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

Sponsor: Shantha Biotechnics PVT LTD. **Drug substance(s):** SHANCHOL™ (Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine)	**Study Identifiers:** NCT00760825 **Study code:** CH-WC-02
Title of the study: An Open label post licensure trial to evaluate the safety and immunogenicity of indigenously manufactured Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine (SHANCHOL™)	
Study center(s): 1 center in India	
Study period: Date first subject/patient enrolled: 08/Mar/2012 Date last subject/patient completed: 10/Jan/2013	
Phase of development: Phase 4	
Objectives: To confirm the safety of the oral killed bivalent cholera vaccine produced by Shantha Biotechnics in healthy adult and children volunteers. To determine the immune responses to the oral killed bivalent cholera vaccine produced by Shantha Biotechnics among healthy adult and children volunteers.	
Methodology: Open label trial in healthy adults and children allocated to receive two doses of the vaccine	
Number of subjects/patients**:** Planned: 200 Randomized: 200 Treated: 200 **Evaluated:** Safety: 200 Immunogenicity: 193	

Diagnosis and criteria for inclusion:

Inclusion Criteria

- Male or female adults aged 18-40 years and children aged 1 - 17 years who the investigator believes will comply with the requirements of the protocol (i.e. available for follow-up visits and specimen collection).
- For females of reproductive age, they must not be pregnant (as determined by verbal screening).
- Written informed consent obtained from the subjects or their parents/guardians, and written assent for children aged 12 – 17 years.
- Healthy subjects as determined by:
  - Medical history
  - Physical examination
  - Clinical judgment of the investigator

Exclusion Criteria

- Ongoing serious chronic disease
- Immunocompromising condition or therapy
- Diarrhea (3 or more loose/more watery stools within a 24-hour period) 6 weeks prior to enrollment
- One or two episodes of diarrhea lasting for more than 2 weeks in the past 6 months

- Abdominal pain or cramps, loss of appetite, nausea, general ill-feeling or vomiting in the past 24 hours
- Acute disease one week prior to enrollment, with or without fever. Temperature ≥38ºC (oral) or axillary temperature ≥ 37.5ºC warranted deferral of the vaccination pending recovery of the subject
- Receipt of antibiotics in past 14 days
- Receipt of live or killed enteric vaccine in past 4 weeks
- Receipt of killed oral cholera vaccine

Study treatments

Investigational medicinal product(s): SHANCHOL™ (Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine)

Formulation: Liquid vaccine dose (1.5 mL) containing 4 different strains of *V. cholerae*

Route(s) of administration: Oral

Dose regimen: 1.5 mL given twice orally, 14 days apart

Duration of treatment: The duration of each subject's participation in the trial was 28 days (up to + 32 days).

Criteria for evaluation:

Safety:

- Proportion of subjects with diarrhea
- Proportion of subjects given killed oral cholera vaccine with any of the following adverse events:
  - Immediate reactions within 30 minutes after each dose
  - Serious Adverse Events occurring throughout the trial
  - Reactogenicity: Headache, vomiting, nausea, abdominal pain/cramps, gas, diarrhea, fever, loss of appetite, general ill feeling
    - Diarrhea is defined as having 3 or more loose/watery stools within a 24 hour period.
    - Fever is defined as having an oral temperature of ≥ 38°C or axillary temperature of ≥ 37.5°C

Immunogenicity:

- Proportion of subjects exhibiting 4-fold or greater rises in titers of serum vibriocidal antibodies, relative to baseline, 14 days after the first dose of vaccine and 14 days after the second dose of vaccine.
- Geometric mean serum vibriocidal titers at baseline, 14 days after dose 1, and 14 days after dose 2 of killed oral cholera vaccine.

Statistical methods: A total of 200 subjects, 100 adults and 100 children were included in the study. For safety endpoints, descriptive analyses was used. The number and percentage of subjects with diarrheal adverse event were computed. In addition, the number and percentage of subjects with at least one adverse event (solicited and/or unsolicited) after vaccination and during the 4 weeks follow up period were computed. The number and percentage of subjects with at least one Serious Adverse Event, with the frequencies of each type of event were described. For immunogenicity endpoints, demonstration of a fourfold or greater rise over baseline in serum vibriocidal antibody titer (anti-O1 Inaba, anti-O1 Ogawa and anti-O139 antibody titres) was the primary measure of vaccine immunogenicity. Geometric mean fold rises of serum titres were also analyzed and compared. The number and percentage of subjects (with 95% CI) who exhibited at least a fourfold rise in serum vibriocidal antibody titer after vaccination were compared with the historical data available from the previous immunogenicity studies - phase II and additional Phase III studies with the vaccine. Seroconversion was compared using the chi-square test with Yates correction or by the Fisher's exact test if the numbers were sparse.

