded adverse events (AEs) during four days following immunization (solicited; local and systemic) and incidents occurring till 4 weeks post-vaccination (unsolicited) in the provided diary card. Vital examination (axillary temperature, heart rate and respiration) and clinical examination were done on each visit, follow up visit or at any time during the study, if necessary.

Please cite this article in press as: Mohanty L et al. A randomized, open label trial to evaluate and compare the immunogenicity and safety of a novel liquid hexavalent DTwP-Hib/Hep B-IPV (EasySix™) to licensed combination vaccines in healthy infants. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2017.09.029