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Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Subject: Clinical Review of Supplemental Biologics License Application for Hepatitis A vaccine, inactivated (STN 103475 HAVRIX), manufactured by GlaxoSmithKline

To: BLA STN# 103475/5090

Through: Douglas Pratt, M.D., M.P.H., Chief
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Christian Lynch, Hib assay reviewer

1. Title and General Information

1.1 Title: Medical Officer's Review

1.1.1 STN BLA 103475/5090

1.1.2 Related INDs: ----

1.1.3 Reviewer's Name: Nancy B. Miller, M.D., DVRPA, HFM-485

1.1.4 Submission Date: 12/17/04

1.1.5 Review Completed: 9/20/05

1.2 Product

1.2.1 Proper Name: Hepatitis A Vaccine, Inactivated

1.2.2 Trade Name: HAVRIX

1.2.3 Product Formulation: HAVRIX (Hepatitis A Vaccine, inactivated) is a noninfectious hepatitis A vaccine developed and manufactured by GlaxoSmithKline Biologicals. The virus (strain HM175) is propagated in MRC5 human diploid cells. This suspension is purified through ultrafiltration and gel chromatography procedures. Treatment of the cell lysate with formalin ensures viral inactivation. Viral antigen activity is referenced to a standard using an enzyme linked immunosorbent assay (ELISA) and is expressed in terms of ELISA units (EL.U).

Pediatric/Adolescent Formulation: The one pediatric dose formulation contains 720 EL.U/0.5 mL. Each dose is adsorbed onto 0.25 mg of aluminum as aluminum hydroxide. The vaccine also contains 0.5% (w/v) of 2-phenoxyethanol as a preservative. Other excipients are amino acid supplement (0.3% w/v) in a phosphate buffered solution and polysorbate 20 (0.5 mg/mL). Residual MRC5 cellular proteins (not more than 5 mcg/mL) and traces of formalin (not more than 0.1 mg/mL) are present. Neomycin sulfate (not more than 40 mcg/mL) remains following purification.

Adult Formulation: Each 1.0 mL dose contains not less than 1440 El.U of virus antigen adsorbed onto 0.5 mg aluminum hydroxide.

1.3 Applicant: GlaxoSmithKline Biologicals (GSK)

1.4 Pharmacologic Category: Vaccine

1.5 Proposed Indication: To support extension of the lower age limit for administration to 12 months (from 24 months).

1.6 Proposed Population: 12 months of age and older.

1.7 Dosage Forms and Routes of Administration: HAVRIX is supplied as a slightly turbid white suspension in vials and pre-filled TIP-LOK syringes. HAVRIX is administered by IM injection. In adults, the dose is 1440 EL.U/1 mL given at Month 0 and 6-12 months later. In children and adolescents 12 months through 18 years of age, the dose is 720 El.U/0.5 mL at Month 0 and 6-12 months later.

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3. Executive Summary

The indication for the already licensed inactivated hepatitis A vaccine, HAVRIX, can be extended down to 12 months of age for active immunization against hepatitis A disease. The recommendation of the clinical reviewer is based on the demonstration of non-inferiority of the immune response following 2 doses of HAVRIX (given 6 months apart) in an open, comparative, multicenter study in children 11-13 months and 15-18 months as compared to children 23-25 months of age. The presence of antibody to hepatitis A is considered a demonstration of protection against hepatitis A disease. For initial licensure of HAVRIX in 1995, the protective efficacy and safety were evaluated in a controlled study involving 40,119 children aged 1-16 years of age in Thailand at high risk for hepatitis A infection. The pivotal trial for this supplement also demonstrated that the immune response to 2 doses of HAVRIX (6 months apart) was non-inferior when administered with INFANRIX and OmniHIB* compared to its administration separately. In addition, the trial demonstrated that the seroprotection rate for Haemophilus influenza b (anti-PRP) after a fourth dose OminHIB was non-inferior when administered with HAVRIX and INFANRIX compared to when administered with INFANRIX alone in the 15-18 month old age group. Data were insufficient to demonstrate non-inferiority for the immune response to the antigens contained in INFANRIX. In the pivotal study supporting the new indication, there were no patterns of unusual safety concerns identified. This pivotal study provided 935 subjects for the safety database for subjects < 24 months (and a total of 1084 subjects from 11-25 months of age), and 632 subjects for the According To Protocol cohort for immunogenicity database for ages < 24 months. Three ongoing studies are being conducted to study additional childhood vaccines coadministered with HAVRIX, PREVNAR, MMRII, VARIVAX, DTaP and HIB vaccines. These studies will bring the total database for safety and immunogenicity to approximately 3000 children younger than 24 months of age.

*OmniHIB [Haemohilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)]

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC): Please see product review for comments regarding the assays for pertussis, Haemophilus influenza b, and the ---------- assay.

4.2 Animal Pharmacology/Toxicology: No additional data were provided.

5. Clinical and Regulatory Background

5.1 Disease Studied and Available Interventions:

HAVRIX is indicated for the prevention of hepatitis A infection and associated illness caused by hepatitis A virus.

Immune Globulin is available for post-exposure prophylaxis.

VAQTA is a U.S. licensed, inactivated hepatitis A vaccine, manufactured by Merck, Inc., which is indicated for the prevention of hepatitis A disease for subjects 12 months of age and older.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

VAQTA is another U.S. licensed vaccine for the prevention of hepatitis A. It is indicated for subjects 12 months of age and above.

5.3 Previous human experience with the product or related products as well as foreign experience

HAVRIX has been licensed for use in persons $\geq$ 2 years of age since 1995. The Sponsor estimates that HAVRIX has been administered to 100,000,000 subjects to date, at various doses. Results of a clinical endpoint study to assess the safety and efficacy of the product in subjects 1-16 years of age are described in the label. Results of immunogenicity studies in subjects 1-18 years of age are also described in the label. Efficacy in those over 16 years of age was evaluated by assessing immunogenicity responses after 1 and 2 doses of vaccine. Safety data during clinical trials in more than 31,000 individuals receiving doses ranging from 360 EL.U to 1440 El.U and during postmarketing experience in Europe are also presented in the label.

5.4 Regulatory Background Information

Table 1. Regulatory Background

Initial licensure	2/22/95
Protocol HAV-210	
Submission	7/2/99
Protocol Amendment 01	9/3/99
Protocol Amendment 02	7/12/00
BLA Supplement to lower age indication to 12 months	
Submission	12/17/04
Information Request letter sent	3/18/05
Sponsor Responses to Information Request Letter	6/7/05
Approval	10/17/05

6. Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

One pivotal clinical study and data from three supporting clinical studies were reviewed. The pivotal study was HAV-210, and the supporting studies included HAV-181, 188, and 204. Also reviewed were either clinical study reports and/or synopses of other studies (HAV-116, -118, -119, -126, -132, -206, and ----------) in which a limited number of subjects in the 12-23 month age group received HAVRIX. The supplement was submitted electronically, and the sections reviewed by the clinical reviewer included Items 01 (Index), 02 (Labeling), 03 (Summary), 08 (Clinical Data), 10 (Statistical), 11 (Case Report Tabulations), 12 (Case Report Forms), 13 (Patient Information) and 19 (Financial Information). Serology data were also reviewed in the response to the Information Request letter (sent 3/18/05, responses received 6/7/05).

6.2 Table of Clinical Studies

Table 2. Clinical Studies

Study	Countries	Trial Start	Trial End	Subject Age Range	N planned	N enrolled	Control	Follow-up duration	Formulation
HAV-210	US, Australia	10/7/99	4/9/01	11-25 months	1080	1084	None	7 months	HAVRIX 720 EL.U/0.5 mL 0.25 mg Al(OH)3 INFANRIX OmniHIB
HAV-181 (in collaboration with CDC)	Alaska	1996	2001	6-21 months	240	248	None	12 months plus long term follow-up	HAVRIX 720 EL.U/0.5 mL 0.25 mg Al(OH)3
HAV-188	Israel	12/9/96	12/28/96	2-12 months	400	400	None	Out to 12 months of age	Hepatitis A Vaccine, strain HM 175 (----------) with 720 EL.U/0.5 mL hepatitis A antigen 0.25mg Al(OH)3 DTPa-IPV Haemophilus influenza b conjugate vaccine
HAV-204	Chile	12/21/98	10/22/99	1-2 years	120	120	None	7 months	Inactivated hepatitis A 720 El.U/0.5 mL, strain HM175 (----------) ---------- ------

6.3 Review Strategy

The major part of the review examined the safety and immunogenicity data from the pivotal trial, HAV-210, including the Clinical Study Report and datasets. The clinical study reports for HAV-181, 188 and 204 were also reviewed. The

synopses, clinical study reports (when available), and Case Report Forms of the other trials pertinent to the population for the new indication were briefly reviewed as well.

6.4 Good Clinical Practices and Data Integrity – The pivotal clinical trial, HAV-210, was conducted according to Good Clinical Practice, the Declaration of Helsinki and US 21 CFR Part 50-Protection of Human Subjects and Part 56-Institutional Review Boards), and local rules and regulations of the country. In HAV-188 and HAV-204, it is stated that Good Clinical Practice was followed. HAV-181 was conducted as a collaborative study with the CDC.

6.5 Financial Disclosures: These were provided and no apparent financial conflicts of interest were identified.

7. Human Immunogenicity

Anti-HAV concentrations are measured in comparison with a WHO reference immunoglobulin reagent and expressed as mIU/mL. The concentration of antibody achieved by passive transfer are 10-100 fold lower than those acquired after infection. Concentrations of 10-20 mIU/mL after administration of IG are known to protect against Hepatitis A. In vitro studies using cell culture derived virus indicate that low levels of antibody can be neutralizing. Because no absolute protective level has been defined, generally the lower limit of detection of the assay has been considered as the protective level. Clinical studies of HAVRIX have used levels >15 mIU/mL or >33 mIU/mL as measured by using radioimmunoassays (although the assay in HAV-181 used a > 20mIU/mL cutoff). Clinical studies of VAQTA have historically used levels >10 mIU/mL as measured with a modified radioimmunoassay (HAVAB) as the cutoff for seropositvity.

The duration of protection afforded by HAVRIX has not been established. Therefore it is unknown if the protection provided to immunized children will last until adulthood.

8. Clinical Studies

8.1 Indication #1 – Lower the age indication to 12 months of age from 2 years of age.

8.1.1 Trial #1

8.1.1.1 Protocol HAV-210 – A Phase 4, open, comparative, multicenter study of the immunogenicity and safety of SmithKlineBeecham Biologicals' inactivated hepatitis A vaccine (HAVRIX) 720 El.U/0.5 mL on a 0, 6 month schedule, administered by intramuscular injection, either to children aged (1) 15-18 months old or (2) 11-13 months old, when compared to 23 to 25 month old children; and to determine the immune responses following co-administration of routine childhood vaccines, DTPa and Hib in the 15-18 month age group.

8.1.1.1.1 Objective/Rationale:

The **primary objective** was to demonstrate non-inferiority of the immune response after two doses of HAVRIX when the first dose was given to children

15-18 months of age compared with the immune response in children who received the first dose at 23-25 months of age. If successful, the Sponsor would then demonstrate non-inferiority of the immune response after two doses of HAVRIX when the first dose was given to children 11-13 months of age compared with the immune response in children who received the first dose at 23-25 months of age.

The **secondary objectives** included:

1. Demonstration of non-inferiority of the anti-HAV GMCs after one dose of HAVRIX when given to children 15-18 months of age compared to the anti-HAV GMCs in children 23-25 months of age, and if successful, then demonstrate the non-inferiority of anti-HAV GMCs after one dose of HAVRIX when given to children 11-13 months of age compared with the immune response in children 23-25 months of age after 1 dose.

2. Demonstration of non-inferiority of the immune response to hepatitis A antigen in children 15-18 months old following the administration of HAVRIX with the following vaccines given concomitantly: INFANRIX [GSK Biologicals' diphtheria-tetanus-acellular pertussis (DTPa)] and OmniHIB.

3. Demonstration the non-inferiority of the immune response to the antigens contained in INFANRIX and OmniHIB following concomitant administration of both vaccines with HAVRIX.

4.Demonstration safety of the vaccine in each group.

8.1.1.1.2 Design Overview : This was a prospective, open, comparative, multicenter study with five treatment groups as shown below in the table.

Table 3: Overview of Study Design

Group N(enrolled)	Age at enrollment	Vaccine(s)	Dosing Schedule	Blood Sampling	Immune response for:
1 N=243	11-13 months	HAVRIX	Months 0 and 6	0, 1, 7 months	Anti-HAV
2 N=241	15-18 months	HAVRIX	Months 0 and 6	0, 1, 7 months	Anti-HAV
3 N=242	15-18 months	HAVRIX INFANRIX OmniHIB	Months 0 and 6 Month 0 Month 0	0, 1, 7 months	Months 0 and 1: Anti-HAV, anti-D, Anti-T, anti-PT, anti-FHA, anti-PRN and anti-PRP. Month 7: Anti-HAV
4 N=183	15-18 months	INFANRIX OmniHIB HAVRIX	Month 0 Month 0 Months 1 and 7	0, 1 months 1,8 months	Anti-D, Anti-T, Anti-PT, Anti-FHA, Anti-PRN, and anti-PRP Anti-HAV
5 N=175	23-25 months	HAVRIX	Months 0 and 6	0,1,7 months	Anti-HAV

8.1.1.1.3 Population:

Healthy children 11-25 months of age; 1080 planned.

Inclusion Criteria:

- Healthy male or female 11-13 months, 15-18 months and 23-25 months
- Written informed consent from parent/guardian
- Normal gestational period; previously completed routine childhood vaccination [DTaP and HIB from any licensed US manufacturer] at 2, 4, 6 months of age for all groups, or appropriate primary series at 2,4 months
- Either anti-hepatitis A antibody seropositive or seronegative.

Exclusion Criteria:

- Use of investigational drug or vaccine within 30 days preceding the first dose of study vaccine
- Administration of chronic immunosuppressive or other immune-modifying drugs within a period of 6 months before vaccination or any time during this study period
- Any chronic drug treatment that was to be continued during the study period with the exception of prophylactic antibiotics, multivitamins, and fluoride; planned administration of any vaccine not indicated by the study protocol < 30 days before the first dose of vaccine (although any vaccine recommended by ACIP could be administered > 30 days prior to or after any HAVRIX vaccination; previous vaccination against hepatitis A
- History of hepatitis A; known exposure to hepatitis A
- Known exposure to hepatitis A
- History of non-response to any vaccine in the current routine immunization schedule
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection
- Family history of congenital or hereditary immunodeficiency
- History of allergic disease or reactions likely to be exacerbated by any vaccine component; major congenital defects or serious chronic illness
- History of any neurological disorders or seizures; acute disease at the time of enrollment, and entry could be postponed until resolution of the acute illness [Acute disease was defined as the presence of a moderate or severe illness with or without fever]
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality as determined by physical examination
- Hepatomegaly, right upper quadrant pain or tenderness
- Administration of immunoglobulins and/or any blood products within the three months preceding the first dose of study vaccine or planned administration during the study period
- Any child who received a booster dose of DTaP but did not receive a booster injection for Hib; any child who was 18 months old and had not received the third dose of polio vaccine.

8.1.1.1.4 Products Mandated by the Protocol

HAVRIX: 720 EL.U/0.5 mL given IM at 0 and 6 months (all groups given in the left anterolateral thigh).

INFANRIX: Manufactured by GlaxoSmithKline, and contains diphtheria and tetanus toxoids and acellular pertussis components. All doses were given in the right upper anterolateral thigh.

OmniHIB: Manufactured by Pastuer-Merieux, was supplied in monodose vials. This vaccine was to be given in the right lower anterolateral thigh. Note: OmniHIB is not licensed in the U.S. but is similar to ActHIB.

8.1.1.1.5 Endpoints

Primary Endpoint:

- The anti-HAV (hepatitis A virus) antibody concentrations at Month 7 (Month 8 in Group 4) were reported in responders in each test population. A responder was defined as a subject exhibiting vaccine response, i.e., seroconversion in those subjects initially seronegative or the maintenance of an increase above pre-vaccination concentrations in those subjects who were initially seropositive.

Secondary Endpoints:

- Anti-HAV antibody concentrations at all time points except for Visit 1 in Group 4
- Anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, and anti-PRP antibody concentrations at Month 0 and 1 in Groups 3 and 4

Safety Endpoints

- Occurrence of solicited symptoms after each vaccination in each group
- Occurrence of unsolicited adverse events in each group
- Occurrence of serious adverse events in each group.

Assays Used

- **Anti-HAV antibody**: This was performed by ELISA (----------) with an assay cutoff for seropositivity of 15 mIU/mL. ----------.
- ----------.
- **Anti-Diphtheria antibody:** ELISA (GSK) with an assay cutoff of 0.1 IU/mL

- **Anti-Tetanus antibody:** ELISA (GSK) with an assay cutoff of 0.1 IU/mL

Note: The diphtheria and tetanus assays were recently reviewed by the FDA (see memo of Dr. Willie Vann dated 10/11/05).

- **Anti-PT antibody:** ELISA (GSK) with an assay cutoff of 5 EL.U/mL
- **Anti-FHA antibody:** ELISA (GSK) with an assay cutoff of 5 El.U/mL
- **Anti-PRN antibody:** ELISA (GSK) with an assay cutoff of 5 El.U/mL.

Note: The pertussis assays were recently reviewed by the FDA (see memo of Dr. Bruce Meade, dated 8/30/05).

