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Sponsor: Sanofi Drug substance(s): Pentavalent vaccine (DTwP-HepB-Hib) SHAN 5® (with Shantha pertussis)	Study Identifiers: U1111-1185-3731 Study code: SH505
Title of the study: A Phase III Bridging study to evaluate Immunogenicity and Safety of a Pentavalent vaccine (DTwP-HepB-Hib) SHAN 5® (with Shantha pertussis) as compared to the licensed vaccine, SHAN 5® (with imported pertussis) when administered as three dose primary series at 6-8, 10-12 and 14-16 Weeks of Age in Healthy Indian Infants	
Study center(s): Twelve sites in India.	
Study period: Date first subject enrolled: 16/Jun/2015 Date last subject completed: 16/Jan/2016	
Phase of development: Phase III	

Objectives:

Primary Objective:

Non-inferiority

To demonstrate the non-inferiority of the Pentavalent vaccine (DTwP-HepB-Hib) SHAN 5® (with Shantha pertussis) to licensed vaccine, SHAN 5® (with imported pertussis) in terms of seroprotection/seroresponse rates to all antigens, one month after a three-dose primary series.

Secondary Objectives:

Safety

To describe the safety profile in both groups, one month after each dose of the primary series and any dose of primary series.

To describe the Serious Adverse Events (SAEs) in both groups up to one month post third dose (i.e. the entire duration of the study).

Immunogenicity

To further describe immunogenicity parameters in both groups before the first dose and one month after third dose of primary series.

Methodology:

Multi-center, randomized, single blinded study in 1040 infants followed up for safety and immunogenicity for 28 days following three doses of the vaccine administered at 6-8, 10-12, and 14-16 weeks of age. Two-Arm trial with one arm receiving Pentavalent vaccine (DTwP-HepB-Hib), SHAN 5® (with Shantha pertussis) and the other arm receiving licensed vaccine, SHAN 5® (with imported pertussis).

Number of subjects:	Planned: 1040
	Randomized: 1042
	Treated: 1042
Evaluated:	
	Immunogenicity: 1043
	Safety: 1042

Diagnosis and criteria for inclusion:

Inclusion Criteria:

1. Healthy Infants of either sex between 42-56 days (6 to 8 weeks) of age on the day of enrollment

2. Born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg.

3. Informed consent form signed by parent or legally acceptable representative (LAR) as per local requirements.

4. Subject and parent/LAR are able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria:

1. Participation in another clinical trial in the 4 weeks preceding the trial inclusion or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.

2. Receipt of any vaccine in the 4 weeks preceding the first trial vaccination (except Bacillus Calmette–Guérin (BCG), birth dose Oral Polio Vaccine (OPV) and birth dose of Hepatitis B (Hep B) vaccine).

3. Planned receipt of any other vaccine within the period from 8 days before to 8 days after each trial vaccination except OPV if not given at birth and during National Immunization Day (NID).

4. Previous vaccination against the diphtheria, tetanus, pertussis, hepatitis B (except the birth dose of Hep B vaccine) or *Haemophilus influenza* type b infection with the trial vaccine or another vaccine.

5. Past or current receipt of immunoglobulins, blood or blood-derived products or planned administration during the trial.

6. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy since birth; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks since birth).

7. History of diphtheria, tetanus, pertussis, hepatitis B, or *Haemophilus influenza* type b infections (confirmed either clinically, serologically or microbiologically).

8. Known personal or maternal history of HIV or hepatitis B seropositivity.

9. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the trial vaccine or a vaccine containing the same substances.

10. Known thrombocytopenia, as reported by the parent/ legally acceptable representative.

11. Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion, contradicting intramuscular vaccination

12. Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion. (Chronic illness may include, but is not limited to, cardiac, renal, autoimmune, hepatic, haematological, genetic disorders, atopic conditions, congenital defects, diabetes, convulsions or encephalopathy etc.).

13. Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (axillary temperature ≥ 100.4 °F or ≥ 38 °C) on the day of inclusion (a prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided).

14. Identified as a natural or adopted child of the Investigator, relatives or employee with direct involvement in the proposed study.

