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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi	Study Identifiers: CTRI/2012/08/002872
Drug substance(s): DTwP-Hep B-Hib Liquid Vaccine (SHAN 5®)	Study code: SH501
Title of the study: Safety, Immune Lot-to-Lot Consistency and Non-Inferiority of SHAN 5® (DTwP-HepB-Hib) Vaccine in Comparison to Pentavac SD When Administered as a Single Booster Bose at 15-18 months and Three Doses at 6-8, 10-12 and 14-16 Weeks of Age in Healthy Indian Children and Infants.	
Study center(s): Eleven sites in India.	
Study period: Date first subject enrolled: 23/Aug/2012 Date last subject completed: 10/Jul/2013	
Phase of development: Phase 3	

Objectives:

Primary Objectives

COHORT 1

- To assess the safety profile, 10 days after the booster dose, of the SHAN 5® vaccine as compared to the comparator (Pentavac SD) in terms of incidence of:
- Unsolicited systemic adverse events in the first 30 minutes after each injection.
- Solicited adverse reactions in the first 10 days after injection.
- Unsolicited adverse events in the first 10 days after injection and throughout the follow up period up to Day (D)28.
- Serious adverse events (SAEs) during the first 10 days after injection and throughout the follow up period up to D28.

COHORT 2

- To demonstrate the equivalence of immunogenicity of three lots of DTwP-HepB-Hib vaccine (SHAN 5®) one month after a three-dose primary series (6-8, 10-12 and 14-16 weeks), in terms of:
    - Seroprotection rates for diphtheria (D), tetanus (T), hepatitis B (Hep B), and *Haemophilus influenzae* type b (Hib); and seroresponse rates for anti-whole cell pertussis (wcP) antibodies.
- To demonstrate the non-inferiority of the pentavalent DTwPHepB- Hib vaccine (SHAN 5®) to the licensed pentavalent vaccine (Pentavac SD) in terms of seroprotection/ seroresponse rates to all antigens, 4 weeks after a three-dose primary series. (Pooled Immunogenicity of three lots of SHAN 5® vs Pentavac SD).

Secondary objectives

COHORT 1

- To describe in each group, the immunogenicity parameters for all antigens, one month after the booster dose of the vaccine

COHORT 2

- To describe in each group, including Pentavac SD, the immunogenicity parameters for all antigens, one month after the third dose of the primary series
    - Seroprotection rates for D, T, Hep B, and Hib; and seroresponse rates for anti-purified pertussis (PT) and wcP antibodies.
- To assess the safety profile in each group, one month after each dose of the primary series and for the overall primary series
- To assess the safety profile in each group, 6 months after the primary series.

The safety profile in each group, including Pentavac SD group, was assessed in terms of incidence of:

- Unsolicited systemic adverse events in the first 30 minutes after each injection.
- Solicited adverse reactions in the first 7 days after each injection.
- Unsolicited adverse events in the first 28 days after each injection.
- SAEs during the trial (including the 6-month follow-up period).

Methodology:

Multi-center, randomized, single blinded study in 15 children (15-18 months old) followed up for safety and tolerability for 28 days following single booster dose (Cohort 1) and 1085 infants followed up for immunogenicity for 28 days and safety for six months following three doses of the vaccine administered at 6-8, 10-12 and 14-16 weeks of age (Cohort 2), using Pentavac SD as control vaccine. Two-arm trial in cohort 1 and a Four- arm trial of which three lots are from SHAN 5® vaccine in three arm and one arm receiving Pentavac SD in Cohort 2. This study report presents safety and immunogenicity data up to 28 days post dose 3.

Number of subjects: Planned: 1100

Randomized: 1085

Treated: 1085

Evaluated:

Immunogenicity: 954

Safety: 1085

Diagnosis and criteria for inclusion:

COHORT 1

1. Children between the ages of 15-18 months whose parents/Legally Acceptable Rerpresentative is willing to give written informed consent prior to the study inclusion.