- **Anti-PRP antibody:** ELISA (GSK) with an assay cutoff of 0.15 mcg/mL

Note: The Haemophilus influenza b assay (anti-PRP) was recently reviewed by the FDA (see memo of Mr. Christian Lynch, dated 9/19/05).

Definitions:

- For all antigens, seropositive was defined as antibody concentrations above the cutoff value.
- For anti-HAV antibody, vaccine response was defined in those initially seronegative as development of detectable antibodies to HAV, and in those initially seropositive, maintenance or increase in the anti-HAV antibody concentration after vaccination.
- For diphtheria and tetanus, seroprotection rates were defined as the percentage of subjects with anti-diphtheria and anti-tetanus concentration $\geq$ 0.1 IU/mL.
- For PRP, seroprotection rates were defined as the percentage of subjects with anti-PRP concentrations $\geq$ 1.0 mcg/mL. Seropositivity to PRP was defined as the percentage of subjects with anti-PRP concentrations $\geq$ 0.15 mcg/mL, the assay cutoff.
- For acellular pertussis components (anti-PT, anti-FHA and anti-PRN) seropositivity rates were each defined as the percentage of subjects with concentrations $\geq$ the cutoff value of 5 El.U/mL. Vaccine response to pertussis antigens following the booster dose was defined as the appearance of antibodies in initially seronegative subjects and post-vaccination concentrations $\geq$ 2 times the prevaccination concentrations in initially seropositive subjects.

Changes to the Protocol:

- In Amendment number 2 (7/12/00), the Sponsor replaced the 1999 ACIP recommended immunization schedule with the updated 2000 ACIP recommended childhood schedule. This did not affect the protocol because this was included as a scheduling aid for vaccines not given as part of the protocol.

- In Amendment number 1 (8/20/99), subjects were assigned into groups 3, 4, and 5 instead of being randomized because of input from an investigator meeting held 7/29/99 in Philadelphia, where the investigators noted that timing of the booster vaccine (prior to study entry) varied by study site and according to local interpretation of the ACIP recommendations. Therefore, randomization was not feasible. Also, the blood draw for anti-HAV just prior to the second HAVRIX dose was eliminated.

8.1.1.1.6 Surveillance/Monitoring

Serum antibodies to hepatitis A virus were taken before the first vaccination and 1 month after each vaccination (except for postdose 1 in Group 4). Serum antibodies to diphtheria, tetanus, pertussis (PT, FHA, PRN) and Haemophilus influenza type b were taken before vaccination and 1-month post vaccination with INFANRIX and OmniHIB.

Parents were to fill out a Vaccine Report Card (VRC) for 4 days (Days 0-3) after vaccination for solicited adverse events. The cards were to be returned by mail. The staff would phone parents if necessary. Parents were instructed to record the rectal or axillary T every day for 4 days. They were also to measure the size of the local reaction and to rate the local reactions during the 4 days post-vaccination. The solicited adverse events included pain, redness, swelling, and the solicited general adverse events included drowsiness, fever, irritability/fussiness, and loss of appetite. At visits 1 month after each vaccination, the investigator would ask about other (unsolicited) adverse events. All adverse events within one month after each dose of vaccine were to be recorded on the adverse event form in the subject's CRF, irrespective of severity or whether or not the adverse event was considered vaccine related.

All Serious Adverse Events (SAEs) occurring from the period of the first day of vaccination and ending within one month of administration of the last dose of vaccine was to be recorded. The parent was instructed to call the site for a severe adverse event.

Medications/other vaccinations were to be recorded at each visit. Information was to be recorded by the parent and transferred to the Case Report Form (CRF) by the investigator or staff.

Adverse events were graded as follows:

- **Pain:** Grade 0-absent; Grade 1-minor reaction to touch; Grade 2-cries/protests on touch; Grade 3-cries when limb moved/spontaneously
- **Redness:** Grade 1<5mm; Grade 2≥5 mm to 20mm; Grade 3 >20 mm
- **Fever:** Grade 1 - 100.4°C -101.3°F (38°C-38.5°C); Grade 2 – 101.4°F - 103.1°F (38.6°C-39.5°C); Grade 3 - > 103.1°F (>39.5°C)
- For each solicited systemic symptom, the parent asked if they sought medical attention.

- For all other adverse events (unsolicited adverse events), grading was as follows: Grade 0-none; Grade 1-AE easily tolerated, causing minimal discomfort, not interfering with everyday activities; Grade 2-AE which is sufficiently discomforting to interfere with normal everyday activities; Grade 3-AE which prevents normal, everyday activities.
- Causality was to be assessed by the investigator.
- Outcome was to be assessed.

Reviewer's Comment: For safety endpoints, surveillance appeared appropriate (see Section 8.1.1.1.6).

8.1.1.1.7 Statistical Considerations

- In the original protocol, the intention to treat (ITT) cohort was to include all subjects who received at least one dose of study vaccine and whose post-vaccination safety data are available. For immunogenicity, the ITT cohort would include all vaccinated subjects who have data available. In the clinical study report, the cohort was renamed the Modified Total Cohort. This cohort was modified in the Clinical Study Report (CSR) to include all subjects who were re-allocated to the group corresponding to the vaccine that they actually received. This modification was made because five subjects assigned to Group 2 erroneously received vaccines that were indicated for Group 3; eight subjects assigned to Group 3 erroneously received vaccinations indicated for Group 4; seven subjects assigned to Group 4 erroneously received the vaccinations for Group 3. The Modified Total Cohort for analyses of safety includes all subjects who received at least one dose of study vaccine, who were re-allocated to the group corresponding to the vaccine actually given, and whose post-vaccination reactogenicity data were available. The Modified Total Cohort for the analysis of immunogenicity included all subjects who received at least one dose of study vaccine, who were allocated to the group corresponding to the vaccine actually administered, and whose post-vaccination immunogenicity data were available.

- Unchanged was the According to Protocol Cohort (ATP) for immunogenicity, (except for deletion of reference to a randomization list because of lack of feasibility as noted by investigators in an investigator meeting in 1999.) The ATP cohort for analysis of immunogenicity includes subjects who received the study vaccine, who have sufficient data for immunogenicity analysis, who did not receive forbidden vaccines or treatments, and who had at least one post-vaccination sample drawn per protocol schedule. The ATP cohort for analysis of safety was not included in the final analysis, because the modified total cohort as above was to be used (which is more inclusive).

- In the analysis of demographics, originally age, gender, race, study center and number of subjects were to be tabulated. Study center was deleted in the CSR, and height and weight were added as parameters.

- Confidence Intervals (CIs) for non-inferiority were adapted to 95% instead of 90%, and asymptotic instead of exact methods for proportions were used. Power considerations induced by these modifications were noted in the clinical study report.

- For the anti-HAV antibody, CIs for the GMT ratio (Group X/Group Y) were computed as post-dose 2 (primary objective) and post-dose 1 (secondary objective). GMTs were considered non-inferior if the lower limit of the 2-sided 95% CI on the GMT ratio for Group 1/Group 5 and Group 2/Group 5 were both ≥ 0.5

- For non-inferiority tests for anti-D, anti-T, anti-PRP, the components of acellular pertussis (FHA, PT, PRN), anti-HAV, response rates were used. The 2-sided 95% CI for the group difference (Group X-Group Y) were to be computed. The response rate in Group X was considered to be not inferior to Group Y if the lower (upper) limit of the 95% CI is not less than –Q% (i.e., higher than Q%). For anti-HAV, the Q is defined as 5% and for the other antibodies, Q is 10%.

- Additionally, for the non-inferiority tests for the antigens of the pertussis component (anti-PT, anti-FHA, and anti-PRN) GMTs were to be used assecondary endpoints. The 2-sided 95% CI for the GMT ratio (Group X/Group Y) was to be computed postdose 1. The GMT of Group X would be considered not inferior to Group Y if the lower (or upper) limit of the 95% CI was not lower than 50% (or not higher than 200%).

Reviewer's Comment: Please see separate Statistical Review by Dr. Henry Hsu regarding the statistical analysis (memo dated 9/14/05).

Analysis of Reactogenicity

Local and systemic solicited were considered for 4-days of follow-up (Days 0-3). These were reported in terms of incidence, occurrence and proportion of subjects reporting symptoms. The occurrence and incidence were reported with regard to intensity of the symptoms. The relationship to vaccine was determined by the investigator.

- The occurrence of each solicited symptom was defined as the number of symptom sheets with a report of this particular symptom during the follow-up period. Symptom sheets were transcribed by the investigator from Diary Cards that were completed. The incidence of a solicited symptom was defined as the percentage of symptom sheets with a report of this particular symptom during the follow-up period, based on the total number of symptom sheets completed.

- The safety analysis also reported unsolicited adverse events and reported Serious Adverse Events (SAEs). These were coded using World Health Organization (WHO) Preferred Terms.
- Unsolicited symptoms were investigated in terms of the proportion of subjects reporting unsolicited symptoms during the 31-day follow-up period (Days 0-30) following each vaccination. The denominator used was the number of documented doses. The number of documented doses was defined as doses for which subjects returned completed Diary Cards and/or for which investigators received information by other means (i.e., oral reports at visits or by phone calls, or from nurse's visits to the subjects). This analysis was also done considering the relationship to vaccine and the intensity.
- Unsolicited symptoms were also investigated using a special counting rule. For each subject, each individual unsolicited symptom was classified by WHO Preferred Term following one dose during the 31-day follow-up period was counted once. This counted the number of doses followed by at least one report of unsolicited symptoms so classified by the WHO Preferred Term. These counts were also investigated with regard to relationship to vaccine. SAEs were initially to be reported for the 31 days after each vaccination, but in the final protocol, were to be reported throughout the entire study period.

Reviewer's Comment: In this review, attribution of relationship to vaccine is considered subjective, and is not presented in tables shown.

8.1.1.2 Results

8.1.1.2.1 Populations Enrolled/Analyzed

Population enrolled – 1085 subjects were enrolled and 1084 vaccinated. One subject in Group 2 (#1170 at center 7) was allocated to Group 2 but the parents withdrew consent prior to the first vaccination. Table 14 (p. 63, CSR of Study 210, not shown here) shows the number of subjects vaccinated by center (modified Total Cohort). There were 15 sites: 14 in the US and 1 in Australia. 343 subjects were from the Australian site and 742 subjects were from the US sites. The number of subjects from the US sites ranged from 3 (at site #3) to 134 (at site #16). The numbers in each group at each site were variable, since subjects were assigned based on the age of the subject, and there were different proportions of subjects in Groups 1, 2, 5 (240 in each) compared with Groups 3, 4 (150 in each).

The first subject enrolled 10/7/99 and the last study visit for the last subject enrolled was 4/9/01.

Table 4: Demographics (Modified Total Cohort)

Characteristics	Parameters	Group 1 N=243	Group 2* N=241	Group 3** N=183	Group 4*** N=175	Group 5 N=242	Total
Age (months)	Mean	11.8	16.3	15.7	15.6	23.7	16.7
	Minimum	11	14	14	14	22	11
	Maximum	13	18	18	18	35	35
Gender	Male	133 (54.7%)	124 (51.7%)	108 (59%)	88 (50.3%)	115 (47.5%)	568 (52.4%)
	Female	110 (45.3%)	117 (48.3%)	75 (41%)	87 (49.7%)	127 (52.5%)	516 (47.6%)
Race	White	154 (63.4%)	134 (55.6%)	104 (56.8%)	108 (61.7%)	160 (66.1%)	660 (60.9%)
	Black	29 (11.9%)	20 (8.3%)	13 (7.1%)	13 (7.4%)	22 (9.1%)	97 (8.9%)
	Oriental	5 (2.1%)	8 (3.3%)	5 (2.7%)	4 (2.3%)	6 (2.5%)	28 (2.6%)
	Other	55 (22.6%)	79 (32.8%)	61 (33.3%)	50 (28.6%)	54 (22.3%)	299 (27.6%)

Group 1 (11-13 months) = Havrix at Months 0, 6
Group 2 (15-18 months) = Havrix at Months 0, 6
Group 3 (15-18 months) = Havrix+Infanrix+OmniHIB at Months 0, Havrix at 6 months
Group 4 (15-18 months) = Infanrix+OmniHIB at Month 0, Havrix at Months 1 and 7
Group 5 (23-25 months) = Havrix at Months 0, 6
*5 subjects assigned to Group 2 were re-allocated to Group 3 because they erroneously received the vaccines indicated for Group 3.
**8 subjects assigned to Group 3 were re-allocated to Group 4 because they erroneously received the vaccines indicated for Group 4.
***7subjects assigned to Group 4 were re-allocated to Group 3 because they erroneously received the vaccines indicated for Group 3.
From Table 18, p. 70, CSR HAV-210

Reviewer's Comments: The demographic data were fairly similar across groups 1-5, except for the difference in ages as specified by the protocol. The demographics for the ATP cohort (Table 19 of the CSR, p. 72, not shown here) and the characteristics are similar to the Modified Total Cohort above.

Table 5 below presents the subjects enrolled, completed and withdrawn by Group and reason. These subjects were eliminated from the ATP analysis for immunogenicity and the line listings are shown in Supplement 4 (pp. 120-122, CSR HAV-210, not included in this review). The number of subjects enrolled, completed and withdrawn from the Modified Total Cohort with the reason for withdrawal are shown in the following table.

Table 5: Number of subjects enrolled, completed, and withdrawn with reason for withdrawal (Modified Total Cohort)

	Enrolled	Completed	Withdrawn	A	B	C	D	E	F	G	H
Overall	N=1085	N=997	N=88	1	4	3	20	16	33	8	3
Group											
1	243	234	9	0	1	0	3	3	2	0	0
2*	242	222	20	1	1	2	4	4	8	0	0
3**	183	165	18	0	0	0	3	3	9	1	2
4***	175	150	25	0	2	0	7	4	6	5	1
5	242	226	16	0	0	1	3	2	8	2	0

A-SAE
B-NSAE
C-Protocol Violation
D-Consent withdrawal
E-Migration from study area
F-Lost to follow-up (subject with incomplete vaccination course)
G-Lost to follow-up (subject with complete vaccination course)
H-Others
*,**,*** - see legend to Table 4 above
Table 15, p. 64, CSR HAV-210

The 1 subject who withdrew due to a Serious Adverse Event (SAE) and the 4 subjects who withdrew secondary to Non-Serious Adverse Events (NSAE) are described in Section 8.1.1.2.3, Safety Outcomes, Withdrawals Due to NSAEs and SAEs.

There were three subjects (2 from Group 2 and 1 from Group 5) who were enrolled in violation of the entry criteria (outside the age window). These three subjects did receive two doses of HAVRIX, but were excluded from the immunogenicity analysis because they did not have blood samples drawn following either dose. They were included in the analysis of safety.

Three subjects were withdrawn for other reasons as follows:
Subject 1569 (Group 3, Center 10) was excluded for non-compliance.
Subject 1813 (Group 3, Center 13) was vaccinated with VAQTA at a site other than the study site.
Subject 1700 (Group 4, Center 8) was withdrawn for unknown reason.

As noted above for the changes in the cohorts, 20 subjects in the 15-18 month age group at three of the study centers (Centers 9, 12, and 16) were erroneously given vaccine of another group as follows:
Five assigned to Group 2 actually received the vaccine for Group 3.
Eight subjects assigned to Group 3 actually received the vaccine indicated for Group 4.
Seven subjects assigned to Group 4 actually received the vaccine indicated for Group 3.
Therefore, the Total Cohort was modified for the re-allocation of those subjects to the group corresponding to the vaccine(s) they actually received, rather than to the group to which they were assigned. There were no errors in the assignment of subjects to the correct group based on their age.

Data regarding compliance in returning completed symptom sheets are presented (Table 17, p. 68, CSR HAV-210, not shown here). These ranged from 92.3% (Dose 2, Group 3) to 99.1% (Dose 2, Group 1)

8.1.1.2.2 Immunogenicity (Efficacy) Endpoints/Outcomes: Immunogenicity analyses were performed for the According To Protocol (ATP) cohort and the Modified Total Cohort (MTC). The ATP analysis was primary and the MTC analysis was secondary.

There were 881 eligible subjects for the ATP analysis for immunogenicity 11-25 months of age.
Results of the immunogenicity analyses for the ATP and MTC were similar.

Primary Objective: Non-inferiority of anti-HAV Geometric Mean Concentrations (GMCs) in responders post Dose 2 HAVRIX between 15-18 months group and 23-25 months group, and if demonstrated, non-inferiority with respect to anti-HAV GMCs in responders between 11-13 month group and the 23-25 month age group.