15. Subject with definite seizure disorder and getting anticonvulsant therapy.

Study treatments

Investigational medicinal product: Pentavalent Vaccine (DTwP-HepB-Hib) SHAN 5® (with Shantha Pertussis)

Formulation: Liquid sterile suspension

Route(s) of administration: Intramuscular

Dose regimen: One 0.5 mL injection at 6-8, 10-12 and 14-16 weeks of age

Non-investigational medicinal product: Pentavalent Vaccine (DTwP-HepB-Hib) SHAN 5® (with imported Pertussis)

Formulation: Liquid sterile suspension

Route(s) of administration: Intramuscular

Dose regimen: One 0.5 mL injection at 6-8, 10-12 and 14-16 weeks of age

Duration of treatment: 10 weeks

Duration of observation: 28 days follow-up period after each dose administration

Criteria for evaluation:

Immunogenicity:

Primary endpoint

The following serological endpoints were assessed one month after the third dose of the primary series (V04, D84) for non-inferiority analyses:

- Seroprotection for diphtheria (D), tetanus (T), hepatitis B (Hep B), and *Haemophilus influenzae* type b (Hib) antigens with the following endpoints:
  - Anti-D: Antibody (Ab) titers ≥ 0.01 IU/mL
  - Anti-T: Ab titers ≥ 0.01 IU/mL
  - Anti-HBs: Ab titers ≥ 10 mIU/mL
  - Anti- Purified capsular Hib Polysaccharide (PRP): Ab titers ≥ 0.15 mcg/mL
- Seroresponse for Pertussis (anti-wP) antigen with the following endpoint:
  - Subjects with an increase of anti-wP antibody titers from pre-dose 1 to one month post third dose:
    - In initially seropositive subjects (> 11 NTU [Novatech Unit]), a post vaccination titer more than or equal to the pre-vaccination titer was considered as a seroresponse.
    - In initially seronegative subjects (≤ 11 NTU), a post vaccination titer > 11 NTU was considered as a seroresponse.

Secondary endpoints

Endpoints for immune responses at baseline and one month after third dose (descriptive) includes:

<u>At baseline (pre-primary) (D0, Visit 1), before the first dose:</u>

- Antibody titers above the following cut-off for each valence
  - Anti-D antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
  - Anti-T antibody titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
  - Anti-Hep B antibody titers ≥ 10 mIU/mL

- Anti-PRP antibody titers ≥ 0.15 mcg/mL

- Individual Diphtheria, Tetanus, Hep B, PRP, wP concentration /titers (pre dose Geometric Mean Titer [GMT])

<u>One month after the third dose (post dose 3) of study vaccine (D84, Visit 4, at approximately 18-20 weeks of age):</u>

- Antibody titers above the following cut-off for each valence
  - Anti-D antibody titers ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-T antibody titers ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
  - Anti-HBs antibody titers ≥ 100 mIU/mL
  - Anti-PRP antibody titers ≥ 1.0 mcg/mL
- Subjects with ≥ 4-fold rise in anti-whole cell pertussis (wP) antibody titers
- Ratio (post dose 3 /pre-primary) of individual Ab titers for all Abs (GMTR)
- Antibody titers for each valence (post dose GMT)

Enzyme linked immune sorbent assay (ELISA) technique was used for estimation of antibody titers against D, T, Hep B, PRP/Hib, and wP. All immunological assays were carried out at the Quest Diagnostic India Ltd. (QDI), Gurgaon, India and Focus diagnostic, USA.

Safety:

The following endpoints were assessed one month after each dose and any dose of primary series for the safety evaluation:

- Occurrence of any solicited and unsolicited adverse events reported in the 30 minutes after vaccination.
- Occurrence of the following solicited (terms pre-listed in the eCRF) injection site reactions between Day (D)0 and D7 after vaccination:
  - Tenderness
  - Erythema
  - Swelling
- Occurrence of the following solicited systemic reactions between D0 and D7 after vaccination:
  - Fever
  - Vomiting
  - Crying abnormal
  - Drowsiness
  - Appetite lost
  - Irritability
- Occurrence of unsolicited adverse events between D0 and D28 after vaccination.
- Occurrence of any Serious Adverse Events (SAE) throughout the study.

Other recorded or derived endpoints were described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the Adverse Events (AE) led to early termination from the study, seriousness, or outcome.

Statistical methods:

Non-inferiority

The differences in seroprotection/seroresponse rates according to the valence between the two vaccines i.e. Test [SHAN 5® (with Shantha pertussis)] vs Reference [SHAN 5® (with imported pertussis)] was calculated. The clinically relevant limit for non-inferiority was −10% for D, T, Hep B, Hib, and wP antigens. The statistical method was based on the lower bound of the two-sided 95% CI of the observed difference of the seroprotection/seroresponse rates.