2. Children with good general health as determined by: Medical history, Physical examination and Clinical judgment of the investigator

3. Children who have completed primary immunization series of diphtheria, tetanus, pertussis by virtue of previous immunization and have not received the booster dose scheduled at 15-18 months of age.

4. Children who require a dose of Hepatitis B as per National Immunization schedule/Indian Association of Pediatrics (IAP) recommendation because of one of the following reasons:

i) Has not received any dose of Hepatitis B or

ii) Have not completed primary vaccination against Hepatitis B

5. Children who require a dose of Haemophilus influenzae type b as per National Immunization schedule/IAP recommendation because of one of the following reasons:

i) Has not received any dose of Hib or

ii) Completed primary vaccination against Hib but not received the booster dose.

6. Judged to be able to attend all scheduled study visits and to comply with study procedures.

COHORT 2

1. Infants between 6-8 weeks of age on the day of inclusion

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

3. Informed consent form signed by one or both parents or by the legally acceptable representative as per local requirements

4. 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 first trial vaccination

2. Planned participation in another clinical trial during the present trial period

3. Known or suspected congenital or acquired immunodeficiency, immunosuppressive therapy, or long-term systemic corticosteroids therapy (prednisone or equivalent at ≥ 0.5 mg/kg/day) for more than 2 consecutive weeks within the past 2 months)

4. 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. (The list of vaccines components is included in the investigator's brochure)

5. Chronic illness at a stage that could interfere with trial conduct or completion, in the opinion of the Investigator (Chronic illness may include, but is not limited to, haematological, hepatic, renal, cardiac or respiratory disease or autoimmune disorders, diabetes, atopic conditions, congenital defects, convulsions, or encephalopathy etc.)

6. Blood or blood-derived products received in the past (since birth) or current or planned administration during the trial (including immunoglobulins) that might interfere with the assessment of the immune response.

7. Any vaccination before trial vaccination except oral poliovirus vaccine (OPV), HepB and Bacille Calmette-Guérin (BCG) given at birth. (Cohort 2 only)

8. Any planned vaccination until one month after the last trial vaccination except;

i) OPV (For both the Cohorts)

ii) BCG if not given at birth (Cohort 2 only).

9. Documented history of pertussis, tetanus, diphtheria, poliomyelitis, Haemophilus influenzae type b or Hepatitis B infection(s) (confirmed either clinically, serologically or microbiologically)

10. Previous vaccination against pertussis, tetanus, diphtheria or Haemophilus influenzae type b infections (Cohort 2 only)

11. Known personal or maternal history of HIV, Hepatitis B (hepatitis B surface antigen) or Hepatitis C seropositivity.

12. Known coagulopathy, thrombocytopenia or a bleeding disorder preceding inclusion contraindicating intramuscular vaccination

13. History of seizures

14. Febrile illness (temperature ≥38.0°C) or moderate or severe acute illness/infection on the day of inclusion, according to the Investigator judgment

Study treatments

Investigational medicinal product: DTwP-HepB-Hib combined vaccine SHAN 5®

Formulation: Liquid sterile suspension, supplied in a 0.5 mL single dose vial

Route of administration: Intramuscular injection into the anterolateral area of the thigh

Dose regimen: Single booster dose at age 15 to 18 months or 3 doses of the vaccine each administered at 6-8, 10-12 and 14-16 weeks of age

Non-investigational medicinal product: Pentavac SD™ (DTwP-Hep B-Hib combined vaccine

Formulation: Liquid sterile suspension, supplied in a 0.5 mL single dose vial

Route(s) of administration: Intramuscular injection into the anterolateral area of the thigh

Dose regimen: Single booster dose at age 15 to 18 months or 3 doses of the vaccine each administered at 6-8, 10-12 and 14-16 weeks of age

Duration of treatment:

COHORT 1: 4 weeks

COHORT 2: 32 weeks

Duration of observation:

30 minutes following each vaccine administration.

