

RESULTS SUMMARY

Name of Sponsor/Company: Scandinavian Biopharma Holding AB, Industrivägen 1, 171 48 Solna, Sweden	
Name of Finished Product: ETVAX®	
Name of Active Ingredients: Four inactivated recombinant <i>E. coli</i> strains expressing the colonization factors (CFs) CFA/I, CS3, CS5, CS6, and LCTBA, and dmLT	
Title of Study: A Phase 1 age descending placebo controlled clinical trial to examine the safety, tolerability, and immunogenicity of an oral inactivated ETEC Vaccine (ETVAX®) with dmLT adjuvant in healthy adults and children in Zambia	
Investigator(s): Dr. Roma Chilengi Centre for Infectious Disease Research in Zambia (CIDRZ) Plot 34620 Off Alick Nkhata Rd, Mass Media, PO Box 34681 Lusaka, ZAMBIA	
Study Centre: Centre for Infectious Disease Research in Zambia (CIDRZ) Plot 34620 Off Alick Nkhata Rd, Mass Media, PO Box 34681 Lusaka, ZAMBIA	
Studied period (years): 1 Date of first participant first study visit: 21 September 2019 Date last participant last study visit: 10 September 2020	Phase of development: Phase 1

Objectives and Endpoints:

Primary Objective:

Safety:

To evaluate the safety and tolerability of orally administered ETVAX[®], containing 4 different inactivated *E. coli* strains over-expressing respectively CFA/I, CS3, CS5 and CS6, a hybrid LCTBA protein antigen, and the double mutant *E. coli* heat-labile enterotoxin (dmLT) adjuvant, specifically:

1. To evaluate the safety of one full dose of ETVAX[®] (including 10 µg of dmLT) in adults.
2. To evaluate the safety of 3 doses given on day 1, 15 and 90 of 1/4 and 1/8 adult dose of ETVAX[®] (including 2.5 µg of dmLT) to 10-23 month and 6-9 month old children.

Secondary Objectives:

Immunogenicity:

1. To determine vaccine-induced plasma IgA and IgG antibody responses against LTb on day 1, 8 and 28 in adults and on day 1, 22 and 97, i.e. 7 days after the second and third dose respectively in children.
2. To determine the vaccine-specific plasma IgA antibody response against CFA/I, CS3, CS5, and CS6 in healthy children on day 1, 22 and 97.
3. To determine the vaccine-induced faecal SIgA/total SIgA immune responses against LTb, CFA/I, CS3, CS5, and CS6 in healthy children on day 1, 22 and 97.

Note: The protocol cited serum as the blood samples for immunogenicity analysis; instead plasma samples were evaluated.

Exploratory Objective:

1. To assess memory B-cell responses to LTb, CFA/I, CS3, CS5, and CS6 in adults.

Primary Endpoints

Safety and Tolerability:

- Proportion (%) of participants experiencing SAEs
- Proportion (%) of participants experiencing AEs
- Proportion (%) of participants experiencing vaccine induced reactogenicity events

Secondary Endpoints

Immunogenicity

- Antibody response (\geq two-fold increase in antibody titres between baseline and post-immunization), geometric mean antibody titre levels (GMT), and geometric mean fold rise (GMFR) between baseline and postimmunization to CFA/I, CS3, CS5, CS6 and LTb as measured by faecal SIgA responses in children.
- Antibody response (\geq two-fold increase in antibody titres between baseline and post-immunization), GMT, and GMFR to CFA/I, CS3, CS5, CS6 and LTb as measured by plasma IgA in children, and for LTb also by plasma IgG responses (only IgA and IgG antibody responses against LTb in adults).
- Antibody response (\geq two-fold increase in antibody titres between baseline and post-immunization), GMT, and GMFR to CFA/I, CS3, CS5, CS6 and LTb as measured by faecal SIgA and/or plasma IgA responses in children.

Exploratory Endpoint

Analysis of exploratory objective will be addressed and results thereof reported through an academic PhD research project at CIDRZ.