A non-inferiority testing approach was used to compare seroprotection (D, T, HBs, PRP) and seroresponse (wP) rates, one month after the third injection between the two products on the following hypotheses:

H0 (i): $P_{\text{Pentavalent Test Vaccine}} - P_{\text{Pentavalent Reference Vaccine}} \leq -\delta$

H1 (i): $P_{\text{Pentavalent Test Vaccine}} - P_{\text{Pentavalent Reference Vaccine}} > -\delta$

With

- δ non-inferiority clinical margin set at 10% for each antigen
- i valence in {D, T, HBs, PRP, wP}

The statistical methodology was based on the use of the two-sided 95% CI of the differences between the two products in their seroprotection/seroresponse rates.

Overall non-inferiority hypothesis will be demonstrated if each of the 5 lower bounds of two-sided 95% CIs is above the - δ.

The 95% CI for differences was calculated using Wilson score method without continuity correction.

Descriptive statistics was produced.

Safety data at each time point was summarized by vaccine group.

Immunogenicity endpoints were also summarized by vaccine group. The following parameters was used:

- Percentage of subjects with titers above predefined cut-off as per secondary endpoints
- Percentage of subjects with ≥4 Fold rise in anti-whole cell pertussis (wP) antibody titers
- Geometric mean ratio (GMTR) of individual Ab titers
- GMT or GMC for each valences

Immunogenicity criteria were described for available blood samples before the first dose and one month after the third dose of the combined vaccines. Reverse Cumulative Distribution Curves (RCDCs) of individual titers were also presented.

The main safety and immunogenicity parameters were described with 95% CI.

Populations

For non-inferiority test, Per protocol analysis set (PPAS) was used as the main analysis, and confirmed by an analysis made on the full analysis set (FAS) as a sensitivity analysis. For other descriptive immunogenicity criteria, results were presented for the FAS and the PPAS.

For safety, the safety analysis set (SafAS) was used.

Other analysis set could be also used for demography, disposition, or listings.

Summary:

Population Characteristics:

A total of 1043 subjects were screened and 1042 were randomized at V01 (Day 0) from 16 June 2015 to 17 October 2015. Of these subjects, 522 subjects were randomized to the SHAN 5® (with Shantha pertussis) group (Group-I) and 520 subjects to the SHAN 5® (with imported pertussis) group (Group-II) respectively. Though it was initially planned to recruit a sample size of 1040, since one of our site recruited extra 2 subjects apart from the regular randomization block of “8”, we finally landed up 1042 recruited subjects for FAS.

The demographic and baseline characteristics at V01 of the subjects included in each group are summarized for the FAS in Table below:

Demographic and baseline characteristics - FAS			
	SHAN 5® (with Shantha Pertussis) (N=522)	SHAN 5® (with imported Pertussis) (N=520)	All (N=1042)
FAS	522	520	1042
	Sex:		
Male: n (%)	282 (54.0)	270 (51.9)	552 (53.0)
Female: n (%)	240 (46.0)	250 (48.1)	490 (47.0)
Sex ratio: Male/Female	1.18	1.08	1.13
	Age at V01 (week)*		
Mean (SD)	6.36 (0.527)	6.34 (0.506)	6.35 (0.516)
Median	6.00	6.00	6.00
Min; Max	5.00; 8.00	6.00; 8.00	5.00; 8.00
	Weight at birth (kg))		
Mean (SD)	2.91 (0.306)	2.93 (0.310)	2.92 (0.308)
Median	2.85	2.90	2.90
Min; Max	2.50; 4.34	2.50; 4.08	2.50; 4.34
	Subject born at full term of pregnancy (>= 37 weeks): n (%)		
Yes	522 (100.0)	520 (100.0)	1042 (100.0)

n: number of subjects fulfilling the item listed according to the FAS

Q1; Q3: first quartile; third quartile

%: percentages are calculated according to the subjects available in the FAS

* Based on age derived

Immunogenicity Results:

Primary immunogenicity objective, using protocol-defined thresholds for seroprotection, the SHAN 5® (with Shantha Pertussis) vaccine was shown to be non-inferior to the SHAN 5® (with imported Pertussis) vaccine, in terms of seroprotection rates to anti-D, anti-T, anti-PRP and anti-Hep B. But the confidence interval around the point estimate of the seroresponse rate to anti-pertussis (anti-wP) was very marginally out of predefined limit. Though the lower limit of the 2-sided 95% confidence interval was fixed at -10%, this study results a lower limit of -10.35%. However this marginal difference between SHAN 5® (with Shantha pertussis) and the current marketed product SHAN 5® (with imported pertussis) has limited clinical relevance as other immunogenicity parameters (GMTs and distribution curves) show a comparable immune response in both treatment groups and as the lower than expected observed seroresponse rates in both groups could explain the slight decrease below -10% of the lower bound of the 95% CI.