Criteria for evaluation:

Safety:

COHORT 1:

The primary endpoints for the safety evaluation were:

- The occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination for any unsolicited systemic adverse events reported in the 30 minutes after vaccination.
- The occurrence, time to onset, number of days of occurrence, and severity of the following solicited (terms pre-listed in the Case Report Form [CRF]) injection site reactions between D0 and D10 after vaccination:
    - Injection site tenderness
    - Injection site erythema
    - Injection site swelling
- The occurrence, time to onset, number of days of occurrence, and severity of the following solicited systemic reactions between D0 and D10 after vaccination:
    - Fever
    - Vomiting
    - Crying abnormal
    - Drowsiness
    - Appetite lost
    - Irritability

- The occurrence, nature (MedDRA preferred term), time to onset, duration, severity, and relationship to vaccination of unsolicited adverse events between D0 and D10 and throughout the follow up period, up to D28 after each vaccination.
- The occurrence, nature, relationship to vaccination and seriousness criterion of any SAEs occurring throughout the follow up period, up to D28.

COHORT 2

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

Seroprotection rates for D, T, Hep B, and Hib with the following endpoints:

- Anti-D and anti-T Antibody titers ≥0.01 IU/mL
- Anti-HBs Antibody titers ≥10 mIU/mL

Anti-Polyribosyl Ribitol Phosphate （PRP) Antibody titers ≥ 0.15 µg/mL

Seroresponse rates for pertussis antigen (Anti-wcP antibody titers)

- In initially seropositive subjects, a post vaccination titer more than or equal to the pre-vaccination titer were considered seroresponse.
- In case of initial seronegative subjects, the response was considered according to assay cut-off (i.e. >11 Novatec Unit [NTU])

Immunogenicity:

Endpoints for the immune response (descriptive):

- Antibody titers above a cut-off for each valence at Visit (V)01(Cohort 1 and 2)
    - Anti wcP antibody titers in positive range as per assay cut-off (i.e. > 11 NTU)
    - Anti-PRP antibody ≥ 0.15 µg/mL & ≥ 1.0 µg/mL
    - Anti-HBs antibody titers ≥ 10 mIU/mL & ≥ 100 mIU/mL
    - Anti-D antibody titers ≥ 0.01 IU/mL and ≥ 1.0 IU/mL
    - Anti-T antibody titers ≥ 0.01 IU/mL and ≥ 1.0 IU/mL
    - Anti-PT antibody titers ≥ 45 IU/mL
        - Antibody titers above a cut-off for each valence at V04 (for Cohort 2) and V03 (for Cohort 1):
    - Anti wcP antibody titers in positive range as per assay cut-off (i.e. > 11 NTU)
    - Anti-PRP antibody titers ≥ 0.15 µg/mL & ≥1.0 µg/mL
    - Anti-HBs antibody titers ≥ 10 mIU/mL & ≥100 mIU/mL
    - Anti-D antibody titers ≥ 0.01 IU/mL and ≥ 1.0 IU/mL
    - Anti-T antibody titers ≥ 0.01 IU/mL and ≥ 1.0 IU/mL
    - Anti-PT antibody titers ≥ 45 IU/mL
    - Anti-PT antibody titer ratio V03/V01 (Cohort 1) and V04/V01 (Cohort 2)

Safety: (Cohort 2)

The secondary endpoints for the safety evaluation were:

- The occurrence, nature (MedDRA preferred term), duration, intensity, and relationship to vaccination for any unsolicited systemic adverse events reported in the 30 minutes after each vaccination.
- The occurrence, time to onset, number of days of occurrence, and severity of the following solicited (terms pre-listed in the CRF) injection site reactions between D0 and D7 after each vaccination:
    - Injection site tenderness
    - Injection site erythema
    - Injection site swelling
- The occurrence, time to onset, number of days of occurrence, and severity of the following solicited systemic reactions between D0 and D7 after each vaccination:

- Fever
- Vomiting
- Crying abnormal
- Drowsiness
- Appetite lost
- Irritability

- The occurrence, nature (MedDRA [Medical Dictionary for Regulatory Activities] preferred term), time to onset, duration, severity, and relationship to vaccination of unsolicited adverse events between D0 and D28 after each vaccination.
- The occurrence, nature, relationship to vaccination and seriousness criterion of any SAE occurring throughout the trial, up to V05 in Cohort 2 (six months post third dose).