Table 6: Anti-HAV seropositivity rates and GMCs according to pre-vaccination status (ATP cohort for immunogenicity)

				S+ (≥15 mIU/mL)				GMC (mIU/mL)		
	Pre-vacc					95% CI			95% CI	
Group	status	Timepoint	N	n	%	LL	UL	Value	LL	UL
1	S-	PRE	204	0	0.0	0.0	1.8	7.5	7.5	7.5
	S-	PI(M1)	201	178	88.6	83.3	92.6	46.1	39.7	53.4
	S-	PII(M7)	204	204	100.0	98.2	100.0	1486.5	1297.7	1702.9
	S+	PRE	14	14	100.0	76.8	100.0	47.1	28.8	77.0
	S+	PI(M1)	14	13	92.9	66.1	99.8	46.1	23.0	92.6
	S+	PII(M7)	14	14	100.0	76.8	100.0	666.9	239.8	1854.8
	Total	PRE	218	14	6.4	3.6	10.5	8.4	7.9	9.0
	Total	PI(M1)	215	191	88.8	83.8	92.7	46.1	39.9	53.2
	Total	PII(M7)	218	218	100.0	98.3	100.0	1411.9	1224.9	1627.5
2	S-	PRE	196	0	0.0	0.0	1.9	7.5	7.5	7.5
	S-	PI(M1)	192	171	89.1	83.8	93.1	57.4	48.9	67.4
	S-	PII(M7)	196	196	100.0	98.1	100.0	1619.8	1411.9	1858.3
	S+	PRE	4	4	100.0	39.8	100.0	18.1	14.2	23.1
	S+	PI(M1)	3	3	100.0	29.2	100.0	129.7	23.6	712.2
	S+	PII(M7)	4	4	100.0	39.8	100.0	2612.6	785.4	8690.4
	Total	PRE	200	4	2.0	0.5	5.0	7.6	7.5	7.8
	Total	PI(M1)	195	174	89.2	84.0	93.2	58.1	49.6	68.1
	Total	PII(M7)	200	200	100.0	98.2	100.0	1635.4	1428.1	1872.7
3	S-	PRE	129	0	0.0	0.0	2.8	7.5	7.5	7.5
	S-	PI(M1)	128	108	84.4	76.9	90.2	40.7	34.1	48.5
	S-	PII(M7)	129	129	100.0	97.2	100.0	1508.8	1270.9	1791.2
	S+	PRE	2	2	100.0	15.8	100.0	38.2	0.3	4994.9
	S+	PI(M1)	2	2	100.0	15.8	100.0	33.5	0.0	185173
	S+	PII(M7)	2	2	100.0	15.8	100.0	955.7	11.5	79231.8
	Total	PRE	131	2	1.5	0.2	5.4	7.7	7.4	8.0
	Total	PI(M1)	130	110	84.6	77.2	90.3	40.5	34.1	48.2
	Total	PII(M7)	131	131	100.0	97.2	100.0	1498.3	1264.9	1774.8
4	S-	PI(M1)	113	0	0.0	0.0	3.2	7.5	7.5	7.5
	S-	PIII(M8)	113	113	100.0	96.8	100.0	1477.6	1247.8	1749.6
	S+	PI(M1)	2	2	100.0	15.8	100.0	19.6	1.5	257.6
	S+	PIII(M8)	2	2	100.0	15.8	100.0	2636.0	5.9	1184535
	Total	PI(M1)	115	2	1.7	0.2	6.1	7.6	7.4	7.8
	Total	PIII(M8)	115	115	100.0	96.8	100.0	1492.5	1263.0	1763.8
5	S-	PRE	203	0	0.0	0.0	1.8	7.5	7.5	7.5
	S-	PI(M1)	201	193	96.0	92.3	98.3	83.0	71.3	96.7
	S-	PII(M7)	203	203	100.0	98.2	100.0	1852.6	1628.7	2107.3
	S+	PRE	8	8	100.0	63.1	100.0	31.5	16.8	59.2
	S+	PI(M1)	8	8	100.0	63.1	100.0	169.2	64.3	445.3
	S+	PII(M7)	8	8	100.0	63.1	100.0	4179.7	2667.0	6550.3
	Total	PRE	211	8	3.8	1.7	7.3	7.9	7.6	8.3
	Total	PI(M1)	209	201	96.2	92.6	98.3	85.3	73.4	99.1
	Total	PII(M7)	211	211	100.0	98.3	100.0	1910.7	1683.8	2168.1

Taken from Table 20, p. 74, CSR HAV-210

The results in the above table were compared to the results for the MTC (Supplement 18, p. 131, CSR HAV-210, not shown here). The GMCs were similar. In the MTC, one subject in Group 4 who was initially seronegative did not convert to seropositive after dose 2. (Otherwise, there was 100% seropositivity in all other groups.)

Reviewer's Comment: When reviewing Table 6 above, all groups, whether seropositive or seronegative in the ATP analysis, seroconverted after the second dose of vaccine, and the GMCs were similar overall. Those who were initially seropositive had more robust responses after Dose 2 in Groups 2-5 compared with Group 1. It is noted that there were very few subjects who were initially seropositive in Groups 2-5 and somewhat more on Group 1. In the 11-13 month old subjects who were initially seropositive, the antibody concentration at one month post-dose 2 was 666.9 mIU/mL. This value is well above what is thought to be the protective level (detection of antibody to hepatitis A). Although the value was somewhat lower than in those children who were initially seronegative, the level is still expected to provide protection against hepatitis A disease. Overall, the GMCs increased with increasing age. .

Statistical Comparison: The Anti-HAV GMC ratios (GMCs calculated for responders) with the 95% asymptotic CIs between the comparison groups are presented in Table 7 as shown below. The control group in these comparisons is Group 5 (children 23-25 months of age at the time of the first dose).

Reviewer's Comment: Even when the analysis was conducted including non-responders, the LB of the 95% CI is still > 0.5.

Table 7-Anti-HAV GMC ratios at 1 month post dose 2 (ATP)

Test			Control			GMC Ratio* (Test/Control)	95% CI
Age Group	n	GMC	Age Group	n	GMC		
15-18 mos	200	1635.4	23-25 mos	211	1910.7	0.87	0.73, 1.05
11-13 mos	216	1461	23-25 mos	211	1910.7	0.76	0.63, 0.91

n= responders
N=number with results
*Adjusted for country and baseline assessment
From Table 21, CSR HAV-210, p. 123

The results for all subjects were similar.

Reviewer's Comment: The only difference between the results for the ATP cohort and cohort with all subjects is 2 non-responders in the 11-13 month old age group. The criterion for success is still met, because the 95% CI of the GMC ratios are between 0.5 and 2. When describing these results in the label, it is noted that the ratios were considered similar (non-inferior) because the lower bound of the 95% CI for the GMC ratio was $\geq$ 0.5.

The data for the subjects who were initially seropositive were provided in a table included in response to an Information Request (IR) letter of 3/18/08

(responses submitted 6/7/05). The table submitted includes the data for the two non-responders in Group 1 as well. Both of the nonresponders in Group 1 still had evidence of antibodies to hepatitis A, albeit at low levels. In subject #50 (11 months of age), the prevaccination concentration was 100 mIU/mL, the postdose 1 value was 50 mIU/mL, and the postdose 2 value was 65 mIU/mL. In subject #274, the prevaccination level was 57 mIU/mL, the postdose 1 level was 48 mIU/mL, and the postdose 2 level was 19 mIU/mL.

Reviewer's Comment: Subjects in the 11-13 month old age group had, in general, adequate responses postdose 2. There were fewer subjects in the older age groups who were initially seropositive.

The Reverse Cumulative Curves for post-dose 1 and 2 are found in Supplement 9, CSR HAV-210, p. 125 and Supplement 10, CSR HAV-210, p. 126, respectively (not shown here). These curves are not included in this review, but it is noted that the curves for all groups are nearly superimposable after the second dose. After the first dose, the curves for Groups 1, 2, and 3 are shifted slightly as compared to Group 5.

Secondary Objective: Non-inferiority between anti-GMCs **1 month after Dose 1** of HAVRIX in responders for hepatitis A between children 15-18 months of age, and if demonstrated, then to show the non-inferiority between the 11-13 month old children and the 23-25 months old children.

Table 8 presents the anti-HAV GMC ratios (GMCs calculated in responders) with the 95% asymptotic CIs following Dose 1 of HAVRIX in the ATP cohort for immunogenicity. Non-inferiority was shown, since the lower bound of the 95% CI of the GMC ratio (test/control) for each group is > 0.5.

Table 8: Anti-HAV GMC ratios (GMCs calculated on responders 1-month post-dose 1 of Havrix (ATP cohort for immunogenicity)

Test			Control			GMC Ratio* (Test/Control)	95% CI
Age Group	n	GMC	Age Group	n	GMC		
15-18 mos	174	74.4	23-25 mos	201	94	0.81	0.67, 0.99
11-13 mos	184	58.6	23-25 mos	201	94	0.62	0.51, 0.75

n= responders
N=number with results
*Adjusted for country and baseline assessment
From Table 22, CSR HAV-210, p. 76

Table 9 presents anti-HAV GMC ratios calculated on all subjects in the ATP cohort for immunogenicity, responders and nonresponders, 1 month post dose 1 HAVRIX. Non-inferiority is again shown for the 15-18 month old children as compared to the 23-25 month olds, but not for the 11-13 month olds.

Table 9-Anti-HAV GMC ratios (GMCs calculated on responders and nonresponders) 1-month post dose 1 HAVRIX (ATP cohort for immunogenicity)

Test			Control			GMC Ratio* (Test/Control)	95% CI
Age Group	n	GMC	Age Group	n	GMC		
15-18 mos	195	58.1	23-25 mos	209	85.3	0.71	0.57, 0.88
11-13 mos	215	46.1	23-25 mos	209	85.3	0.52	0.42, 0.64

n= responders
N=number with results
*Adjusted for country and baseline assessment
From Supplement 6, CSR, HAV-210, p. 123

In CBER's Information Request letter dated 3/18/05 (comment 2b), the sponsor was asked to indicate which subjects were not included in the analyses for Table 8 (above), but were included in the analyses in Table 9 (above). The Sponsor provided an answer in their response to FDA dated 6/7/05 (STN 103475/5090.5000). A table is provided on p. 13 of the response document (which is not reproduced here) and gives the subject numbers for those who did not become seropositive at 1 month after Dose 1, and the actual titers were provided for each of the subjects, broken down by seroststaus for each group. The actual titers were obtained from Appendix IIIA in this Response letter (pp. 73-192). It is noted that all subjects had a titer $\geq$ 15 mIU/mL at 1 month after Dose 2.

Supplement 7, which is not shown in this review (CSR HAV-210, p. 124) presents the anti-HAV vaccine response **1-month post dose 1** for all subjects in the ATP cohort for immunogenicity, broken down by group. (This is different than the seropositvity rate presented in Table 20, because to have a vaccine response in those who were originally seropositive, these children needed to have maintenance or increase in titers.) Although they retained seropositivity, a very few had decreases in antibody levels. As compared to post-dose 2 vaccine response rates (seronegative became seropositive, and seropositive maintained or increased the antibody level), the post-dose 1 vaccine response rates were lower for all groups as follows:

- Group 1: 85.6% [95% CI: 80.2%, 90%]. For seropositives, 42.9% had a vaccine response (6/14), and 88.6% of the seronegatives had a vaccine response (178/201).
- Group 2: 89.2% [95% CI: 84%, 93.2%]. For seropositives, 100% had a vaccine response (3/3), and 89.1% of the seronegatives had a vaccine response (171/192).
- Group 3: 83.8% [95% CI: 76.4%, 89.7%]. For seropositives, 50% had a vaccine response (1/2), and 84.4% of seronegatives had a vaccine response (108/128).
- Group 5: 96.2% [95% CI: 92.6%, 98.3%]. For seropositives, 100% had a vaccine response (8/8), and 96% of seronegatives had a vaccine response (193/201).

Reviewer's Comment: Although there is a somewhat lower vaccine response rate in the youngest age group and in those who received HAVRIX after Dose 1, nearly 100% vaccine response was observed after the second dose of the vaccine. In review of the demographic dataset and the serology results provided in the Information Request response for 11-13 month old children, the number of children 11 months of age, 12 months of age, and 13 months of age with serology data were assessed by this reviewer, which demonstrated similar results. Tables 10 and 11 (constructed by clinical reviewer) presents the vaccine response and seropositivity rates post-dose 1 (Table 10) and post-dose 2 (Table 11)

Table 10: Vaccine Response and Seropositivity Rates in Children 11 months, 12 months, and 13 months of age at first dose (all subjects with serology): Post-Dose 1

Age at first vaccination	N with prevaccination serology	N (%) initially seropositive	N with postdose 1 serology	Vaccine Response post-dose 1 (N/%)	Seropositvity Rate post-dose 1 (N/%)
11 month old	57	5 (8.8%)	56	45 (80.4%)	49 (87.5%)
12 month old	173	11 (6.4%)	170	151 (88.8%)	152 (89.4%)
13 month old	3	0	3	3 (100%)	3 (100%)

Table 11: Vaccine Response and Seropositvity Rates in Children 11 months, 12 months and 13 months of age at first dose (all subjects with serology): Post-dose 2

Age at first vaccination	N with postdose 2 serology	Vaccine Response post-dose 2 (N/%)	Seropositvity Rate post-dose 2 (N/%)
11 month old	57	56 (98.2%)	57 (100%)
12 month old	167	166 (99.4%)	167 (100%)
13 month old	3	3 (100%)	3 (100%)

Reviewer's Comment: Tables 10 and 11 demonstrate that children who received the first dose at 11 months of age had a nominally lower vaccine response (seronegative to seropositive; seropositive with maintenance or increase) as compared to children who received the first dose at 12 months of age after one dose of vaccine, although the seropositivity rates were 88-89%. After 2 doses of vaccine, seropositvity rates in all age groups were 100%. Only three children received the first dose of vaccine at age 13 months.

Secondary Objective: Demonstrate noninferiority of the immune response to Hepatitis A antigen in 15-18 month old subjects who received HAVRIX alone compared to those who received concomitant administration of HAVRIX + INFANRIX + OmniHIB (Group 2 compared with Group 3), at **1-month post dose 2**. Anti-HAV vaccine response 1-month post dose 2 of HAVRIX in the ATP cohort for immunogenicity is shown in Table 23 (not shown here, from CSR. HAV-210, p. 77). All subjects in the ATP cohort for Groups 2-5 had a vaccine response. In Group 1 (11-13 month old subjects), 2 of the 14 who were initially seropositive did not have a vaccine response (14.3%), and 100% of those initially seronegative in this age group had a vaccine response (204/204). The overall vaccine response in children 11-13 month old age

group was 99.1% (95% CI: 96.7, 99.9). The data for the modified Total Cohort is provided in Supplement 20 (not shown here, from CSR HAV-210, p. 133). The results for the ATP cohort and MTP cohort are similar. The only difference is that in Group 4, there was one initially seronegative subject who did not have a vaccine response, and the overall vaccine response rate in that group is 99.2% (95% CI: 95.9,100). In Group 4, Subject 1728 remained seronegative after Dose 2 HAVRIX. This child received HAVRIX without co-administered vaccines.

A comparison of the anti-HAV vaccine responses between Groups 2 and 3 (nonconcomitant vs. concomitant vaccines) is provided in Table 12, below. Vaccine response rates in Groups 2 and 3 post-dose 2 were 100%. The LL of the 95% CI was higher than the pre-defined clinical limit for non-inferiority (-5%). Therefore, the Sponsor concluded that non-inferiority was demonstrated with respect to anti-HAV responses postdose 2 of HAVRIX between subjects 15-18 months old vaccinated with HAVRIX alone compared with subjects that received HAVRIX with INFANRIX+OmniHIB.

Table 12-Difference in anti-HAV responses in subjects 15-18 months of age one month post dose 2 of HAVRIX given either alone (Group 2) or given with INFANRIX+OmniHIB (Group 3) (ATP Cohort for Immunogenicity)

Group	N	%	Group	N	%	Group 3-2	95% CI
2	200	100	3	131	100	0	-1.88, 2.85

Vaccine Response: Maintenance or increase in GMCs in those who were initially seropositive, and conversion from seronegative to seropositive in those who were intially seronegative.
From Table 24, CSR HAV-210, p. 78

The Sponsor also provided this comparison for anti-HAV response rates after **Dose 1 HAVRIX** when given with or without INAFNRIX and OmniHIB. These data are shown in Table 13, below. This was not a pre-specified objective, but a higher vaccine response rate (89%) in Group 2 (nonconcomitant) as compared to a vaccine response rate of 83% in Group 3 (concomitant) was observed, and this would fail a non-inferiority comparison.

Table 13-Difference in anti-HAV vaccine response in 15-18 month old subjects one-month post dose 1 of HAVRIX administered either alone (Group 2) or with INFANRIX+OmniHIB (Group 3) (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Group 3-2	95% CI
2	195	89.23	3	130	83.85	**-5.38**	**-13.06,** 2.29

From Supplement 8, CSR, HAV-210, p. 124

Reviewer's Comment: The serology data were reviewed for those in Group 3 (the concomitant group) and Group 2 (HAVRIX alone) to assess the percentage of subjects who were seropositive after 1 dose of HAVRIX. Of 164 subjects in Group 3 with serology data available post-dose 1, 23 subjects were seronegative (14%), and 86% were seropositive. Of the 226 subjects in Group 2 with serology data available post-dose 1, 21

were seronegative (9.3%), and 90.7% were seropositive. The primary objective, however, was to show non-inferiority of vaccine response to HAVRIX after 2 doses of vaccine, whether given with or without concomitant vaccines.

Secondary Objective: Demonstrate non-inferiority of the immune response to the antigens contained in INFANRIX and OmniHIB following concomitant administration of both vaccines with HAVRIX.

Anti-Diphtheria (anti-D) and anti-Tetanus (anti-T) immune responses at 1 month after INFANRIX (Group 3, Concomitant, and Group 4, Non-concomitant) in 15-18 month old children.

These data are summarized in Table 25 (not shown here, from CSR HAV-210, p. 79), and show seroprotection rates and GMCs. For the ATP cohort for immunogenicity, 100% of subjects in Group 3 (132/132) and Group 4 (115/115) had levels of seroprotection to anti-D ($\geq$0.1 IU/mL). 100% of subjects in Group 3 (131/131) and Group 4 (114/114) had levels of seroprotection to anti-T ($\geq$ 0.1 IU/mL).