Methodology:

This was a single site, double-blind, placebo-controlled, age-descending study that started testing the ETEC vaccine with mucosal adjuvant dmLT in healthy adults (Cohort A) and then sequentially in children aged 10-23 months old (Cohort B) and 6-9 months old (Cohort C). All participants in Cohort A received one full dose of ETVAX® (including 10 µg dmLT) or placebo on Day 1; all participants in Cohorts B and C received three doses of either 1/8 or 1/4 of the adult dose of the ETEC vaccine + 2.5 µg dmLT, or placebo on Days 1, 15 and 90 on an outpatient basis. Before moving to the next lower age cohort, available safety data through Day 8 (Cohort A) or Day 22 (Cohort B) was evaluated and reviewed by the Data Safety Monitoring Board (DSMB), after which they made a recommendation to proceed to the next age cohort.

Number of Participants (planned and analyzed):

A total of 246 participants were planned to be enrolled.

In total 246 participants were enrolled and randomized in the study: 40 participants were 18-45 years old (30 randomized to receive full vaccine dose + 10 µg dmLT; 10 to receive placebo), 60 participants were 10-23 months old (20 participants were randomized each to receive 1/8 vaccine dose + 2.5 µg dmLT, 1/4 vaccine dose + 2.5 µg dmLT, and placebo), 146 participants were 6-9 months old (55 participants were randomized each to receive 1/8 vaccine dose + 2.5 µg dmLT and 1/4 vaccine dose + 2.5 µg dmLT; 36 to receive placebo). One participant randomized to receive 1/8 vaccine dose + 2.5 µg dmLT in the 6-9 month age group discontinued from the study prior to the first vaccination and was therefore not included in the safety population.

Two hundred thirty-two (232) participants had a pre-vaccination and at least one post-vaccination immunogenicity assessment and were included in the full analysis population: 40 participants in Cohort A (18-45 years old), 59 participants in Cohort B (10-23 months old) and 133 participants in Cohort C (6-9 months old).

Two hundred fifteen (215) participants received all planned vaccinations, had required immunogenicity assessments, with no major deviations determined to potentially interfere with immunogenicity assessments, were included in the per protocol population: 40 participants in Cohort A (18-45 years old), 56 participants in Cohort B (10-23 months old) and 119 participants in Cohort C (6-9 months old).

Diagnosis and Main Criteria for Inclusion:

Participants were adults and children generally in good health. Eligibility was determined based on the assessment of medical history, laboratory results, clinical examination, complying with all inclusion and exclusion criteria, appropriate parental understanding of the study and completion of the consent process.

Test Product, Dose, Mode of Administration:

Tetravalent ETEC vaccine including LCTBA and double mutant LT (dmLT) and effervescent powder for oral solution (bicarbonate buffer)

Dose:

Cohort A:

ETEC vaccine full dose + 10 µg dmLT + 150 ml buffer

Cohorts B and C:

ETEC vaccine 1/4 dose + 2.5 µg dmLT + 10 ml buffer (2x concentration)

ETEC vaccine 1/8 dose + 2.5 µg dmLT + 10 ml buffer (2x concentration)

The vaccine was given together with sodium bicarbonate effervescent granules. For use, one sachet (5.6 g) of buffer powder was dissolved in 150 ml water (cohort A) and in 75 ml water (cohorts B and C) and mixed with the appropriate volume of vaccine suspension prior to oral administration. The buffer was used to neutralize gastric acidity upon ingestion.

Mode of administration: Oral

Duration of treatment:

Cohort A: 1 dose at Day 1, with follow-up until 28 days after the vaccination

Cohorts B and C: 3 doses at Day 1, 15 ± 2, 90 ± 2, with follow-up until 120 days after the first vaccination (30 days after the third vaccination)

Reference Therapy, Dose, Mode of Administration:

Placebo for ETVAX®: effervescent powder for oral solution (sodium bicarbonate buffer)

Dose:

Cohort A: 150 ml

Cohorts B and C: 10 ml of 2x concentration

Mode of administration: Oral

Criteria for Evaluation:**Safety**

Adverse events were reported from the time of signed informed consent through the completion of the study. For participants who withdrew from the study, attempts were made to follow-up on safety information until the completion of the study.