Statistical methods:

Primary objectives of Cohort 2

Lot-to-lot consistency analysis:

- Three paired equivalence tests on seroprotection/seroresponse rates according to the valence, one month after the third dose of DTwP-HepB-Hib Vaccine (SHAN 5®)
- The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the differences of the seroprotection/seroresponse rates between the pairs of lots for all antigens

Non-inferiority analysis:

- The differences in seroprotection/seroresponse rates according to the valence between the DTwP-HepB-Hib Vaccine (SHAN 5®) pooled lots and Pentavac SD (comparator) were calculated based on the demonstration of lot-to-lot consistency. The relevant limit for non-inferiority was (−10%) for D, T, wcP, Hep B, and PRP antigens. The statistical methodology was based on the lower bound of the two-sided 95% CI of the difference of the seroprotection/seroresponse rates.

Primary Analysis (Cohort 2)

Consistency

Hypothesis for Consistency of Seroprotection/Seroresponse

An equivalence testing approach was used to test seroprotection (D, T, Hep B and Hib) and seroresponse (wcP), one month after the third injection between each pair of lots (i, k) for each valence 'j' on the following hypotheses:

$$H_0^{ikj}: \left| P_i^j - P_k^j \right| \geq \delta$$

$$H_0^{ikj}: \left| P_i^j - P_k^j \right| < \delta$$

with

- δ equivalence limit is set at 10% for each valence
- i, k in {1,2,3}= number of lot, i δk
- j valence in {D, T, Hep B, PRP, wcP}

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

Individual equivalence hypothesis was considered to be demonstrated if the 95% CI falls entirely within the (-δ, δ) equivalence interval.

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

Overall Hypotheses for Consistency of Seroprotection/ Seroresponse

The overall hypothesis is:

H_{0G}: Equivalence between the three lots is not demonstrated for at least one valence

H_{1G}: Equivalence between the three lots is demonstrated for all the 5 valences

- Equivalence for seroprotection/seroresponse among the three lots was demonstrated if the overall null hypothesis for all valences is rejected (D, T, Hep B, PRP, wcP).

Overall Conclusion for Consistency

Consistency between lots was to be concluded if consistency of immunogenicity is demonstrated based on the seroprotection/seroresponse rates for all the valences.

Non-Inferiority Testing

If equivalence among the three lots is demonstrated for seroprotection/seroresponse, a non-inferiority testing approach will be used to test if overall response obtained by pooling the three lots is noninferior to the response obtained with Pentavac SD vaccine.

The non-inferiority objective was tested on pooled SHAN 5® lots if lot-to-lot consistency is demonstrated on seroprotection/seroresponse rates for each valence.

Individual Hypotheses: (Hypotheses for Each Valence)

The null hypothesis: The difference in terms of percentage of seroprotected/seroconverted subjects, between investigational vaccine (SHAN 5® pooled lot) and Pentavac SD is less than or equal to the clinically relevant limit for non-inferiority ($-\delta i$).

The individual tested hypotheses for valence i will be as follows:

$H^i_0: P^i_{Tested} - P^i_{Reference} \leq -\delta^i$

$H^i_0: P^i_{Tested} - P^i_{Reference} > -\delta^i$

δ^i non-inferiority limit is set at 10% for D, T, Hep B, PRP, and wcP.

Non-inferiority for valence i will be demonstrated if the lower limit of the two-sided 95% CI is greater than δ^i

Overall Immunogenicity Hypothesis

The overall null hypothesis: For at least one valence i, the difference in percentages of seroprotected/seroconverted subjects, between investigational vaccine (three lots pooled of SHAN 5®) and Pentavac SD is less than or equal to the clinically relevant limit for non-inferiority ($-\delta^i$).