The Reverse Cumulative Curves for anti-D and anti-T are provided in Supplement 11 (not shown here, from CSR HAV-210, p. 126) and Supplement 12 (not shown here, from CSR, HAV-210, p. 127), respectively. RCD curves for Group 3 and its comparator, Group 4, and are nearly superimposable.

Groups 3 and 4 were compared statistically. Table 14 summarizes the differences in the percentage of subjects seroprotected for diphtheria and tetanus between Group 3 (concomitant HAVRIX+INFANRIX+OmniHIB in 15-18 month olds) and Group 4 (INFANRIX+OmniHIB only).

Table 14-Difference in the percentage of subjects seroprotected for diphtheria and tetanus one month after vaccination with INFANRIX+OmniHIB with an without coadministration of HAVRIX (ATP Cohort for Immunogenicity)

Antibody	Group	N	%	Group	N	%	Difference	Value	95% CI
Anti-D	3	132	100	4	115	100	Group 3-Group 4	0	-3.23, 2.83
Anti-T	3	131	100	4	114	100	Group 3-Group 4	0	-3.26, 2.85

From Table 26, CSR HAV-210, p. 80

These data demonstrate that 100% of subjects in both groups in the ATP cohort were seroprotected ($\geq$ 0.1 IU/mL) against D and T when they received INFANRIX+OmniHIB+/-HAVRIX. Because the difference between the 2 groups was 0% and the LL of the 95% CI around the difference is higher that the pre-defined clinical limit for non-inferiority [-10%], non-inferiority for these antigens was concluded.

Anti-Pertussis Immune Responses: The anti-pertussis immune responses 1 month after one dose of INFANRIX is summarized in Table 16 below in terms of seropositivity rates [SPR] (defined as concentrations $\geq$ 5 El.U/mL) and GMCs). These data show that the SPR for anti-PT was 99.2% for Group 3 and 99.1% for 4. The GMCs were lower for anti-PT in the concomitant

group (Group 3, 68.4 El.U/mL) compared with the non-concomitant group (Group 4, 83.3 EL.U/mL). This same table shows the SPRs for anti-FHA in both Groups 3 and 4 are 100%, although the GMCs were slightly lower in the concomitant group (Group 3, 418.5 EL.U/mL) compared with the nonconcomitant group (Group 4, 451.4 EL.U/mL). The SPR for anti-PRN (anti-pertactin) was 99.2% in the concomitant group (Group 3) and 99.1% for the non-concomitant group (Group 4). The GMC was slightly less in Group 3 (193.2 EL.U/mL) compared with Group 4 (219.8 EL.U/mL).

Vaccine response to pertussis antigens following the booster dose was defined as the appearance of antibodies ($\geq$ 5 EL.U/mL) in initially seronegative subjects, and $\geq$ 2 times the pre-vaccination concentrations among children who are initially seropositive.

Table 15: Anti-PT, anti-FHA and anti-PRN seropositivity rates and GMCs one month following administration of *Infanrix* (ATP cohort for immunogenicity) with (Group 3) and without (Group 4) Havrix

				S+ (≥5 EL.U/mL)				GMC (EL.U/mL)		
						95% CI			95% CI	
Antibody	Group	Timepoint	N	n	%	LL	UL	Value	LL	UL
Anti-PT	3	PRE	131	82	62.6	53.7	70.9	8.0	6.6	9.8
		PI(M1)	128	127	99.2	95.7	100.0	68.4	57.9	80.9
	4	PRE	120	79	65.8	56.6	74.2	7.4	6.2	8.9
		PI(M1)	114	113	99.1	95.2	100.0	83.3	71.7	96.8
Anti-FHA	3	PRE	130	113	86.9	79.9	92.2	27.5	21.5	35.3
		PI(M1)	131	131	100	97.2	100.0	418.5	363.4	481.8
	4	PRE	120	111	92.5	86.2	96.5	29.0	23.3	36.1
		PI(M1)	116	116	100	96.9	100.0	451.4	397.6	512.4
Anti-PRN	3	PRE	130	85	65.4	56.5	73.5	10.4	8.2	13.3
		PI(M1)	131	130	99.2	95.8	100.0	193.2	155.4	240.2
	4	PRE	120	75	62.5	53.2	71.2	9.5	7.6	11.9
		PI(M1)	115	114	99.1	95.3	100.0	219.8	177.2	272.7

S+ = seropositivity
N = number of subjects with available results
n/% = number/percentage of subjects with concentrations within the specified range
From Table 29 from CSR, HAV-210, p. 82

The results in Supplement 22 (not shown here, from CSR HAV-210, p. 135) for the Modified Total Cohort for these same parameters are similar to the results above.

Table 16 presents the anti-PT, anti-FHA, anti-PRN vaccine response 1 month after INFANRIX among subjects for whom paired baseline and follow-up sera were available. Table 17 shows that the anti-PT vaccine response (total) in Group 3 (concomitant) was 90.6% compared with 96.5% for Group 4 (non-concomitant). There were lower responses in those in Group 3 who were

initially seropositive for anti-PT (86.4%) compared with those who were initially seronegative (97.8%). There was a similarly lower response in Group 3 for anti-FHA in those who were initially seropositive (93.8%) compared with those who were initially seronegative (100%). For anti-FHA, the overall response in Group 3 was 94.6% compared with 97.4% in Group 4. For anti-PRN, the overall response in Group 3 was 95.3% compared with 98.3% in Group 4. The reverse cumulative curves for anti-PT, anti-FHA and anti-PRN are shown in Supplement 14 (p. 128, CSR HAV-210), Supplement 15 (p. 128, CSR HAV-210), and Supplement 16 (p. 129, CSR HAV-210), respectively. (None of these curves are shown here).

Table 16: Anti-PT, anti-FHA and anti-PRN vaccine response one month following vaccination with *Infanrix* (ATP cohort for immunogenicity) administered with (Group 3) or without (Group 4) Havrix

				Vaccine Response			
						95% CI	
Antibody	Group	Pertussis pre-vacc. status	N	n	%	LL	UL
Anti-PT	3	S+	81	70	86.4	-	-
		S-	46	45	97.8	-	-
		Total	127	115	90.6	84.1	95
	4	S+	73	70	95.9	-	-
		S-	41	40	97.6	-	-
		Total	114	110	96.5	91.3	99
Anti-FHA	3	S+	112	105	93.8	-	-
		S-	17	17	100	-	-
		Total	129	122	94.6	89.1	97.8
	4	S+	107	104	97.2	-	-
		S-	9	9	100	-	-
		Total	116	113	97.4	92.6	99.5
Anti-PRN	3	S+	84	79	94.0	-	-
		S-	45	44	97.8	-	-
		Total	129	123	95.3	90.2	98.3
	4	S+	72	71	98.6	-	-
		S-	43	42	97.7	-	-
		Total	115	113	98.3	93.9	99.8

N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
From Table 30 CSR, HAV-210, p. 83

Supplement 23 (not shown here, CSR HAV-210, p. 136) shows the same results for the Modified Total Cohort, and they are again very similar to those of the ATP cohort.

Tables 17 and 18 summarize the differences in anti-PT, anti-FHA, and anti-PRN vaccine responses and GMC ratios between Group 3 (concomitant) and Group 4 (nonconcomitant). Table 17 shows the difference in vaccine response rates 1 month after vaccination with INFANRIX +/- HAVRIX between Group 3 and Group 4 in the ATP cohort for immunogenicity. The

percentage represents the percentage of subjects who were seropositive (anti-PT concentrations ≥ 5 IU/mL, anti-FHA concentrations ≥ 5 El.U/mL, and anti-PRN concentrations ≥ 5 El.U/mL. Table 18 shows the GMC ratios 1 month after vaccination with INFANRIX +/- HAVRIX.

Table 17: Difference in anti-PT, anti-FHA and anti-PRN vaccine response rates one month following vaccination with *Infanrix* with (Group 3) and without (Group 4) coadministration with *Havrix* (ATP cohort for immunogenicity)

									95% CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference calculated**	**Value %**	**LL**	**UL**
Anti-PT	3	127	90.55	4	114	96.49	Group 3 – Group 4	-5.94	**-12.05**	0.17
Anti-FHA	3	129	94.57	4	116	97.41	Group 3 – Group 4	-2.84	-7.70	2.02
Anti-PRN	3	129	95.35	4	115	98.26	Group 3 – Group 4	-2.91	-7.26	1.44

N = number of subjects with available results
% = percentage of subjects seropositive (anti-PT concentrations ≥5.0 IU/mL, anti-FHA concentrations ≥5 EL.U/mL,
anti-PRN concentrations ≥5 EL.U/mL)
From Table 31, CSR HAV-210, p. 84

Table 18: Anti-PT, anti-FHA and anti-PRN GMC ratios one month following vaccination with *Infanrix* and *OmniHIB* with (Group 3) and without (Group 4) coadministration with *Havrix* (ATP cohort for immunogenicity)

	Group 3		**Group 4**		**GMC**	**95% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**Ratio**	**LL**	**UL**
Anti-PT	128	68.4	114	83.3	0.82	0.65	1.03
Anti-FHA	131	418.5	116	451.4	0.93	0.77	1.12
Anti-PRN	131	193.2	115	219.8	0.88	0.65	1.19

Group 4 (15-18 months of age) = *Infanrix* + *OmniHIB* at Month 0, *Havrix* at Months 1 and 7
N = number of subjects with available results
From Table 32, CSR HAV-210, p. 84

Anti-PT Response

In Table 17, it is noted that one month post-vaccination, 90.6% of subjects 15-18 months of age in Group 3 (concomitant) developed a vaccine response compared to 96.5% of subjects who received the vaccines non-concomitantly. The difference in vaccine response was –5.94% [95% CI: -12.05, 0.17]. The LL of the 95% CI on the difference in vaccine response was lower than the prespecified difference of –10%, and therefore, non-inferiority with respect to anti-PT vaccine response could not be concluded.

In Table 18, for the anti-PT GMCs, the ratios of GMCs in Group 3 at 1 month after INFANRIX and others (including HAVRIX) compared to Group 4 at 1

month after INFANRIX + OmniHIB but without HAVRIX was (68.4 EL.U/mL)/(83.3 EL.U/mL) = .82 [95% CI: 0.65-1.03]. Since the LL of the 95% CI is higher than 0.5, non-inferiority could be concluded with respect to anti-PT GMCs.

Anti-FHA Response

In Table 17 shown above, in Group 3, the vaccine response 1 month after INFANRIX (concomitant) was 94.6% and 97.4% 1 month after the nonconcomitant administration of INFANRIX in Group 4. This was a difference of –2.84% [95% CI: -7.70,2.02]. The LL was > -10% so non-inferiority with respect to anti-FHA vaccine response was concluded.
In Table 18, shown above, for anti-FHA GMCs, the ratio in Group 3/Group 4 was (418.5 EL.U/mL)/(451.4 EL.U/mL) = 0.93 [95% CI: 0.77-1.12]. Since the LL of the 95% CI was >0.5, non-inferiority with respect to anti-FHA GMCs was concluded.

Anti-PRN Response

In Table 18, shown above, the difference in vaccine response between Group 3 and Group 4 was 95.3% minus 98.3%, which was –2.91% [95% CI: -7.26, 1.44]. The LL of the 95% CI was > -10%, so non-inferiority was concluded by the Sponsor with respect to anti-PRN vaccine response.
In Table 19, shown above, the ratio of GMCs of Group 3 to Group 4 was (193.2 EL.U/mL)/(219.8 EL.U/mL), which was 0.88 [95% CI: 0.65-1.19]. Non-inferiority with respect to anti-PRN GMCs could be concluded.

Reviewer's Comment: The DTaP brands administered for the primary series was not known. Unless INFANRIX was given after a primary series with INFANRIX or PEDIARIX, there are no data to support the mixing and matching of different brands if DTaP. CBER had requested that the Sponsor provide the brands of DTaP administered for the primary series in the Information Request letter, but this information was not available. Without knowledge of the primary series, the data for the responses to the DTaP antigens are uninterpretable and therefore insufficient to make a label claim for non-inferiority when given with or without HAVRIX. It is noted that in order to participate in the ongoing coadministration study, HAV-232, subjects must have received either INFANRIX or PEDIARIX as the primary vaccine series. The design of this ongoing trial may provide data that is interpretable with regards to the immune response to pertussis antigens.

Supplements 17-24 (not shown here, from CSR, pp. 130-136) present the immunological data for the diphtheria, tetanus, pertussis, and HIB antigens for the Modified Total Cohort (defined as all vaccinated subjects grouped according to the vaccine they actually received rather than according to the vaccine group to which they were assigned). The results of the vaccine responses for the Modified Total Cohorts are similar to those seen in the ATP cohort.

Anti-PRP Immune Response: The anti-PRP immune response 1-month post dose 1 of OmniHIB is summarized in Table 20 in terms of seropositvity rates (defined as concentrations ≥ 0.15 mcg/mL), seroprotection rates (defined as concentrations ≥ 1.0 mcg/mL) and GMCs. There was 100% seropositivity and seroprotection in Groups 3 and 4. Supplement 24 (not shown here from CSR HAV-210, p. 137) presents the results for anti-PRP seropositivity/seroprotection rates and GMCs for Modified Total Cohort, and the seroprotection rates were 99.4% for both Groups 3 and 4, and the seropositivity rates were 100% for these groups. The GMC for Group 3 was 92.4 mcg/mL, and the GMC for Group 4 was 83.5 mcg/mL. The results are therefore very similar to those for the ATP cohort.

Table 19: Anti-PRP seropositivity/seroprotection rates and GMCs one month following administration of OmniHIB (ATP Cohort for Immunogenicity)

			Seropositive (≥ 0.15 mcg/mL)			Seroprotection (≥ 1mcg/mL)			GMC (mcg/mL)	
Group	Timepoint	N	n	%	95% CI	n	%	95% CI	Value	95% CI
3	PRE	130	113	86.9	79.9,92.2	69	44.1	44.1,61.9	1.2	0.9,1.7
	P1(M1)	132	132	100	97.2,100	132	97.2	97.2,100	89	71.4,111
4	PRE	120	98	81.7	73.6,88.1	50	41.7	32.7,51	0.8	0.6,1.1
	P1(M1)	115	115	100	96.8,100	115	96.8	96.8,100	87.3	66.4,114.7

N=number with results
n/%=number/percentage with concentrations within the specified range
PRE=prevaccination; P1(M1)=post-vaccination 1, Month 1
From Table 27, CSR HAV-210, p. 81

Table 20 summarizes the difference in percentage of subjects seroprotected for HIB 1 month after vaccination when INFANRIX +OmniHIB are given with HAVRIX (Group 3) compared with Group 4 (when given alone) in the ATP cohort.

Table 20: Difference in percentage of subjects with anti-PRP concentrations ≥ 1 mcg/mL after vaccination with OmniHIB with or without HAVRIX (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Group 3-4	95% CI
3	132	100	4	115	100	0	-3.23, 2.83

From Table 28, CSR HAV-210, p. 81

Reviewer's Comment: Both groups were seroprotected (100%). The LL of the 95% CI of the difference is greater than the pre-defined clinical limit for non-inferiority (-10%), and therefore non-inferiority between Groups 3 and 4 with respect to HIB was concluded. A statistical comparison was not conducted for the MTC cohort, but there was no difference in seroprotection rates for Groups 3 and 4 (both 99.4% either with or without coadministration of HAVRIX.)

Suboptimal Responses to vaccines

Section 5.2.7 (Table 33, p. 86, CSR HAV-210, not shown here) lists the subjects with suboptimal responses for any vaccine component. Subjects 1564 (Group 4) and 1505 (Group 3) had a suboptimal response to anti-PRN, and were revaccinated with DTaP. Subject 1621 (Group 3) had a suboptimal response to PT, and was revaccinated with DTaP. (This subject was not seropositive after the first dose of HAVRIX, and anti-HAV serology postdose 2 was not performed.) Subject #1728 (Group 4) had a suboptimal response to HAV but could not be located for revaccination. Subject 1596 (Group 4) had a suboptimal response to PT, and subject 1617 (Group 3) also had a suboptimal response to PT. Both declined revaccination by the study center because they preferred follow-up with their own health care providers.

8.1.2.2.3. Safety Outcomes

The subject population evaluated for the primary analysis of safety was the Modified Total Cohort (all vaccinated subjects grouped according to the study vaccine they actually received rather than according to the group to which they were assigned).

There was a high percentage of subjects (90.9%-96.3%) who received both doses of HAVRIX in all groups (Table 34, p. 87, CSR HAV-210, not shown here).

The compliance in all groups was >90% for symptoms sheets returned for both local and systemic symptoms.

Overall Incidence of Symptoms: Table 35 (not shown here, but data included in Tables 22 and 23 below p. 88, CSR HAV-210) details the incidence and nature of any solicited and unsolicited symptom overall in the 4-day follow-up period (Days 0-3) after each dose in the Modified Total Cohort.

First, the groups that received HAVRIX alone were compared.

After **Dose 1:** Group 1 (11-13 month old children), the incidence of general symptoms is higher in Group 1 compared to Group 2 (15-18 month olds) and Group 5 (23-25 month olds), but is about the same for local symptoms.

Reviewer's Comment: The tables below were modified by the reviewer to separate out comparisons among Groups 1, 2, 4, and 5, and between Doses 1 and 2. Also, the first and second dose for Group 4 were included, since these subjects received HAVRIX alone as well.