Any symptom observed after the informed consent form was signed and before the first vaccination, as well as after 7 days post any study vaccination was recorded as an AE. Reactogenicity data (solicited signs or symptoms) were collected through 7 days post-vaccination visit for each vaccination; if a solicited sign or symptom started during the 7 day post-vaccination period and continued beyond Day 7 it continued to be reported as a reactogenicity symptom. Any symptom starting after 7 days post any study vaccination was recorded as an AE. Only when a solicited sign or symptom was considered an SAE, was it reported on an AE/SAE form, in addition to the reactogenicity form. All other safety events that met the definition of an AE or SAE that occurred throughout the study were reported on an AE/ SAE form.

The solicited AEs of nausea (adults only), abdominal pain/stomach ache (adults only), fever, vomiting and diarrhoea were evaluated daily by the research assistant (RA) for 7 days post-vaccination. Unsolicited AEs were assessed through Day 28 (adults only) or Day 120 (children only) and serious adverse events (SAEs) were assessed during the entire duration of the study.

Immunogenicity

Blood and stool samples were collected to evaluate vaccine immunogenicity. Plasma IgA and IgG antibody response to LTB was assessed in adults. In children, plasma IgA antibody response and faecal secretory IgA response to CFA/I, CS3, CS5, CS6 and LTB, and IgG antibody response to LTB were assessed. For all immunological analyses, the response rate and magnitude of antigen-specific responses were analyzed after second and third immunization as specimen availability allowed.

Statistical Methods:

All tabular summaries were presented by age, cohort and treatment group. Categorical data were summarized by the number and percentage of participants falling within each category. Descriptive statistics summarized continuous data: n (non-missing sample size), mean, standard deviation, median, minimum and maximum. Where appropriate (e.g., immunogenicity), geometric means and corresponding 95% confidence intervals were included. All data analyses were conducted using SAS® version 9.4.

Safety

Safety was assessed by analyses of the following primary endpoints (events), where the unit of analysis in each case was the proportion of participants with at least one event:

- Solicited gastrointestinal reactions
- Solicited systemic reactions
- Unsolicited adverse events

- Adverse events where there is a reasonable possibility that the study product caused the event (i.e., are suspected adverse reactions)
- Serious adverse events

The incidence of any adverse events (AEs) was determined post-vaccination.

The solicited AEs of nausea (adults only), abdominal pain/stomach ache (adults only), fever, vomiting and diarrhoea were tabulated by cohort and treatment group.

Grade severities were tabulated for each solicited AE, as well as for the maximum grade severity of all solicited AEs. Incidence rates of severities ≥ 3 (grade 3=severe) were compared between treatment groups (active vs placebo, and between doses within active) using a 2-tailed Fisher's exact test. No adjustment for multiple comparisons was made as the primary purpose of statistical comparisons was to screen potential AEs that need further clinical evaluation. Therefore, they were not considered formal statistical hypothesis testing, and it was acknowledged that there was an inflated Type I error rate (i.e. inflated false statistical significances) due to performing multiple testing without an adjustment. Tabulations were prepared based on the timeframe of within 7 days of each vaccination and within 7 days of any vaccination.

Adverse events reported after the first vaccination during the course of the study (through Day 28 for adults and Day 120 for children) were tabulated by cohort and treatment group for the following:

- Number of subjects experiencing at least 1 AE
- Number of subjects experiencing at least 1 treatment related AE
- Number of subjects experiencing at least 1 serious AE
- AE tabulations by body system and preferred term within 7 days of vaccination 1
- AE tabulations by body system and preferred term within 7 days of vaccination 2
- AE tabulations by body system and preferred term within 7 days of vaccination 3
- AE tabulations by body system and preferred term at any time following treatment

The incidence rates were compared between treatment groups (active vs placebo, and between doses within active) using a 2-tailed Fisher's exact test. No adjustment for multiple comparisons was made. P-values were reported only for the incidence of any AEs ≥ 1 , related AEs ≥ 1 , and serious AEs ≥ 1 .