Summary:

Population characteristics:

- Planned sample size: Total 200 subjects, 100 adults and 100 children

- Actual number of subjects enrolled: Total 200 subjects, 100 adults and 100 children
- Number of subjects completed: Total 193 subjects, 97 adults and 96 children
- Number of subjects discontinued: Total 7 subjects, 3 adults (consent withdrawal (n=1), loose stools (n=1), and pregnancy(n=1)) and 4 children (consent withdrawal (n=2), fever (n=1), and viral upper respiratory tract infection (n=1))
- Sample size for the analyses: total 200 subjects (100 adults and 100 children) for the safety analysis, total 193 subjects (97 adults and 96 children) for the ITT analysis and total 192 subjects (96 adults and 96 children) for the PP analysis.

Safety results:

Of the 100 healthy adult subjects and the 100 healthy children subjects enrolled:

- No Serious Adverse Events were reported during the study.
- 1 adult subject (1%) experienced mild diarrhea (on Day 13). None of the children had experienced diarrhea.
- 4 adult subjects (4%) experienced AEs within 30 minutes of the vaccine doses. All these AEs were mild in intensity. None of the children reported AEs within 30 minutes of the vaccine doses.
- 47 adult subjects (47%) had reported solicited AEs (Reactogenicity) during the study. The commonly reported solicited adverse events were headache and general ill feeling. Most of the AEs were mild to moderate in intensity. Only one subject reported an AE (abdominal cramps) which was of severe intensity and resolved by the following day.
- 13 children (13%) had reported solicited AEs (Reactogenicity) during the study. The commonly reported solicited adverse events were general ill feeling and headache. One child experienced severe headache and general ill feeling 2 days after the 2nd dose (on Day 16) which resolved within the following day.
- 37 adult subjects (37%) reported unsolicited AEs. The commonly reported unsolicited AEs in adults were headache, abdominal pain or cramps and general ill feeling.
- 16 children (16%) reported unsolicited AEs. The commonly reported unsolicited AEs in children were fever, cough and abdominal pain.
- All the unsolicited AEs reported were considered to be unrelated or unlikely to be related to the study vaccine.

Immunogenicity results:

Proportion of subjects that showed seroconversion (4-fold or greater rises in titers of serum vibriocidal antibodies, relative to baseline) for *V. cholerae O1 Inaba*, among adults was 68% and 55.7% after 1st dose and 2nd dose respectively. Among children, it was 80.2% and 68.8% after 1st dose and 2nd dose respectively.

Proportion of subjects that showed seroconversion for *V. cholerae O1-Ogawa*, among adults was 47.4% and 45.4% after 1st dose and 2nd dose respectively. Among children, it was 72.9% and 67.7% after 1st dose and 2nd dose respectively.

Proportion of subjects that showed seroconversion for *V. cholerae* O139, among adults was 19.6% and 20.6% after 1st dose and 2nd dose respectively. Among children, it was 26% and 18.8% after 1st dose and 2nd dose respectively.

The children cohort showed a higher seroconversion response to the vaccine for *V. cholerae O1 Inaba, V. cholerae O1-Ogawa and V. cholerae O139* when compared to that in the adult cohort.

In both the adult and children cohorts, geometric mean serum vibriocidal titers were observed to be increased from baseline to 14 days after dose 1 and also from baseline to 14 days after dose 2 of the vaccine for *V. cholerae O1 Inaba, V. cholerae O1-Ogawa and V. cholerae O139.*

The geometric mean-fold (GMF) rise in titres relative to baseline for *V. cholerae O1 Inaba, V. cholerae O1-Ogawa and V. cholerae O139* after 1st dose was 7.56, 3.83, and 1.67 respectively in adults and 14.25, 10.79, and 2.02 respectively in children. The GMF rise after 2nd dose was 5.14, 3.07, and 1.52 respectively in adults and 8.23, 7.77, and 1.63 in children respectively.

The proportion of subjects who seroconverted in the present study were compared to that in the previous immunogenicity studies

- In adults, the proportion of subjects who showed seroconversion *for V. cholerae O1- Inaba* and for *V. cholerae O139* in the present study was higher when compared to that in the previous studies but the difference is statistically significant (p=0.04) only for *V. cholerae O139* after 2nd dose.

- In children, the proportion of subjects who showed seroconversion for *V. cholerae O1-Inaba* and for *V. cholerae O139* in the present study was lower than that in the previous studies. But the differences in the proportion between the present study and the previous studies was not statistically significant.

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