Table 21: Percentages of subjects in Groups 1, 2, 4, and 5 with symptoms within 4 days after Dose 1 (with 95% CIs) (MTC Cohort)

	Any Symptom (95% CI)	Local Symptom (95% CI)	General Symptom (95% CI)
Group 1 (11-13 months)	62.5% (56%,68.6%)	30.4% (24.7%, 36.7%)	56.3% (49.7%, 62.7%)
Group 2 (15-18 months)	56.8% (50.3%, 63.2%)	27.8% (22.2%,33.9%)	47.1% (40.6%, 53.6%)
Group 5 (23-25 months)	55.8% (49.3%, 62.2%)	28.8% (23.1%, 34.9%)	46.6% (40.2%, 53.2%)
Group 4 (15-18 months) After INFANRIX + OmniHIB 1 month earlier	55.9% (47.9%, 63.7%)	31.7% (24.6%, 39.5%)	43.1% (35.3%, 51.2%)

From Table 35, CSR HAV-210, p. 88

After **Dose 2**: the incidences of any solicited and unsolicited symptom and general symptoms were higher in Group 1 compared with Groups 2 and 5, but local symptoms were similar in all groups.

Table 22: Percentages of subjects in Groups 1, 2, 4, and 5 with symptoms within 4 days after Dose 2 (with 95% CIs) (MTC Cohort)

	Any Symptom (95% CI)	Local Symptom (95% CI)	General Symptom (95% CI)
Group 1 (11-13 months)	55.2% (48.5%, 61.7%)	27.6% (21.9%, 33.8%)	47.4% (40.8%, 54.1%)
Group 2 (15-18 months)	51.2% (44.3%, 58%)	30.4% (24.4%, 37%)	41.6% (34.9%, 48.6%)
Group 5 (23-25 months)	48.2% (41.6%, 55%)	28.9% (23.1%, 35.3%)	37.7% (31.3%, 44.5%)
Group 4 (15-18 months) After INFANRIX + OmniHIB 1 month earlier	55.6% (47.3%, 63.7%)	41.6% (33.6%, 50%)	36% (28.3%, 44.2%)

From Table 35, CSR HAV-210, p. 88

Next, the groups that received INFANRIX +OmniHIB +/-HAVRIX were compared (Groups 3 and 4).

The incidences of any symptom, general symptoms, and local symptoms were higher in Group 3 (the concomitant group) compared to those in Group 4 (who received INFANRIX + OmniHIB without HAVRIX), although both groups had higher incidences of symptoms than subjects who received HAVRIX alone.

Table 23: The percentages of subjects in Groups 3 and 4 with symptoms within 4 days after INFANRIX + OmniHIB +/- HAVRIX (95% CI)

	Any Symptom (95% CI)	Local Symptom (95% CI)	General Symptom (95% CI)
Group 3 (15-18 months) AFTER INAFANRIX and OmniHIB **with HAVRIX**	80.3% (73.3%, 85.9%)	57.9% (50.3%, 65.2%)	68.9% (61.5%, 75.5%)
Group 4 (15-18 Months) AFTER INFANRIX and OmniHIB **without HAVRIX**	72.3% (64.9%, 78.8%)	52% (44.3%, 59.7%)	60.2% (52.5%, 67.6%)

From Table 35, CSR HAV-210, p. 88

Table 24 (from Supplement 25, CSR HAV-210, p. 139) provides the incidence and nature of **any solicited and unsolicited symptom during the 4 day period** overall per subject (all doses together). Similar patterns are noted when compared to symptoms/all doses, but the numbers/percentages are higher overall/subject.

Table 24: Incidence of any solicited and unsolicited adverse symptoms reported during the 4 days after vaccination per subject (95% CI) (MTC cohort)

	Any symptom	General Symptom	Local Symptom
Group 1 (11-13 months old)	74.7% (68.7%, 60.1%)	68.9% (62.6%, 74.7%)	41.9% (35.6%, 48.4%)
Group 2 (15-18 months old)	71.4% (65.2%, 77%)	58.8% (52.2%, 65%)	42.3% (36%, 48.8%)
Group 3 (15-18 months old) (INFANRIX + OmniHIB with HAVRIX)	82.3% (76%, 87.6%)	75% (68%, 81.1%)	61.3% (53.8%, 68.5%)
Group 4 (15-18 months old (INFANRIX + OmniHIB with HAVRIX separately)	83.2% (76.8%, 88.5%)	76.9% (69.9%, 82.9%)	61.3% (53.6%, 68.6%)
Group 5 (23-25 months old)	70.5% (64.3%, 76.2%)	60.7% (54.2%, 66.9%)	41.9% (35.6%, 48.4%)

(From Supplement 25, CSR HAV-210, p. 139)

Again, more subjects had symptoms in Groups 3 and 4 (who received INFANRIX + OmniHIB) compared with the other groups.

A post-hoc analysis was requested to assess if there were any significant differences between the solicited adverse events that occurred in Group 3 as compared to Group 4. GSK provided the following analysis. Drowsiness and loss of appetite occurred at statistically significantly higher rates in subjects 15 to 18 months of age who received OMNIHIBand INFANRIX concomitantly with HAVRIX as compared to subjects 15 to 18 months of age who received OMNIHIB and INFANRIX (drowsiness 34% and 22% and loss of appetite 29% and 19%, respectively). With the exception of fever ($\geq$ 39.5° C), the solicited general symptoms occurred at statistically significantly higher rates in subjects 15 to 18 months of age who received OMNIHIB and INFANRIX concomitantly with HAVRIX as compared to subjects 15 to 18 months of age who received HAVRIX alone (irritability 46% and 30%,

drowsiness 34% and 17%, and loss of appetite 29% and 17%, respectively). P-values were provided for these analyses in the table below.

Table 26: Percentage of subjects reporting a specified symptom and P-value for the differences between group 3 (OmniHIB + Infanrix + Havrix) and group 4 (OmniHIB + Infanrix) during the 4-day follow-up period after the first dose of vaccines (Modified Total Cohort)

Symptom	Group 3 OmniHIB + Infanrix + Havrix (15-18 mos) (95% CI)	Group 4 OmniHIB + Infanrix (15-18 mos) (95% CI)	P value (Group 3 vs. Group 4)
Drowsiness (any)	33.9% (27.0, 41.1%)	22.4% (16.3, 29.4%)	**0.017**
Irritability (any)	46.3% (38.8, 54.0%)	36.5% (29.2, 44.2%)	0.062
Loss of appetite (any)	29.4% (22.8, 36.7%)	18.8% (13.2, 25.5%)	**0.022**
Fever (Grade 3)	2.3% (0.6, 5.7%)	2.4% (0.6, 5.9%)	0.954

From Supplement 29, CSR 210, p. 147 and post-hoc analysis provided by sponsor

Table 27: Percentage of subjects reporting a specified symptom and P-value for the differences between group 3 (OmniHIB + Infanrix + Havrix) and group 2 (Havrix alone) during the 4-day follow-up period after the first dose of vaccines (Modified Total Cohort)

Symptom	Group 3 OmniHIB + Infanrix + Havrix (15-18 mos) (95% CI)	Group 2 (Havrix alone) (15-18 mos) (95% CI)	P value (Group 3 vs. Group 4)
Drowsiness (any)	33.9% (27.0, 41.1%)	16.5% (12.0, 21.9%)	**< 0.001**
Irritability (any)	46.3% (38.8, 54.0%)	29.7% (23.9, 35.9%)	**< 0.001**
Loss of appetite (any)	29.4% (22.8, 36.7%)	16.5% (12.0, 21.9%)	**.002**
Fever (Grade 3)	2.3% (0.6, 5.7%)	1.7% (0.5, 4.3%)	0.671

From Supplement 29, CSR 210, p. 147 and post-hoc analysis provided by sponsor

Tables 28, 29, and 30 show the incidence and nature of **Grade 3 solicited and unsolicited symptoms** in the four days after each dose in the modified total cohort. In general, these incidences were < 5% in all groups who received HAVRIX alone.

Table 28: Percentages and 95% CIs of subjects in Groups 1, 2, 4, and 5 with Grade 3 symptoms in the 4 days after Dose 1 (HAVRIX alone) (MTC Cohort)

	Any Grade 3 Symptom (95% CI)	Grade 3 Local Symptom (95% CI)	Grade 3 General Symptom (95% CI)
Group 1 (11-13 months)	4.2% (2%, 7.5%)	0% (0%, 1.5%)	4.2% (2%, 7.6%)
Group 2 (15-18 months)	4.1% (2%, 7.4%)	1.2% (0.3%, 3.6%)	3.4% (1.5%, 6.5%)
Group 5 (23-25 months)	2.1% (0.7%, 4.8%)	0.4% (0%, 2.3%)	1.7% (0.5%, 4.2%)
Group 4 (15-18 months) After INFANRIX + OmniHIB 1 month earlier	1.9% (0.4%, 5.3%)	0.9% (0.1%, 3.2%)	2.7% (1%, 5.8%)

From Table 36, CSR HAV-210, p. 89

Table 29: Percentages and 95% CIs of subjects in Groups 1, 2, 4, and 5 with Grade 3 symptoms in the 4 days after Dose 2 (HAVRIX alone) (MTC Cohort)

	Any Grade 3 Symptom (95% CI)	Grade 3 Local Symptom (95% CI)	Grade 3 General Symptom (95% CI)
Group 1 (11-13 months)	2.2% (2%, 7.5%)	0.9% (0.1%, 3.1%)	1.7% (0.5%, 4.4%)
Group 2 (15-18 months)	2.8% (1%, 5.9%)	0.5% (0%, 2.5%)	2.9% (1.1%, 6.1%)
Group 5 (23-25 months)	3.5% (1.5%, 6.9%)	0.9% (0.1%, 3.2%)	2.7% (1%, 5.8%)
Group 4 (15-18 months) After INFANRIX + OmniHIB 1 month earlier	4% (1.5%, 8.4%)	0.7% (0%, 3.7%)	3.4% (1.1%, 7.7%)

From Table 36, CSR HAV-210, p. 89

Overall, there were generally <1% local Grade 3 symptoms in the groups that received HAVRIX alone, except 1.2% in Group 2 after dose 1. There were somewhat lower Grade 3 general symptoms after the second dose except in Group 4, where these were slightly higher.

The percentages of Grade 3 symptoms were higher in Groups 3 and 4 when they received INFANRIX and OmniHIB, as compared to those who received HAVRIX alone. The percentages of subjects with Grade 3 symptoms in the 4 days after Dose 1 who received INFANRIX and OmniHIB with or without HAVRIX are shown in Table 30 below.

Table 30: The percentages and 95% CIs of subjects in Group 3 (OmniHIB + Infanrix with Havrix) and Group 4 (OmniHIB + Infanrix without Havrix) with Grade 3 symptoms (95% CI)

	Any Grade 3 Symptom (95% CI)	Grade 3 Local Symptom (95% CI)	Grade 3 General Symptom (95% CI)
Group 3 (15-18 months) AFTER INAFANRIX and OmniHIB **with HAVRIX**	14.6% (9.8%, 20.7%)	9% (5.2%, 14.2%)	7.9% (4.4%, 12.9%)
Group 4 (15-18 Months) AFTER INFANRIX and OmniHIB **without HAVRIX**	13.9% (9.1%, 19.9%)	9.2% (5.4%, 14.6%)	5.3% (2.4%, 9.8%)

From Table 36, CSR HAV-210, p. 89

Table 31 provides the percentage and 95% CIs of any Grade 3 solicited and unsolicited symptom during the 4-day period overall by subject in the Modified Total Cohort. The numbers overall/subject are somewhat higher than when calculated overall/dose, but with similar patterns as above.

Table 31: Incidence of any Grade 3 solicited and unsolicited adverse symptom reported during the 4 days after vaccination per subject (95% CI) (MTC cohort)

	Any Grade 3 symptom 95% CI	Grade 3 General Symptom 95% CI	Grade 3 Local Symptom 95% CI
Group 1 (11-13 months old)	6.2% (3.5%, 10.1%)	5.8% (3.2%, 9.6%)	0.8% (0.1%, 3%)
Group 2 (15-18 months old)	6.2% (3.5%, 10.1%)	5.4% (2.9%, 9.1%)	1.7% (0.5%, 4.2%)
Group 3 (15-18 months old) (INFANRIX + OmniHIB with HAVRIX)	17.7% (12.4%, 24%)	11.1% (6.9%, 16.6%)	8.8% (5.1%, 14%)
Group 4 (15-18 months old (INFANRIX + OmniHIB with HAVRIX separately)	18.5% (13%, 25.1%)	9.8% (5.8%, 15.3%)	9.8% (5.8%, 15.3%)
Group 5 (23-25 months old)	5.4% (2.9%, 9%)	4.2% (2%, 7.6%)	1.2% (0.3%, 3.6%)

From Supplement 26, CSR HAV-210, p. 140

Reviewer's Comment: There was generally a low percentage of subjects with Grade 3 symptoms in the 4 days after vaccination in those subjects who received HAVRIX alone.

Specific Adverse Events

Solicited Local Signs and Symptoms

Table 32 presents the number and percentages of doses followed by any and Grade 3 solicited local symptom within the 4-day period in the Modified Total Cohort.

Table 32: Incidence and 95% CI of solicited local symptoms within the 4-day period by dose (MTC)

	Group 1 N=472		Group 2 N=458		Group 3 N=341		Group 4 N=484		Group 5 N=465	
Symptom	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI
Pain										
Any	75	15.9% (12.7, 19.5%)	75	16.4% (13.1, 20.1%)	81	23.8% (19.3, 28.6%)	64	13.2% (10.2, 16.6%)	97	20.9% (17.3, 24.8%)
Grade 3	1	0.2% (0.0, 1.2%)	3	0.7% (0.1, 1.9%)	1	0.3% (0.0, 1.6%)	1	0.2% (0.0, 1.1%)	1	0.2% (0.0, 1.2%)
Redness										
Any	101	21.4% (17.8, 25.4%)	89	19.4% (15.9, 23.4%)	73	21.4% (17.2, 26.1%)	62	12.8% (10.0, 16.1%)	77	16.6% (13.3, 20.3%)
Grade 3	1	0.2% (0.0, 1.2%)	1	0.2% (0.0, 1.2%)	0	0.0% (0.0, 1.1%)	0	0.0% (0.0, 0.8%)	2	0.4% (0.1, 1.5%)
Swelling										
Any	41	8.7% (6.3, 11.6%)	41	9.0% (6.5, 11.9%)	37	10.9% (7.8, 14.6%)	30	6.2% (4.2, 8.7%)	37	8.0% (5.7, 10.8%)
Grade 3	0	0% (0.0, 0.8%)	0	0% (0.0, 0.8%)	3	0.9% (0.2, 2.5%)	0	0.0% (0.0, 0.8%)	0	0.0% (0.0, 0.8%)

N=number of doses for which at least one symptom sheet was completed
n/%=number/percentage of doses with reports of a specified symptom
From Table 37, CSR 210, p. 91

The solicited local symptoms were pain, redness, and swelling at the HAVRIX injection site. Group 3 had the highest percentage of subjects with pain/redness/swelling of all groups for all symptoms. The percentages/subject are somewhat higher than when presented per subject, as shown below in Table 33.

Table 33: Incidence and 95% CI of solicited local symptoms within the 4-day period by subject (MTC)

	Group 1 N=241		Group 2 N=241		Group 3 N=181		Group 4 N=173		Group 5 N=241	
Symptom	N	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI
Pain										
Any	62	25.7% (20.3, 31.7%)	63	26.1% (20.7, 32.2%)	70	38.7% (31.5, 46.2%)	48	27.7% (21.2, 35.1%)	80	33.2% (27.3, 39.5%)
Grade 3	1	0.4% (0.0, 2.3%)	3	1.2% (0.3, 3.6%)	1	0.6% (0.0, 3.0%)	1	0.6% (0.0, 3.2%)	1	0.4% (0.0, 2.3%)
Redness										
Any	77	32.0% (26.1, 38.2%)	71	29.5% 23.8, 35.7%)	58	32.0% (25.3, 39.4%)	46	26.6% (20.2, 33.8%)	59	24.5% (19.2, 30.4%)
Grade 3	1	0.4% (0.0, 2.3%)	1	0.4% (0.0, 2.3%)	0	0.0% (0.0, 2.0%)	0	0.0% (0.0, 2.1%)	2	0.8% (0.1, 3.0%)
Swelling										
Any	35	14.5% (10.3, 19.6%)	36	14.9% (10.7, 20.1%)	33	18.2% (12.9, 24.6%)	25	14.5% (9.6, 20.6%)	33	13.7% (9.6, 18.7%)
Grade 3	0	0.0% (0.0, 1.5%)	0	0.0% (0.0, 1.5%)	3	1.7% (0.3, 4.8%)	0	0.0% (0.0, 2/1%)	0	0.0% (0.0, 1.5%)

N=number of subjects for which at least one symptom sheet was completed
n/%=number/percentage of subjects with reports of a specified symptom
From Supplement 28, CSR 210, p. 145

Following administration of HAVRIX only, redness was the most frequently occurring solicited local symptom in Group 1 and 2, whereas pain at the injection site was the most frequently occurring symptom in Group 5.

Reviewer's Comment: Overall, the rates of pain, redness, and swelling at the Havrix injection sites were similar in Groups 1, 2, and 5. Grade 3 symptoms were seen in <1% in all groups.