Immunogenicity

Descriptive summary statistics were presented for the five primary antigens in the ETVAX[®] vaccine (LTB, CFA/I, CS3, CS5, and CS6) by faecal SIgA and plasma IgA, and plasma IgG for LTB.

Post-baseline antigen titre values that were below baseline were replaced with the baseline value for the purpose of calculating geometric mean titre values, geometric mean ratios of post baseline to baseline, and the tabulations of fold rises.

Antibody levels were summarized by treatment group at Day 1 (baseline), Day 8 and Day 28 (adults, Cohort A only), and at Day 1, Day 22 and Day 97 (children, Cohorts B & C only). The number of observations, GMT, and 95% CI of the GMT was reported. The GMT was calculated as the antilog of the mean of the log-transformed (log10) plasma IgA titres and faecal SIgA/total SIgA level titres. The 95% CIs of the GMT was based on the t-distribution to provide population estimates and was presented as the antilog.

At baseline, the treatment groups were compared with an analysis of variance model (ANOVA) with log10 titre as the dependent variable and treatment group as a fixed factor. Pairwise comparisons among the treatment groups were conducted using t-tests and the pooled mean square error from the ANOVA model. Two-sided 95% confidence intervals (CI) were constructed for each treatment group and for each pairwise treatment difference.

For post-baseline values, the treatment groups were compared with an analysis of covariance model (ANCOVA) with log10 titre as the dependent variable, treatment group a fixed factor, and baseline as a continuous covariate. Pairwise comparisons among the treatment groups were conducted using t-tests and the pooled mean square error from the ANCOVA model. Two-sided 95% confidence intervals (CI) were constructed for each treatment group and each pairwise treatment difference (ex. 1/8 dose vs placebo, 1/4 dose vs placebo, 1/4 vs 1/8 dose).

Changes from baseline in the log10 transformed values were compared among the treatment groups with an analysis of covariance model (ANCOVA) with a fixed factor and baseline as a continuous covariate. The

geometric mean fold rises of plasma and faecal immune responses in children were calculated after vaccination 2 (vaccination 2 antibody titre/ baseline), after vaccination 3 (vaccination 3 antibody titre/ baseline), and for the maximum of responses after vaccination 2 and 3 compared to baseline (maximum of vaccination 2 and vaccination 3 antibody titre/ baseline). The number of observations, GMFR with 95% confidence intervals were reported. Pairwise comparisons were performed using a t-test, and the p-value was determined for each pairwise comparison, at each timepoint, and for each antigen. To adjust for the multiplicity of comparisons, Holm's correction was applied to the p-values.

Scatter plots of fold rises were presented for faecal and plasma IgA responses for each antigen side-by-side, for vaccination 2 over baseline, vaccination 3 over baseline, and the maximum of vaccination 2 and 3 over baseline. A multiplicative scale was used for the vertical axis.

The proportion of subjects having a ≥ 2 -fold increase in IgA plasma responses against 0, 1, 2, 3, 4, and all 5 antigens (LTB, CFA1, CS3, CS5, CS6) from baseline after vaccination 2, after vaccination 3, and after either vaccination 2 or 3, was presented for each treatment group. The same was presented for ≥ 2 -fold increase in SIgA faecal response. Similar presentations of plasma IgA responses were presented for a ≥ 4 -fold increase. These analyses were presented for Cohorts B and C individually and combined.

The proportion of subjects exhibiting ≥ 2 (≥ 4) fold rise to at least 3 of the antigens were compared for each pairwise comparison, using Fisher's Exact 2-tailed test. Holm's correction was applied to the p-values.