Non-inferiority of the investigational vaccine (three pooled lots) was demonstrated if the overall null hypothesis is rejected, that is, individual null hypotheses for all valences are rejected.

H^G_0 : at least one H^i_0 *not rejected*

H^G_1 : all H^i_0 *are rejected*

The hypothesis of primary analysis (seroprotection/seroresponse consistency, or non-inferiority) was tested on the per protocol set and then on the Full Analysis Set (FAS) to confirm the results.

Secondary Analyses (Cohort 2)

Descriptive statistics was produced:

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

Immunogenicity endpoints were presented by vaccine group. The following parameters were used:

Geometric mean of Antibody titers (GM of titers).

Geometric mean of individual Antibody titers ratio V04/V01 for PT

Percentage of subjects with titers above predefined thresholds, including those of defined seroprotection and seroconversion rates.

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

Cohort 1

Similar as Cohort 2 analyses was done, using descriptive methods.

Populations

For Cohort 2, the primary and the secondary endpoints were presented on the per protocol set and then on the FAS to confirm the results.

Sample size [Cohort 2]

A total of 1085 subjects were included in the study (Cohort 2). Subjects were randomly allocated to one of the four groups (Groups 1, 2, 3 for three lots of SHAN 5®, and 4 for [Pentavac SD]) using the 2:2:2:1 repartition.

310 subjects per investigational vaccine lot of (SHAN 5®) and 155 subjects in the Pentavac SD group was recruited so that the following power for the different tests would achieved (based on statistical simulation):

- Equivalence between the three lots in terms of immunogenicity: with an alpha level of 2.5% (one-sided hypotheses) and under the assumption that only 90% of subjects would be evaluable on the per protocol set, the overall power will be around 82%.

Non inferiority of the pooled investigational vaccine group (SHAN 5®) versus Pentavac SD group in terms of immunogenicity: with an alpha level of 2.5% (one-sided hypotheses), and under the assumption of 90% of subjects would be evaluable on the per protocol set, the overall power was assumed to be around 97%.

Summary:

Population characteristics:

A total of 1293 subjects were screened and 1085 were enrolled. Of these subjects, 310 subjects were randomized to each of the SHAN 5® groups, the SHAN 5® (Lot A) Group-1, SHAN 5® (Lot B) Group-2, SHAN 5® (Lot C) Group-3 and 155 subjects in Pentavac SD.
For both Cohort 1 and 2 in the full analysis set (FAS), the treatment groups during single dose booster phase of Cohort 1 were similar in terms of sex distribution, mean age, weight, height, head circumference and BMI-body mass index. This was also the case with the safety analysis set (SafAS).

Safety results:

Four SAEs, including two deaths, were reported till one month post-dose 3 however none were considered related to vaccination. There was no difference between the unsolicited events reported from SHAN 5® or Pentavac SD groups in both cohorts. The events reported were considered to be the usual childhood events and not related to vaccination. No difference between the SHAN 5® and the Pentavac SD groups could be identified based on the time to onset, duration and intensity of the reported events.

Immunogenicity:

For Lot-to lot consistency three paired equivalence tests were performed one month after third dose for seroresponse /seroprotection titers according to the valences. For each valence and each equivalence test the 95% CI lay between –δ to +δ with the exception of Group1 vs Group 2 and Group 2 vs Group 3 pair for anti-wcP. This indicated that the consistency for wcP, was marginally out of specification mentioned in the Protocol. For each valence, the lower limit of 95% CI was greater than – δ (-10%) and thus SHAN 5® was considered to be non-inferior to Pentavac SD vaccine. A descriptive review of the Secondary immunogenicity endpoints demonstrates the immune response (seroprotection/ seroresponse rates and Geometric Mean Concentrations) was similar among all study/ analysis groups.

Issue date: 26-Oct-2020