When HAVRIX was administered with INFANRIX and OmniHIB, pain at the injection site was the most frequent local symptom following administration of both INFANRIX and OmniHIB in Groups 3 and 4. Subjects in Group 3 had somewhat higher overall rates of pain, redness, and swelling at the HAVRIX, INFANRIX and OmniHIB sites compared with subjects in Group 4. Grade 3 reactions were also low, although slightly higher for redness with INFANRIX in both Groups and swelling with INFANRIX in both groups. Similar findings were noted in the incidence of local symptoms in the 4 days after vaccination by dose and by subject. Slightly higher percentages were noted for solicited local symptoms when analyzed by subject.

Supplement 27 (not shown here, pp. CSR HAV-210, pp. 141-144) presents the incidence of any solicited and Grade 3 solicited local symptom overall and by dose, broken down by vaccine administered. Grade 3 symptoms are very low (generally <1%) at the HAVRIX site.

By definition, all local symptoms were considered causally related to study material.

Solicited General signs and symptoms

Table 34 below presents the number and percentage of doses followed by any and Grade 3 within the 4-day follow-up period for the Modified Total Cohort. The solicited general symptoms are drowsiness, irritability, loss of appetite and temperature.

As for the local solicited symptoms, Group 3 had the highest incidence of general solicited symptoms.

Table 34: Incidence and 95% CI of solicited general symptoms within the 4-day period by dose (MTC)

	Group 1 N=470		Group 2 N=445		Group 3 N=333		Group 4 N=479		Group 5 N=458	
Symptom	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI
Drowsiness										
Any	74	15.7% (12.6, 19.4%)	68	15.3% (12.1, 19.0%)	87	26.1% (21.5, 31.2%)	79	16.5% (13.3, 20.1%)	63	13.8% (10.7, 17.3%)
Grade 3	1	0.2% (0.0, 1.2%)	2	0.4% (0.1, 1.6%)	3	0.9% (0.2, 2.6%)	5	1.0% (0.3, 2.4%)	1	0.2% (0.0, 1.2%)
Irritability										
Any	153	32.6% (28.3, 37.0%)	110	24.7% (20.8, 29%)	119	35.7% (30.6, 41.1%)	140	29.2% (25.2, 33.5%)	104	22.7% (18.9, 26.8%)
Grade 3	4	0.9% (0.2%, 2.2%)	7	1.6% (0.6, 3.2%)	7	2.1% (0.8, 4.3%)	4	0.8% (0.2, 2.1%)	1	0.2% (0.0, 1.2%)
Loss of Appetite										
Any	83	17.7% (14.3, 21.4%)	76	17.1% (13.7%, 20.9%)	85	25.5% (20.9, 30.6%)	87	18.2% (14.8, 21.9%)	69	15.1% (11.9, 18.7%)
Grade 3	4	0.9% (0.2, 2.2%)	3	0.7% (0.1, 2.0%)	7	2.1% (0.8, 4.3%)	5	1.0% (0.3, 2.4%)	3	0.7% (0.1, 1.9%)
Temp.										
Any	73	15.5% (12.4, 19.1)	58	13.0% (10.0, 16.5%)	59	17.7% (13.8, 22.3%)	77	16.1% (12.9, 19.7%)	48	10.5% (7.8, 13.7%)
Grade 3	2	0.4% (0.1, 1.5%)	5	1.1% (0.4, 2.6%)	4	1.2% (0.3, 3.0%)	9	1.9% (0.9, 3.5%)	2	0.4% (0.1, 1.6%)

N=number of doses for which at least one symptom sheet was completed
n/%=number/percentage of doses with reports of a specified symptom
From Table 38, CSR 210, p. 94

Table 35: Incidence and 95% CI of solicited general symptoms within the 4-day period by subject (MTC)

	Group 1 N=241		Group 2 N=239		Group 3 N=180		Group 4 N=173		Group 5 N=239	
Symptom	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI	n	% 95% CI
Drowsiness										
Any	63	26.1% (20.7, 32.3%)	60	25.1% (19.7, 31.1%)	75	41.7% (34.4, 49.2%)	57	32.9% (26.0, 40.5%)	51	21.3% (16.3, 27.1%)
Grade 3	1	0.4% (0.0, 2.3%)	2	0.8% (0.1, 3.0%)	3	1.7% (0.3, 4.8%)	5	2.9% (0.9, 6.6%)	1	0.4% (0.0, 2.3%)
Irritability										
Any	112	46.5% (40.0, 53.0%)	90	37.7% (31.5, 44.1%)	93	51.7% (44.1, 59.2%)	97	56.1% (48.3, 63.6%)	86	36.0% (29.9, 42.4%)
Grade 3	4	1.7% (0.5, 4.2%)	7	2.9% (1.2, 5.9%)	7	3.9% (1.6, 7.8%)	4	2.3% (0.6, 5.8%)	1	0.4% (0.0, 2.3%)
Loss of Appetite										
Any	69	28.6% (23.0, 34.8%)	61	25.5% (20.1, 31.5%)	71	39.4% (32.2, 47.0%)	68	39.3% (32.0, 47.0%)	60	25.1% (19.7, 31.1%)
Grade 3	4	1.7% (0.5, 4.2%)	3	1.3% (0.3, 3.6%)	7	3.9% (1.6, 7.8%)	5	2.9% (0.9, 6.6%)	3	1.3% (0.3, 3.6%)
Temp.										
Any	62	25.7% (20.3, 31.7%)	53	22.2% (17.1, 28.0%)	50	27.8% (21.4, 34.9%)	58	33.5% (26.5, 41.1%)	44	18.4% (13.7, 23.9%)
Grade 3	2	0.8% (0.1, 3.0%)	5	2.1% (0.7, 4.8%)	4	2.2% (0.6, 5.6%)	9	5.2% (2.4, 9.6%)	2	0.8% (0.1, 3.0%)

N=number of subjects for which at least one symptom sheet was completed
n/%=number/percentage of subjects with reports of a specified symptom
From Supplement 30, CSR 210, p. 150

Supplement 29 (not shown here, CSR HAV-210, pp. 147-149) presents the incidence of any, Grade 3, related and Grade 3 related solicited general symptoms overall and by dose. These results are similar to the results shown in Table 33 above. There were slightly fewer subjects with fever after Dose 2 compared with Dose 1, although in Group 5, there were slightly more after Dose 2 (10.5% and 11.4% for Doses 1 and 2, respectively). There were slightly more symptoms in general after Dose 1 than after Dose 2 (except for drowsiness in Group1). The majority of the fevers were mild to moderate in intensity.

Table 35 presents the incidence of solicited general symptoms within 4 days after vaccination by subject. In this analysis, Groups 3 and 4 were more similar, and overall percentages were higher than when calculated by dose (Table 34).

The most frequently occurring general solicited symptom for all groups, regardless of age, was **irritability**. General solicited symptoms rated as Grade 3 were generally infrequent in all groups.

Unsolicited Symptoms
Unsolicited symptoms were coded by the use of the WHO Dictionary of Adverse Reaction Terminology, and every verbatim term was matched to the appropriate WHO Preferred Term. The count of the WHO Preferred Terms may not necessarily correspond to the number of subjects having an AE. A subject may have developed the same signs and symptoms at different time periods, or a subject may have developed different signs and symptoms coded to different WHO Body System classes.

These data are presented in the CSR in the Table noted below. This reviewer ordered the symptoms in decreasing order for each unsolicited symptoms, and below are presented the most common unsolicited symptoms over the 31 days after vaccination that occurred at a rate > 1%.
Table 36 shows the percentage of subjects with ANY unsolicited symptom in the 31 days after vaccination. The symptoms noted below occurred generally > 1% in each group, and are arranged in descending order (approximately, since the percentages were not averaged overall).

Table 36: Percentages (> 1%) of subjects with any unsolicited symptoms occurring within 31 days after vaccination classified by WHO Preferred Term (MTC)

Symptom	Group 1 N=241	Group 2 N=241	Group 3 N=181	Group 4 N=173	Group 5 N=241
	n/%	n/%	n/%	n/%	n/%
≥ 1 unsolicited general symptom	63.5%	59.3%	52.5%	66.5%	56.8%
URI	19.1%	16.6%	15.5%	23.7%	15.4%
Otitis media	17.8%	13.7%	10.5%	11.6%	7.9%
Diarrhea	9.5%	9.1%	7.2%	5.2%	6.6%
Rhinitis	7.9%	8.7%	8.3%	10.4%	6.6%
Viral Infection	5.8%	7.1%	3.9%	9.2%	6.6%
Fever	8.7%	7.9%	6.1%	7.5%	7.1%
Vomiting	5.8%	9.1%	7.2%	5.8%	4.6%
Injury	2.9%	3.3%	3.9%	5.8%	4.1%
Coughing	5.8%	5.4%	6.6%	5.8%	5.8%
Injection site reaction	1.2%	1.7%	5.5%	2.9%	2.5%
Rash	4.1%	0.8%	3.9%	1.7%	2.9%
Toothache	4.1%	2.5%	2.8%	7.5%	1.2%
Pharyngitis	3.3%	2.1%	1.7%	4.6%	2.5%
Asthma	3.7%	0.8%	2.2%	2.9%	2.1%
Eczema	2.1%	0.8%	0.6%	3.5%	0.8%
Constipation	2.1%	1.2%	0.0%	1.7%	0.4%
Conjunctivitis	3.3%	2.5%	2.2%	1.7%	2.1%
Gastroenteritis	2.9%	2.5%	1.1%	2.9%	3.3%
Contact Dermatitis	2.5%	2.5%	0.0%	1.2%	1.2%
Allergy	2.5%	0.0%	1.7%	0.6%	0.8%
Pneumonia	2.1%	1.2%	0.0%	1.7%	0.4%
Moniliasis	2.1%	0.0%	0.6%	0.0%	0.4%
Varicella	1,7%	0.4%	0.6%	1.7%	0.0%
Sinusitis	1.2%	0.4%	1.7%	1.2%	0.8%
Stridor	1.2%	0.8%	0.6%	1.7%	1.2%
Bronchitis	1.2%	0.4%	0.6%	1.2%	0.4%

N=number of subjects with at least one documented dose

Table 37 presents the percentage of subjects with Grade 3 unsolicited symptoms in the 31 days after vaccination. Most of these adverse events were related to commonly seen infections in the pediatric population.

Table 37: Percentages (> 1% in at least one group) of subjects with any Grade 3 unsolicited symptoms occurring within 31 days after vaccination classified by WHO Preferred Term (MTC)

Symptom	Group 1 N=241	Group 2 N=241	Group 3 N=181	Group 4 N=173	Group 5 N=241
	%	%	%	%	%
≥ 1 unsolicited Grade 3 general symptom	5.4%	8.3%	8.3%	11%	6.2%
Conjunctivitis	3.3%	2.5%	2.2%	1.7%	2.1%
Otitis Media	0.8%	1.2%	1.7%	2.3%	1.2%
Viral Infection	0.0%	0.4%	1.1%	2.3%	0.4%
Fever	1.2%	1.2%	0.6%	1.7%	0.8%
Vomiting	0.4%	1.2%	1.1%	0.6%	0.0%
Stridor	0.0%	0.0%	0.6%	1.2%	0.0%
Pharyngitis	1.2%	0.4%	0.0%	0.0%	0.0%
Bronchitis	0.4%	0.0%	0.0%	1.2%	0.0%
Gastroenteritis	0.0%	0.4%	0.0%	1.2%	0.0%
Rash erythematous	1.2%	0.0%	0.6%	1.2%	0.4%
Diarrhea	0.4%	0.8%	1.1%	0.6%	0.8%
Injection site reaction	0.0%	0.0%	1.1%	0.0%	0.0%

N=number of subjects with at least one documented dose
From Table 40, CSR 210, p. 102-3

Other symptoms are not shown here because they were for the most part <1% in all groups.

There was one child in Group 1 who was reported as having ataxia. Details were requested in an Information Request (IR) letter. The event was short-lived (app. 2 days after Dose 1) and was not felt to represent a neurological problem because the subject recovered quickly and went on to receive the second dose of vaccine without reported ill effect.
There were subjects with gait abnormalities, and information was requested in an IR letter as well. The AEs appeared to be related to thigh discomfort, and quickly resolved in all cases.

Concomitant Medications/Vaccines: Table 38 provides a summary of subjects who were given at least one concomitant medication by group. This ranged from 58.7% in Group 5 to 71.5% in Group 3.

Table 38: Number of subjects who received at least one concomitant medication (Modified Total cohort)

Group	N	n	%
1	243	173	71.1
2	246	158	64.2
3	179	128	71.5
4	174	116	66.7
5	242	142	58.7

From Table 42, CSR HAV-210, p. 106

Table 39 shows the number and percentage of subjects who received an analgesic, anti-inflammatory, antipyretic during the 4-day follow-up after each dose. The Sponsor indicated it was not able to determine with certainty if any subject received the medication prophylactically in anticipation of a vaccine reaction. It is noted that there were fewer percentages of subjects given such a medication postdose 2 as compared to postdose 1. (The Dose 3 designation represents Dose 2 of HAVRIX for Group 4).

Table 39: Number of subjects who received an analgesic, anti-inflammatory, antipyretic agent during the 4-day follow-up period following each dose (Modified Total cohort)

Group	Dose 1		Dose 2		Dose 3*	
	N	n (%)	N	n (%)	N	n (%)
1	243	50 (20.6)	234	31 (13.2)	-	
2	246	49 (19.9)	228	18 (7.9)	-	
3	179	61 (34.1)	162	13 (7.8)	-	
4	174	41 (23.6)	160	25 (15.6)	161	21 (13.0)
5	242	23 (9.5)	230	23 (10.0)	-	

From Table 43, CSR HAV-210, p. 107

*Dose 3 represents the second dose of Havrix given to Group 4 participants

Subject 0047 in Group 1 (Center 10) received Immune Globulin (IG) as treatment for Kawasaki's disease in violation of the protocol and was excluded from the immunogenicity analysis. (This subject nonetheless had a good response to the vaccine as noted in the serology data.) No other meds/vaccines forbidden by the protocol were administered to any other participant.

Serious Adverse Events:

Table 40, below, provides a listing of the SAEs that occurred in this study. (From Table 44, CSR HAV-210, pp. 108-110, and case reports in Appendix IIE SARR [not shown here, CSR HAV-210, pp. 160-248]). The reporting period included the interval between the receipt of the first dose of study vaccine and 30 days after the last dose of study vaccine for each subject. 42 SAEs were noted for 38 subjects.

All but two recovered [subject 01111 in Group 2 with insulin dependent diabetes and subject 02211 in Group 5 who died as a result of an accident], and all but three experienced events were considered by the investigators to be unrelated to vaccine. The investigator at Center 5 considered the febrile seizure reported in subject 01230 in Group 2 to have a suspected relationship to the vaccine, and the investigator at Center 99 considered both the gastroenteritis reported for subject 01651 (Group 3) and inflamed eczema for subject 02093 (Group 5) to have an unlikely relationship to vaccine.

Table 40: Listing of Serious Adverse Events In Study HAV-210

Subject	Age/Gender	Event	Group	Days postdose	Further vaccination
01230	18 Mos/Male	**Febrile seizure**	2	2 days posdose 2	No-LTF
01011	17 Mos/Female	**Febrile seizure**	2	27 days postdose 2	Yes
01829	15 Mos/Female	**Febrile seizure**	4	1 day postdose Infanrix + OmniHIB	Yes-received 2 doses of Havrix after event
00208	19 Mos/Male	**Seizure**	1	37 days postdose 2	N/A
00107	13 Mos/Female	**Exacerbation of asthma**	1	45 days postdose 1	Yes
01214	17 Mos/Male	**Bronchiolitis, asthma** **Otitis media, myringotomy tubes** **Laryngospasm with surgery** **Bronchospasm with surgery**	2	4 days postdose 1 99 days postdose 1	Yes
01099	21 Mos/Male	Increased **asthma** symptoms	2	112 days posrdose 1	Yes
01633	18 Mos/Male	1st **asthma** attack	3	95 days postdose 1	Yes
01678	20 Mos/Male	1st **asthma** attack	4	137 days postdose 1	Yes
01910	19 Mos/Male	**Bronchiolitis**	4	34 days postdose 1	Yes
00069	16 Mont/Male	**Bronchiolitis/RSV**	1	131 days postdose 1	Yes
01668	18 Mos/Male	**Viral Pneumonia**	4	40 days postdose 1	Yes
01107	17 Mos/Female	**Suspected sleep apnea** (unconfirmed)	2	21 days postdose 1	Yes
01555	22 Mos/Male	**Rotavirus infection**	3	123 days postdose 1	No-LTF
01521	18 Mos/Female	**Rotavirus infection**	3	106 days postdose 1	Yes
01588	19 Mos/Male	**Gastroenteritis**	4	55 days postdose 1	Yes
01651	22 Mos/Female	**Gastroenteritis**	3	154 days postdose 1	Yes
02119	28 Mos/Female	**Gastroenteritis**	5	166 days postdose 1	Yes
02082	21 Mos/Female	**GE reflux** (history vomiting)	5	12 days postdose 1	Yes
01083	20 Mos/Female	**Viral hepatitis** (EBV IgM +)	2	142 days postdose 1	No-withdrew consent
10852	18 Mos/Male	**Viral illness**	2	36 days postdose 1	Yes
01029	24 Mos/Female	**Viral illness** (possible UTI)	2	14 days postdose 2	N/A
01613	21 Mos/Male	Bilateral **Otitis Media**	3	146 days postdose 1	Yes
01689	16 Mos/Male	Recurrent **Otitis media**	3	30 days postdose 1 148 days postdose 1	Yes
01091	19 Mos/Male	**Sleeping disorder/bilateral tympanic tubes**	2	55 days postdose 1	Yes
01092	19 Mos/Female	**Sleeping disorder/bilateral tympanic tubes**	2	55 days postdose 1	Yes
01093	20 Mos/Female	**Septic Athritis**	2	59 days postdose 1	Yes
00046	18 Mos/Male	**Retropharyngeal abscess**	1	142 days postdose 1	Yes
02093	27 Mos/Female	**Eczema**	5	75 days postdose 1	Yes
01247	21 Mos/Female	**Papular urticaria**	2	151 days postdose 1	No-withdrawn due to SAE
00047	16 Mos/Male	**Kawasaki's disease**	1	106 days postdose 1	No-moved
01111	20 Mos/Male	**IDDM** **Otitis Media** **Gastroenteritis**	2	115 days postdose 1 136 days postdose 1 8 days postdose 2	Received 2 doses
02049	21 Mos/Male	**Increased Lead Level**	5	79 days postdose 1	Yes
02211	31 Mos/Male	**Accidental ----------**	5	31 days postdose 2	N/A
01631	19 Mos/Female	**Jammed Left thumb**	3	123 days postdose 1	Yes
00078	16 Mos/Female	**Consumed detergent,** **Viral illness**	1	92 days postdose 1	Yes
01705	22 Mos/Female	**Levothyroxine OD**	3	8 days postdose 2	N/A
01716	20 Mos/Female	**Tenormin OD**	4	122 days postdose 1	Yes

Seizures:

1. Subject 01230 experienced a febrile seizure 2 days after dose 1 that was considered possibly related to the vaccine, although the child was receiving treatment for otitis media at the time of vaccination, and was also diagnosed with a viral infection at the time of the seizure.
2. Subject 01011 experienced a febrile seizure 27 days after dose 1, but was also diagnosed with otitis media and bronchitis at the time of the seizure.
3. Subject 01829 experienced a seizure before Havrix was administered (but 1 day after the child received INFANRIX and OmniHIB.
4. Subject 00208 had a seizure 37 days after dose 2 HAVRIX and 5 days after the child received multiple vaccines (including MMR, IPV, INFANRIX, and HIB.)