A comparison of results after receiving 3 doses versus 2 doses was completed. Subjects were categorized into 4 categories according to whether they had ≥ 2 fold rise to at least 3 of the antigens after dose 2 and dose 3, after dose 2 only, after dose 3 only, or after neither dose. This 2-by-2 table was presented for each treatment group (placebo, 1/8 dose vaccine, 1/4 dose vaccine) and tested for symmetry via McNemar's test. These summaries were presented for Cohorts B and C individually and combined.

Due to the exploratory nature of all statistical comparisons for immunogenicity endpoints, all testing and estimations were carried out using a 2-sided 5% Type I error rate without an adjustment for multiple comparisons. However, within each immunogenicity endpoint in Cohorts B and C, Holm's correction for multiple testing was applied to control the multiple comparisons associated with multiple treatment cohorts. Holm's correction was applied for Cohorts B and C, to the 3 comparisons p-values (1/8 dose vs. placebo, 1/4 dose vs. placebo, 1/4 dose vs. 1/8 dose).

Summary – Conclusions

Safety Results:

The objective of this study was to evaluate the safety and tolerability of orally administered ETVAX[®] with dmLT adjuvant in adults and in children aged 10-23 months and 6-9 months.

One full dose of ETVAX[®] (including 10µg of dmLT) in adults was shown to be safe and tolerable. There were no significant differences in the frequency of solicited reactogenicity events or unsolicited adverse events between the full dose of ETVAX[®] (including 10µg of dmLT) and placebo. All solicited reactogenicity events and unsolicited adverse events were rated as mild or moderate.

Three vaccine doses given on Days 1, 15 and 90 of 1/4 dose of ETVAX[®] (including 2.5 µg of dmLT) and 1/8 dose of ETVAX[®] (including 2.5 µg of dmLT) to 10-23 month and 6-9 month old children were also shown to be safe and tolerable. There were no significant differences in the frequency of solicited reactogenicity events or unsolicited adverse events between vaccine and placebo recipients for the 1/4 dose of ETVAX[®] (including 2.5 µg of dmLT) and 1/8 dose of ETVAX[®] (including 2.5 µg of dmLT).

In the 6-9 month cohort, the proportion of participants experiencing vomiting was statistically significantly higher in the ETVAX[®] 1/4 dose (including 2.5 µg dmLT) group than the ETVAX[®] 1/8 dose (including 2.5 µg dmLT) group (20.0% vs 5.6%, p=0.0422). In the 1/4 dose group, the proportion of participants who vomited within 7 days of a vaccination increased from 4/55 (7.3%) after the first vaccination to 8/55 (14.5%) after the second vaccination, including 1 participant who vomited after both the first and second vaccination. No participants in the 6-9 month cohort in the 1/4 dose group vomited after the third vaccination. The incidence of vomiting increased with the increasing dose (from 1/8 to 1/4 dose) in 6-9 month olds, however rates of vomiting in the 10-23 month cohort were higher than in the 6-9 month cohort and did not differ between doses (15.0% in placebo, 30.0% in 1/4 and 1/8 dose groups for the 10-23 month cohort). In the 10-23 month age group all events of vomiting were rated as mild, and in the 6-9 month age group 12/16 (75%) of the events of vomiting were rated as mild and 4/16 (25%) were rated as moderate.

The majority of solicited systemic adverse reactions reported in children across treatment groups were mild (Grade 1) in severity. All severe (Grade 3) reactions reported were fever. In the 10-23 month old cohort, 1 participant in each the 1/8 dose group and 1/4 dose group experienced fever rated as severe after vaccination 2. In the 6-9 month cohort, 1 participant in the 1/8 dose group experienced fever rated as severe after vaccination 1, and 1 experienced fever rated as severe after vaccination 3. One (1) participant in the 1/4 dose group experienced fever rated as severe after vaccination 1, and 1 participant experienced fever rated as severe after vaccination 2 and also experienced fevers rated as moderate in severity after vaccinations 1 and 3.