		SHAN 5® (with Shantha Pertussis)		SHAN 5® (with imported Pertussis)		Product comparison [SHAN 5® (Shantha Pertussis) vs SHAN 5® (imported Pertussis)]	
Antigen	Criterion post-dose 3	n/M	% (95% CI)	n/M	% (95% CI)	Difference (%)	95% CI (2-sided)
Anti-D (ELISA - IU/mL)	Seroprotection (i.e., >= 0.01 IU/mL)	448/450	99.6 (98.4; 99.9)	447/450	99.3 (98.1; 99.9)	0.22	(-1.02; 1.54)
Anti-T (ELISA - IU/mL)	Seroprotection (i.e., >= 0.01 IU/mL)	450/450	100.0 (99.2; 100.0)	450/450	100.0 (99.2; 100.0)	0.00	(-0.85; 0.85)
Anti-wP (ELISA - NTU)	Seroresponse*	260/450	57.8 (53.1; 62.4)	278/450	61.8 (57.1; 66.3)	-4.00	(-10.35; 2.40)
Anti-PRP (ELISA - mcg/mL)	Seroprotection (i.e., >= 0.15 mcg/mL)	447/450	99.3 (98.1; 99.9)	445/450	98.9 (97.4; 99.6)	0.44	(-0.98; 1.97)
Anti-HBs (ELISA - mIU/mL)	Seroprotection (i.e., >= 10 mIU/mL)	428/450	95.1 (92.7; 96.9)	438/450	97.3 (95.4; 98.6)	-2.22	(-4.88; 0.31)

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with available data for the relevant endpoint
* Subjects with an increase of anti-wP antibody titers from pre dose 1 to one month after third dose:
In initially seropositive subjects (> 11 NTU), a post vaccination titer more than or equal to the pre-vaccination titer will be consider as a seroresponse.
In initially seronegative subjects (<= 11 NTU), a post-vaccination titer > 11 NTU will be consider as a seroresponse.

Secondary immunogenicity objectives (descriptive analysis of other seroprotection thresholds and GMTs) confirm what has been observed on primary analysis. SHAN 5® (with Shantha Pertussis) investigational group showed similar seroprotection rates to the SHAN 5® (with imported Pertussis) comparator group for almost all antigens (anti-D, anti-T and anti-PRP).

Though numerically lower seroprotection/seroresponse observed for anti-wP, anti-HBs, anti-PT and anti-FHA, the differences were not significant as their 95% CIs are overlapping.

A similar pattern was also observed with GMTs and GMTRs.

Safety Results:

Within 30 minutes after any vaccination 70 (13.4%) in SHAN 5® (with Shantha pertussis) group and 73 (14.0%) in SHAN 5® (with imported pertussis) group experienced immediate solicited injection site reactions (tenderness) which were of grade 1 or grade 2 intensity.

Within 7 days after vaccination, 77.9% of subjects in SHAN 5® (with Shantha pertussis) (Group I) experienced at least 1 solicited reaction: 68.8% experienced at least 1 solicited injection site reaction and 64.3% experienced at least 1 solicited systemic reaction.

Within 28 days after any vaccination a total of 2.5% in SHAN 5® (with Shantha pertussis) (Group I) and 2.1% in SHAN 5® (with imported pertussis) (Group II) experienced at least 1 unsolicited AE. In SHAN 5® (with imported pertussis) (Group II) one subject experienced unsolicited AR it was reported as non-serious AR. There are total of six SAEs (including one death) reported in four subjects. Two (0.4%) in SHAN 5® (with Shantha pertussis) (Group I) and 2 (0.4%) subjects in SHAN 5® (with imported pertussis) (Group II) till one month post dose 3. All the SAEs and death case were assessed to be unrelated to the study vaccines
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