Reviewer's Comment: The first two subjects had other illnesses that may caused the seizures; the third had not yet received HAVRIX; and the fourth child had a seizure more than 1 month after receiving HAVRIX.

Asthma:

1. Subject 00107 had an exacerbation of asthma 45 days after dose 1.
2. Subject 01214 had bronchiolitis (later diagnosed as asthma) and otitis media after dose 1, and experienced laryngospasm during surgery myringotomy tube placement. This same subject had bronchospasm during adenoidectomy surgery 99 days after dose 1.
3. Subject 01099 had increased asthma symptoms 112 days after dose 1.
4. Subject 01633 had a first asthma attack 95 days after dose 1. There was a family history of asthma.
5. Subject 01678 had a first asthma episode 137 days after dose 1. There was a family history of asthma.

Reviewer's Comment: The first, second and third subjects had histories of asthma prior to dose 1. The first and third subjects had exacerbations a relatively long time after dose 1, and the second subject whose exacerbation occurred 4 days after dose 1 also had otitis media at the time of the exacerbation. The fourth and fifth subjects had a family history of asthma, and the events occurred a relatively long time after dose 1.

Respiratory Illnesses:

1. Subject 01910 had a history of cardiac murmur and developed bronchiolitis 34 days after dose 1.
2. Subject 00069 developed bronchiolitis app. 4.5 months after dose 1.
3. Subject 01668 developed pneumonia 40 days after dose 1.
4. Subject 01107 developed shortness of breath 21 days after dose 1. Testing for oxygen desaturation was not conclusive, but the diagnosis was suspected sleep apnea. The child recovered and received the second dose without problem.

Reviewer's Comment: The events in the first 3 subjects were unlikely to have been related to vaccine because of the relatively long time periods, and the event in the fourth subject was not confirmed.

Gastrointestinal events:

1. Subject 01555 had rotavirus infection 123 days after dose 1.
2. Subject 01521 had rotavirus infection 106 days after dose 1.
3. Subject 01588 had gastroenteritis 55 days after dose 1.
4. Subject 01651 had gastroenteritis 154 days after dose 1.
5. Subject 02119 had gastroenteritis 166 days after dose 1.
6. Subject 02082 had GE reflux 12 days after dose 1 (but had a history of vomiting prior to the event).

Reviewer's Comment: There is no apparent relationship to the vaccine in the first 5 subjects because of the long time periods, and the sixth subject had a history of vomiting prior to vaccination.

Other Infections:

There were 9 subjects who experienced other infections. The shortest interval between vaccination and event was 14 days after dose 2 (Subject 01029), and the relationship to vaccination is not definitive.

Reviewer's Comment: It is noted that the histories for Subjects 01091 and 01092 were identical, occurred on the same day, and at the same center, so it is not clear that this was a duplicate report or whether these were fraternal twins that somehow had the same exact event occur on the same day.

Skin Disorders:

1. Subject 02093 developed widespread eczema 75 days after dose 1. The investigator could not definitively rule out a relationship to vaccination, although the child did go onto receive dose 2 without reported problems.
2. Subject 01247 developed popular urticaria 151 days after dose 1, which was felt to be related to an infection. The child did not receive the second dose because of the SAE.

Reviewer's Comment: There was a relatively long time period between vaccination and the events above, so relationship to vaccine is not clear.

Kawasaki's disease:

1. Subject 00047 developed Kawasaki's disease 106 days after dose 1 and 10 days after receiving DTaP, IPV and ActHIB.

Reviewer's Comment: This event also took place a relatively long time period after receipt of dose 1, so relationship to HAVRIX is not clear.

Insulin Dependent Diabetes Mellitus, Otitis Media, and Gastroenteritis:

1. Subject 01111 dveloped IDDM approximately 3.5 months after dose 1, with otitis media occurring soon after, and then Campylobacter gastroenteritis 8 days after dose 2.

Reviewer's Comment: The relationship of IDDM to receipt of vaccination is not definitive given the relatively long time period between vaccination and the event. The otitis media and Campylobacter infections are unlikely related to the vaccine.

Accidental injuries, death, and ingestions:
There were 6 such subjects.

Reviewer's Comment: There is no apparent relationship between these events and vaccination with HAVRIX.

In summary, there were 38 subjects (37 if subjects 01091 and 01092 are the same subject) with 42 SAEs. 34 /38 occurred after Dose 1, and 4/38 occurred after Dose 2. There were 6 SAEs in Group 1, 12 SAEs in Group 2, 8 SAEs in Group 3, 6 SAEs in Group 4, and 5 in Group 5. There were 16 (?15) females with an SAE and 23 males with an SAE.

Deaths: There was one death (Subject 02211, Group 5), with an accidental ---------- days after Dose 2 HAVRIX. There was no apparent relationship to the vaccine and the death.

Withdrawals due to Non-Serious Adverse Event or Serious Adverse Event
One subject was withdrawn due to an SAE. Subject 01247 at Center 16 was hospitalized due to papular urticaria at Day 151 after Dose 1 HAVRIX. The subject recovered.
Four subject were withdrawn due to NSAEs:
Subject 229 (Group 1) experienced general symptoms of mild drowsiness and moderate to severe irritability Days 0-3 following Dose 1. According to the investigator, the symptoms had a suspected relationship to vaccine.
Subject 1024 (Group 2) after Dose 1 experienced moderate (10 mm) redness, a solicited local reaction on the day of vaccination. This was felt to be vaccine related.
Subject 1020 (Group 4) suffered a severe viral illness 33 days after Dose 1 HAVRIX. This adverse event resolved after 9 days.
Subject 1840 (Group 4) suffered mild chickenpox 25 days after Dose 1 HAVRIX. The adverse event resolved after 9 days.

8.1.1.3 Comments – Conclusion Regarding Data for Protocol HAV-210 (Reviewer's Opinion)

This study was conducted to support lowering the age indication for HAVRIX to 12 months in the US. A new efficacy trial was not conducted, but efficacy

was inferred from adequate immune response to the vaccine in the 12-23 month old age group. Protective efficacy with HAVRIX has been previously demonstrated in a double blind, randomized, controlled study in school children (ages 1 to 16years) in Thailand who were at high risk of HAV infection. Subjects with detectable antibodies to hepatitis A antigen are thought to be protected against hepatitis A disease.

HAV-210 had the following objectives with the following results:

- The study demonstrated its primary objective that there were non-inferior immune responses to hepatitis A antigen after 2 doses of HAVRIX in children 15-18 months of age as compared to children 23-25 months of age children, and in children 11-13 months of age as compared to children 23-25 months of age by comparing anti-HAV GMC data. This was demonstrated for responders and also for responders and non-responders together in the ATP cohort for immunogenicity.
- The study demonstrated a secondary objective that there were non-inferior immune responses to hepatitis A antigen by anti-HAV GMC data 1 month after dose 1 HAVRIX in children 15-18 months of age as compared to children 23-25 months of age in the responders in the ATP cohort. However, this non-inferiority was not demonstrated in both responders and non-responders for the 11-13 month old children as compared to children 23-25 months of age. This would indicate that two doses of the vaccine would be necessary in the 11-13 month old age group in order to elicit GMCs comparable to the 23-25 month old children. However, the seropositivity rate (different from the vaccine response rate used in this analysis) ranged from 87.5%-88.8% in the 11-12 month olds after the first dose of vaccine (percentage positive in subjects with serology data available after first dose), so that most subjects should be protected against hepatitis A disease even after 1 dose
- The study demonstrated non-inferiority of the immune response to hepatitis A antigen in 15-18 month old children who received concomitant administration of HAVRIX + INFANRIX + OmniHIB compared to who received HAVRIX alone at 1 month postdose 2 HAVRIX. Non-inferiority was not shown for the immune response to hepatitis A antigen in this group 1 month postdose 1, however. Two doses of HAVRIX would be necessary to provide similar vaccine responses. However, in a post-hoc assessment done with the serology data for Groups 2 (non-concomitant) and 3 (concomitant) show that the seropositivity rates are 90.7% and 86%, respectively, so most subjects should be protected post-dose 1.
- The study demonstrated the non-inferiority of the immune response to HIB in 15-18 month old children as measured by the percentage of subjects seroprotected against HIB disease ($\geq$ 1 mcg/mL anti-PRP) when given OmniHIB with INFANRIX, with or without HAVRIX.
- The data were not sufficient to demonstrate a similar immune response to all antigens contained in INFANRIX when given with OmniHIB with or without HAVRIX. The sponsor did not meet the specified criteria for

success for demonstrating equivalence in anti-PT vaccine response rates, and the DTaP-containing vaccines administered as the primary vaccination course were not known.

- Safety: The one death that occurred in this study was due to an accidental ----------. There was one febrile seizure 2 days after vaccination with Dose 1 HAVRIX in a 17 month old child who was on treatment for otitis media at the time of vaccination, and was also diagnosed as having a viral illness at the time of the fever and seizure. Other serious adverse events were often associated with other medical conditions. There was a higher rate of solicited general adverse events in the 11-13 month old age group as compared to the 15-18 month old age group and the 23-25 month old age group after both doses, although the rates for local adverse events were similar among these three groups. There were lower incidences for general adverse events in all groups after Dose 2 as compared to Dose 1. The groups that received INFANRIX and OmniHIB had higher rates of both general and local adverse events compared to the groups that received HAVRIX alone, and in a post-hoc analysis, were noted to be statistically significant for drowsiness, irritability, and loss of appetite. The groups that received INFANRIX, OmniHIB, and HAVRIX also had statistically significant higher rates for drowsiness and loss of appetite as compared to the group that received INFANRIX and OmniHIB. In the groups that received HAVRIX alone, the most common solicited local adverse events included pain and redness at the injection site. The most common solicited general adverse event was irritability. Fever (> 100. 4° F) occurred in 10.5% in the 23-25 month old age group to 15.5% in the 11-13 month old age group when HAVRIX was given alone. Most of the fevers were mild - moderate, and very few were Grade 3 (0.4%-1.1% in the groups that received HAVRIX alone). The percentages of subjects with Grade 3 solicited and unsolicited adverse events in the groups that received HAVRIX alone in the 4 days after vaccination were generally low, with generally < 5% after both doses. There were more Grade 3 adverse events when INAFNRIX and OmniHIB were administered. The most common unsolicited adverse events in the 31 days after each vaccination included upper respiratory infections, otitis media, diarrhea, rhinitis, viral infection, vomiting and fever. Most of the unsolicited symptoms were mild to moderate in severity, and very few (< 1-1.2%) were assessed as Grade 3 in severity.

Therefore, HAVRIX after 2 doses would be expected to provide near 100% protection in children who receive the first dose between 12 and 24 months of age. After 1 dose, the vaccine response rate is lower for the 11-13 month old age group. Still, approximately 87-89% of the youngest age group would be expected to be protected after the first dose (based on the presence of seropositivity), and approximately 100% would be expected to be protected after the second dose of the vaccine.

In summary, this study supports the indication that HAVRIX may be administered to children as young as age 12 months, and the vaccine may be coadministered with Haemophilus influenzae b PRP-T to children 15-18 months of age without impairment of the immune response for anti-PRP seroprotection rates or impairment in post-dose 2 HAVRIX vaccine response rates. The data are insufficient to support coadministration of HAVRIX with DTaP vaccine at this time. There were no unusual safety concerns identified, but additional subjects are being studied in ongoing coadministration studies. As with other routinely administered childhood vaccinations, vaccination in this age group should be postponed until an acute illness has resolved.

Trials, HAV-181, HAV-188, and HAV 204, summarized below, are considered supportive studies for this BLA supplement.

8.1.2 Trial #2

8.1.2.1 Protocol # 208109/HAV-181: Immunogenicity Study of an Inactivated hepatitis A vaccine in infants and young children. (A Collaborative Study of the Indian Health Service, the CDC, and SmithKlineBeecham).

8.1.2.1.1 Objective/Rationale: The study objective that pertains to the present supplement is the determination of the optimum antibody response that can be achieved in infants with passively acquired anti-HAV by using ----------

8.1.2.1.2 of vaccine given at an age when the concentration of passively acquired antibodies have begun to decline.

8.1.2.1.3 Design Overview: This was a single-blinded, randomized clinical trial at the Alaska Native Medical Center and the Anchorage Neighborhood Health Center in Anchorage, AL conducted from 1996-2001. Infants were to be recruited in the first 4 months of life at well baby visits. If the mother agreed, blood would be obtained from the mother and infant to determine serostatus in each.

Table 41: Study Design HAV-181

Group	Number Planned	Dose	Ages at Vaccination
1	60	720 El.U + 0.25 mg aluminum/0.5 mL IM	6, 12 months
2	60	720 El.U + 0.25 mg aluminum/0.5 mL IM	12, 18 months
3	60	720 El.U + 0.25 mg aluminum/0.5 mL IM	15, 21 months

Infants were to be randomized in blocks of 8, doing this separately for seronegative and seropositive mothers.

8.1.2.1.3 Population: healthy Alaska Native American children

Inclusion Criteria:

- Term infant (36-42 weeks gestation) with normal growth and development and considered healthy by the investigator at 6 months of age
- Written informed consent by parent or guardian.

Exclusion Criteria:

- Received or expected to receive IG or blood/blood products while in study; received or expected top receive immunosuppressive therapy for a medical condition within 30 days of vaccination, or known or suspected to have immunodeficiency
- Cannot be reasonably expected to be reliably followed for the duration of the study because the family does not live within the area served by the ANMC
- Currently enrolled in another vaccine trial and/or received a non-FDA approved drug within 30 days prior to study entry
- Severe developmental disability or progressive or unstable neurological disorder.

Procedures Allowed: The infants were to be randomly assigned to study group, based on the anti-HAV status of the mother; and all infants were to receive scheduled routine infant vaccination of DTP, OPV, HIB, MMR and hepatitis B; Table 1 (p. 13, CSR HAV-188, not shown here) shows the timing of the routine infant vaccines for 1996-2001.

8.1.2.1.4 Products Mandated by Protocol

HAVRIX (provided by GSK). Groups 1-3 received HAVRIX 720 EL.U+0.25 mg Aluminum/0.5 mL.

Concomitant vaccinations were as recommended in each of the years of the study (2001, 2000, 1999, 1998, and 1996). These included the following vaccines (depending on the year of the study): Hepatitis B, DTaP or DTP, HIB contaning vaccines, IPV or OPV, PREVNAR, MMR, and Varicella In 2000,

8.1.2.1.5 Endpoints

Immunogenicity:

- Anti-HAV titers (limit of detection ------ mIU/mL) at CDC and GSK using ELISA assay (---------- anti-HAV, ----------). GMCs also calculated. ----------.
- Antibodies to Diphtheria, tetanus, anti-HIB polysaccharide, anti-PT, and anti-PRN were measured at ----------. (Not reviewed because of the differing vaccination schedules.)

8.1.2.1.6 Surveillance

Parents or guardians were given a diary card to record systemic and injection site signs and symptoms Days 0-3 (4 days after vaccination). Diary cards solicited for pain, redness, or swelling at the injection site, and fever, irritability or other changes in behavior, or any illness. Parents were given self-addressed, stamped envelopes in which to return the competed diary card, and were instructed to contact study investigators if they had any concerns.