There was no increase in frequency or severity of systemic reactogenicity with an increasing number of vaccinations or decreasing age.

In 10-23 month olds, at least one unsolicited adverse event was experienced by 18/20 (90%) participants in the placebo group, 19/20 (95%) participants in the ETVAX[®] 1/8 dose (including 2.5 µg dmLT) group and 16/20 (80%) participants in the ETVAX[®] 1/4 dose (including 2.5 µg dmLT) group. In 6-9 month olds, at least one unsolicited adverse event was experienced by 32/36 (88.9%) participants in the placebo group, 43/54 (79.6%) participants in the 1/8 dose group and 47/55 (85.5%) participants in the 1/4 dose group. The majority of unsolicited adverse events in both age cohorts across all treatment groups were classified as MedDRA System Organ Class (SOC) Infection, and infestations, the most frequently reported MedDRA Preferred Term was Upper respiratory tract infection. The majority of unsolicited adverse events were mild or moderate in severity and were rated as not related to the study vaccine. No unsolicited events that were classified as vaccine-related occurred after vaccination 3 in the 10-23 month or 6-9 month old cohorts.

None of the serious adverse events reported was considered related to the study vaccine, and the majority of serious adverse events occurred outside of the 7 day window after any vaccination.

Immunogenicity:

ETVAX[®] full dose (including 10 µg dmLT) induced a statistically significant increase in magnitude of plasma IgA and IgG antibody response against LTB in adults.

ETVAX[®] 1/4 dose (including 2.5 µg dmLT) induced a statistically significant increase in magnitude of plasma IgA and IgG antibody response against LTB and induced a statistically significant increase in magnitude of plasma IgA antibody response against CFA/I, CS3, and CS5 in children aged 6-9 months after 3 vaccinations (Table 1). When analyzing response rates to the different antigens, the response rate to CS6 was found to be in the same magnitude as for the other antigens but did not reach significance due to the high number of responders in placebo.

ETVAX[®] 1/8 dose (including 2.5 µg dmLT) induced a statistically significant increase in magnitude of plasma IgA and IgG antibody response against LTB in children aged 10-23 months and 6-9 months after 2 as well as after 3 vaccinations.

Table 1. Analysis of Plasma IgA Responses: Geometric Mean Titre by Antigen, Vaccination 3 (6-9 Month Olds, PP Population)

	GMT (95% CI)						P-value (adjusted) ^a	
Vaccination 3								
Antigen	Placebo	N	1/8 Dose	N	1/4 Dose	N	1/8 Dose / Placebo	1/4 Dose / Placebo
LTB	126.0 (82.2 , 193.3)	31	816.2 (562.6 , 1184.2)	42	1109.9 (781.1 , 1577.1)	46	< 0.0001	< 0.0001
CFA/I	35.0 (25.3 , 48.3)	31	46.4 (35.1 , 61.3)	42	62.7 (48.1 , 81.8)	46	n.s.	0.0196
CS3	48.7 (31.6 , 75.0)	31	123.5 (85.2 , 179.1)	42	132.5 (92.6 , 189.5)	45	0.0033	0.0018
CS5	25.4 (18.6 , 34.6)	29	33.7 (26.0 , 43.8)	41	49.3 (38.3 , 63.4)	45	n.s.	0.0041
CS6	44.2 (34.5 , 56.7)	31	43.1 (34.8 , 53.4)	42	56.8 (46.2 , 69.8)	45	n.s.	n.s.

1/8 dose= ETVAX[®] 1/8 dose (incl 2.5 µg dmLT); 1/4 dose=ETVAX[®] 1/4 dose (incl 2.5 µg dmLT)

GMT=Antilog of mean log titre value

^a t-test P-value for the specific contrast from the ANOVA model with treatment group as fixed factor, with Holm's correction. If the smallest t-test p-value amongst the 3 comparisons was >0.017 (0.05/3), then Holm's correction procedure was not carried out.

In both age groups of children, plasma and faecal immune responses were strongest to LTB antigen. Faecal SIgA antigen immune response did not reach significance, possibly due to the low sample size of faecal samples available for analysis.

In children aged 6-23 months, the plasma IgA response rate (frequency of at least 2-fold rise) to at least 3 antigens was significantly higher for the 1/4 dose (including 2.5 µg dmLT) group compared to placebo after vaccination 3 (56.7% vs 27.7%, p=0.0099), as was the frequency of at least 4-fold rise to at least 3 antigens (31.7% vs 8.5%, p=0.0127) (Table 2).

Table 2. Analysis of Plasma IgA Responses: Geometric Mean Fold Rise ≥ 2 and ≥ 4 Fold Rise to at Least 3 Antigens (6-23 Month Olds, PP Population)

	N (%)						P-Value (adjusted)		
	Placebo	N	1/8 Dose	N	1/4 Dose	N	1/8 Dose / Placebo	1/4 Dose / Placebo	1/4 Dose / 1/8 Dose
≥ 2 fold rise									
Baseline to Vaccination 2	12 (25.0 %)	48	17 (27.9 %)	61	26 (46.4 %)	56	n.s.	n.s.	n.s.
Baseline to Vaccination 3	13 (27.7 %)	47	23 (38.3 %)	60	34 (56.7 %)	60	n.s.	0.0099	n.s.
Baseline to Maximum of Vaccination 2&3	20 (40.8 %)	49	32 (51.6 %)	62	47 (75.8 %)	62	n.s.	0.0007	0.0171
≥ 4 fold rise									
Baseline to Vaccination 2	5 (10.4 %)	48	3 (4.9 %)	61	7 (12.5 %)	56	n.s.	n.s.	n.s.
Baseline to Vaccination 3	4 (8.5 %)	47	13 (21.7 %)	60	19 (31.7 %)	60	n.s.	0.0127	n.s.
Baseline to Maximum of Vaccination 2&3	9 (18.4 %)	49	16 (25.8 %)	62	23 (37.1 %)	62	n.s.	n.s.	n.s.

1/8 dose= ETVAX[®] 1/8 dose (incl 2.5 µg dmLT); 1/4 dose=ETVAX[®] 1/4 dose (incl 2.5 µg dmLT)

The number (percent) of subjects with titre value at vaccination 2 relative to baseline ≥ 2 for 3 of the 5 antigens (LTB, CFA1, CS3, CS5, CS6). Percentages are calculated relative to this N, which reflect the number of subjects with non-missing data to all 5 antigens.

^aFisher's Exact test (2-tailed). P-value with Holm's correction. If the smallest Fisher Exact test p-value amongst the 3 comparisons was > 0.017 (0.05/3), then Holm's correction procedure was not carried out.

Immunogenicity after 3 vaccine doses appeared to be higher than after 2 doses in children aged 6-23 months, with response rates that were overall higher after 3 vaccine doses than 2. As the study was designed to profile immunogenicity response, it was not likely to be adequately powered to detect differences in specific antigens or vaccine doses.

Conclusions:

The results of this Phase 1 study support the safety, tolerability, and immunogenicity of ETVAX[®] in adults and children in Zambia. No clear safety signals were identified in any age group, and the vaccine safety profile did not differ between doses or number of vaccinations. ETVAX[®] full dose (including 10 µg dmLT) induced a pronounced plasma IgA and IgG antibody response against LTB in adults, and ETVAX[®] 1/8 dose (including 2.5 µg dmLT) and 1/4 dose (including 2.5 µg dmLT) both induced a plasma IgA and IgG antibody response against LTB in children aged 6-23 months after 2 as well as after 3 vaccinations. The 1/4 dose (including 2.5 µg dmLT) also induced a plasma IgA antibody response against CFA/I, CS3, and CS5 in children aged 6-9 months after 3 vaccinations.