At the one month visit after each vaccination, parents who had failed to return a diary card were asked if there were adverse events observed. Along with the child's regular physician, study staff followed the child for 6 months to 2 years (27 months for Group 3). Information on intercurrent outpatient visits and hospitalizations were abstracted from the subject's charts at each well child visit and at each visit 1 month after Hepatitis A vaccine. Hospitalizations and serious adverse events (SAEs) were reviewed by the study investigator. These events, as well as the frequency of reported local and systemic reactions were also reviewed at regular intervals by a DSMC. The incidence of adverse events was to be compared among the groups.

Blood for immune responses was to be taken at the time of the first hepatitis A dose (baseline) at 1, 7 and 12 months thereafter. For children assigned to Group 3, the baseline serology sample was drawn at 13 months (2 months before the first vaccine dose).

8.1.2.1.7 Statistical Consideration regarding HAV

- A sample size of 30 subjects per subgroup (60 subjects per group) resulted in 80% power to detect at least a 2-fold difference in anti-HAV GMCs between subgroups in each group (alpha = 0.05, 2-sided).
- The subjects with anti-HAV > level of detection were considered seropositive. The proportion of subjects who were seronegative was compared within and between groups at various time points using the chi-square or Fisher's exact test, as deemed appropriate. Results at > 8 weeks after vaccination were excluded.
- The 95% CI of the GMCs were calculated using the means and standard deviation of the log of the concentration of anti-HAV antibody levels. GMCs within and between groups were evaluated by comparing the means using the student's t-test.
- Group 3 was considered the control group because at 13 months of age, children assigned to this group had not yet received Hepatitis A vaccine.
- Clinic visits for any reason were grouped in general categories (e.g., rashes, respiratory, GI, injuries, otitis media). The frequency of various categories of sick visits was completed according to group, stratified by age group at the time of visit (6-11 months, 12-14 months, 15-17 months, 18-20 months, and 21-24 months).

8.1.2.2 Results

8.1.2.2.1 Populations Enrolled/Analyzed

248 children received at least one dose of vaccine. 140 born to seronegative mothers were included in the "N" groups, and 108 children born to seropositive mothers were included in the "P" groups. There were 46 subjects in group 1N and 36 subjects in Group 1P. There were 49 subjects in Group 2N and 34 subjects in Group 2P. There were 45 subjects in Group 3N and 38 subjects in group 3P.

Groups were similar with respect to age at baseline blood draw and sex (Table 2, p. 14, CSR HAV-181, not shown here).
Children in the "P" subgroups were more likely to be Hispanic than children in the "N" subgroups ($p<0.0001$).
19 additional children were assigned to Group 1X.
There was some variation in the sexes of subjects in Group 1 (61% female 1N, 42% female 1P) and lesser variation in Group 2 (49% females in Group 2N and 41 % female in Group 2P), and still lesser variation in Group 3 (56% female in Group 3N and 61% female in Group 3P).
There was also some variation in the percentages of subjects represented in different ethnic groups, although most were full Alaska natives, part Alaska natives, and Asian Pacific Islanders.
Concomitant medications were noted.
Withdrawals: Table 3 (p. 15, CSR HAV-181, not shown here) provides the reasons for withdrawals of participants receiving $\geq$ 1 hepatitis A vaccine dose (N=19). 15 withdrew because they moved form the area [7 in 2N, 2 in 1N, 4 in 2P, 1 in 3N, and 1 in 3P]. Two withdrew because they did not return [one in 1N and 1 in 3N]. Two withdrew because they reconsidered [two in 3N].

8.1.2.2.2 Immunogenicity Endpoints/Outcomes

Response to Hepatitis A vaccine: Among children born to seronegative mothers, 54-73% who were seropositive were tested one month after the first dose of vaccine, and all were seropositive at 1 month and 6 months after the second dose of vaccine. Peak GMCs measured 1 month after Dose 2 ranged from 2083 mIU/mL (Group 1N) to 3166 mIU/mL (Group 2N). There were no statistically significant differences in GMCs at any timepoint between Group 3N and either Group 2N or 1N children.

Table 42: Immune Response to Hepatitis A Vaccine, by Group

Group*	Baseline			One month after Dose 1			One Month after Dose 2			Six months after Dose 2		
	N	% +	GMC mIU/mL (95% CI)	N	% +	GMC mIU/mL (95% CI)	N	% +	GMC MIU/mL (95% CI)	N	% +	GMC MIU/mL (95% CI)
1N	46	0	N/A	41	54	49 (33.6,71.5)	44	100	2083 (1462, 2967)	43	100	727 (527, 1003)
1P	36	94	295 (184,473)	32	94	173 (109,272)	34	94	794 (488, 1293)	33	94	229 (143, 367)
2N	49	0	N/A	43	60	54 (37.5, 77.9)	38	100	3166 (2413,4156)	45	100	937 (719,1221)
2P	34	15	18.7 (15.5,22.7)	33	64	44.7 (31.6,63.2)	33	100	2296 (1719,3068)	29	100	698 (499,976)
3N	45	0	N/A	41	73	64.6 (46.1,90.6)	44	100	3153 (2450,4059)	41	100	933 (711,1224)
3P	38	3	15.6 (8.8,16.3)	37	68	70.2 (42.8,115.2)	34	100	2715 (2073,3557)	29	100	909 (633,1306)

From Table 5, p. 17, and Figures 3 and 4, pp. 22-23, CSR, HAV-181
*Group 1N= subjects in Group 1 born to seronegative mothers
*Group 1P = subjects in Group 1 born to seropositive mothers
*Group 2N = subjects in Group 2 born to seronegative mothers
*Group 2P = subjects in Group 2 born to seropositive mothers
*Group 3N = subjects in Group 3 born to seronegative mothers
*Group 3P = subjects in Group 3 born to seropositive mothers

Among children born to seropositive mothers, the proportion of detectable anti-HAV antibodies at the time of the first hepatitis A vaccine decreased across groups, as the age at time of first vaccination increased. Among children in Group 1P, 34 (94%) had detectable anti-HAV antibody at the time of the first vaccine dose at 6 months, with a GMC of 295 mIU/mL. Only 5 (15%) in Group 2P children had detectable anti-HAV levels when they received the first hepatitis A vaccine dose at age 12 months and one Group 3P child had detectable anti-HAV antibodies when the first vaccination was given at 15 months. There were statistical differences in the percentage of those seropositive and the GMCs at all timepoints when group 1N and Group 1P were compared (the youngest age group who received vaccine at 6 and 12 months). All initially seropositive group 1P children remained positive at 1 month after the first vaccine dose. The GMCs among 1P children declined but remained higher than that of the 1N children. Following the second dose of vaccine, all but 2 children were seropositive, but the GMCs among 1P children was significantly lower when compared to 1N children, and remained so at 6 months, after the second dose of vaccine. (The antibody levels are shown above Table 42, and Figure 1, p. 20, CSR HAV-181, latter not shown

here). Of the two children with undetectable antibodies on the Month 7 blood draw, one was positive on the Month 12 draw, and the other did not have a specimen available. (Figure 2, p. 21, CSR HAV-181, not shown here).

There were no statistically significant differences between Groups 2N and 2P or 3N and 3P at any time point after the vaccine series was initiated. The antibody concentration after the first vaccine dose of the 5 initially seropositive children in Group 2P declined or remained similar with respect to baseline, but peak antibody concentrations at 1 month after the second dose ranged form 1513-3543 mIU/mL and were similar to those for Group 2P children without detectable antibody at baseline.

Of vaccinated mothers, four had received one dose at the time of enrollment. The remaining 15 had received both doses. All but one of the vaccinated mothers were anti-HAV positive at the time of enrollment. 5(26%) of children had detectable anti-HAV antibodies at baseline. All 18 infants with available data were seropositive following the 2nd dose of vaccine with a GMC of 2454 mIU/mL [95% CI: 1585, 4526 mIU/mL].

Responses to other vaccines were included in the clinical study report, but because of the different vaccines that were administered depending on the year of immunization, and the small numbers, these data will not be used to support licensure of coadministration of other vaccines with HAVRIX (especially since newer vaccines have replaced some vaccines since 1996-2001). Table 42 above presents the immune responses to Hepatitis A vaccine, by group.

Reviewer's Comment: In this study, the children who received their vaccines at 12 and 18 months and those who received their vaccines at 15 and 21 months were not statistically different (ruled out a > 2 –fold difference in GMCs). The GMCs were statistically lower (> 2-fold difference) for the children who received their vaccines at 6 and 12 months as compared to the children who received the vaccine at 12 and 18 months, and those who received the vaccine at 15 and 21 months. ---------- ---------- in this trial as compared to HAV –210. In addition, there were variable vaccines coadministered with HAVRIX at different time points. However, the data are supportive that HAVRIX, after two doses, will provide an antibody response to hepatitis A antigen that is expected to be protective against hepatitis A disease.

8.1.2.2.3 Safety Outcomes

Other vaccines were usually given with the first dose of hepatitis A vaccine for Groups 1 and 2, and with the second dose of HAVRIX for Group 1. Adverse events were shown by Group and divided by Dose 1 and Dose 2 in Table 43 below.

The most frequently reported solicited adverse event were pain at the injection site, sleepiness and fussiness. The majority of these symptoms resolved within 1-2 days after vaccination.

Following visits during which other vaccines were administered in the left thigh when hepatitis A vaccine was administered in the right thigh, the frequency of local reactions in each thigh was similar.
Fever of one day's duration was reported by 12% of participants after either vaccine dose. Fever of 3 days' duration was uncommon.
Table 34 shows the local and systemic adverse events among participants who returned diary cards by group. Again, the safety results are difficult to interpret because the children received concomitant vaccines with HAVRIX.

Table 43: Solicited Local and Systemic Adverse Events among Participants who Returned Diary Cards by Group

Event	Group 1		Group 2		Group 3		Total	
	*Dose 1 n=69 n (%)	*Dose 2 n=65 n (%)	*Dose 1 n=69 n (%)	**Dose 2 n=56 n (%)	**Dose 1 n=59 n (%)	**Dose 2 n=65 n (%)	Dose 1 n=197 n (%)	Dose 2 n=186 n (%)
Reactions at injection site								
Redness, right thigh	9 (13)	8 (12)	10 (14)	5 (9)	7 (12)	6 (9)	26 (13)	19 (10)
Redness, left thigh	11 (16)	8 (12)	13 (19)	2 (5)	0	0	24 (12)	N/A
Induration, right thigh	6 (9)	7 (11)	11 (16)	5 (9)	7 (12)	3 (5)	24 (12)	15 (8)
Induration, left thigh	6 (9)	9 (14)	14 (20)	0	0	0	20 (10)	N/A
Pain, right thigh	14 (20)	13 (20)	21 (30)	18 (32)	9 (15)	15 (23)	44 (22)	46 (25)
Pain, left thigh	28 (26)	18 (28)	24 (35)	2 (4)	1 (2)	2 (3)	43 (22)	N/A
General symptoms								
Fever for 1 day	7 (10)	11 (17)	10 (14)	5 (9)	8 (14)	6 (9)	25 (13)+	22 (12)++
Fever for 3 days	4 (6)	0	3 (4)	0	0	1 (2)	7 (4)	1 (1)
More sleepy for 1day	19 (28)	19 (29)	19 (28)	12 (21)	20 (34)	11 (17)	58 (29)	42 (23)
More sleepy for 2 days	13 (19)	7 (11)	9 (13)	4	6 (10)	8 (12)	28 (14)	19 (10)
More sleepy for 3 days	3 (4)	2 (3)	4 (6)	2 (4)	0	0	7 (4)	4 (2)
Fussy for 1 day	21 (30)	15 (23)	16 (23)	10 (18)	20 (34)	15 (23)	57 (29)	40 (22)
Fussy for 2 days	12 (17)	10 (15)	14 (20)	8 (14)	6 (10)	8 (12)	32 (16)	26 (14)
Fussy for 3 days	11 (16)	6 (9)	7 (10)	2 (4)	2 (3)	2 (3)	20 (10)	10 (5)
Less hungry for 1 day	7 (10)	7 (11)	6 (9)	3 (5)	6 (10)	8 (12)	19 (10)	18 (10)
Vomiting for 1 day	2 (3)	2 (3)	3 (4)	2 (4)	2 (3)	2 (3)	7 (4)	6 (3)

Hepatitis A vaccine always administered in right thigh
* > 96% of children received other vaccines at same time as hepatitis A vaccine (i.e., in the left thigh)
** < 13% of children received other vaccines at the same time as hepatitis A vaccine (i.e. in the left thigh)
+ Mean reported temperature 100.7 F (range 99.0-103.0F)
++Mean reported temperature 101.3F (range 99.5-105.4F) (From Table 4, CSR HAV-181, p. 16)

Reviewer's Comments: The percentages of subjects with solicited adverse events were generally low across all groups. However, variable vaccines were coadministered depending on the group and the year, so it somewhat difficult to fully interpret the data.

A total of 10 (4%) were hospitalized within one month after receipt of Hepatitis A vaccine. Reasons included surgery (N=4), respiratory infections (N=3), gastroenteritis (N=1), UTI (N=1), and seizure (N=1, reportedly related to electrolyte abnormality). None were judged by the investigator to be related to the vaccine.
One child died at 5 months of age from suffocation, after consent was obtained but before participating in the study. The individual reports for the following SAEs are provided in pp. 20-35, CSR HAV-181. Serious adverse events after 30 days are also provided.

Table 44: Listing of Serious Adverse Events In Study HAV-181 Within 30 days of vaccination

Subject	Age/Gender	Event	Group	Days postdose	Further vaccination
189	7 Mos/Male	Seizure, hyponatremia, vomiting	1P	15 days postdose 1 (also given with OPV, HIB, Hep B, and DTP	Not stated
115	19 Mos/Male	RSV, asthma exacerbation	2N	25 days postdose 2	N/A
144	19 Mos/Male	Persistent otitis media Myringotomy tubes	2N	5 days postdose 2 26 days postdose 2	N/A
222	13 Mos/Female	Croup	1N	25 days postdose 1	Yes
212	7 Mos/Female	Viral Rash UTI and fever Gastroenteritis Otitis Media	1N	28 days postdose 1 30 days postdose 1 20 days postdose 2 1 day postdose 2	N/A
67	7 Mos/Male	Pneumonia, bilateral otitis media	1N	27 days postdose 1	Not stated
108	16 Mos/Male	Hydrocoelectomy and circumcision (history hydrocoele)	3N	26 days postdose 1	Not stated
156	13 Mos Male	Phimosis, circumcision	1N	15 days postdose 2	Yes
221	13 Mos/Male	Bilateral myringotomy tubes for recurrent otitis media	2N	25 days postdose 1	Not stated
297	13 Mos/Male	Adenoidectomy, excision of thyroglossal cyst	3P	2 months postdose 2	N/A

Reviewer's Comment: In subjects 12 months and above, there were no SAEs within 30 days of vaccination that were clearly related to the vaccine. In Subject 189, the 7 month old child who developed a seizure, hyponatremia and vomiting, the child had also received multiple other vaccinations on the same day as HAVRIX. It is difficult to ascribe causality to HAVRIX alone.

The CDC also provided a list of serious adverse events which occurred pre-vaccination or >30 days after vaccination with HAVRIX. These are provided by line listing.

Table 45: Listing of Serious Adverse Events In Study HAV-181 > 30 days after vaccination

Subject	Age	Event	Group	Days postdose	Further vaccination
244	21 Mos	Febrile seizure	2N	45 days postdose 2	N/A
212	13 Mos	UTI and viral rash	1N	31 days postdose 2	N/A
100	12 Mos	Herpangia, mild dehydration	1N	6 months postdose 1	Yes
46	17 Mos	Bronchiolitis, dyspnea	3P	2 months postdose 1	Yes
209	24 Mos	Pneumonia, asthma exacerbation	2N	6 months postdose 2	N/A
226	22 Mos	Pneumonia	3N	3 months postdose 2	N/A
80	29 Mos	Reactive airway disease	2P	11 months postdose 2	N/A
185	14 Mos	Pneumonia, asthma	2P	2 months postdose 2	N/A
208	17 Mos	RSV, Pneumonia, asthma	1P	4 months postdose 2	N/A
163	23 Mos	RSV, Pneumonia, Reactive airway disease	3P	2 months postdose 2	N/A
193	11 Mos	Croup	1N	5 months postdose 1	Yes
220	11 Mos	RSV, Bronchiolitis	1N	5 months postdose 1	Yes
98	12 Mos	Gastroenteritis, dehydration	2P	Uncertain time postdose 1	Yes
15	9.5 Mos 16 Mos	Gastroenteritis Lap oil ingestion, respiratory distress	1N	33 days postdose 2 4 months postdose 2	N/A
24	20 Mos	Carbon dioxide inhalation	2N	7 months postdose 1	Yes
206	14 Mos	Bilateral myringotomies	1N	6 months postdose 1	Yes
214	19 Mos	Bilateral myringotomies	3N	6 months postdose 1	Yes
232`	20 Mos	Circumcision	2N	1 month postdose 2	N/A
202	31 Mos	Biopsy Left Lateral Chest Wall Mass	3P	10 months postdose 2	N/A
169	11 Mos	Bilateral myringotomies	1P	6 months postdose 1	Yes

From CSR HAV-181, pp. 37-8

Reviewer's Comment: In the target age group, 12 months and above, the SAEs that occurred both within 30 days and >30 days after vaccination do not appear related to vaccine and raise no new vaccine safety concerns.

In general, it was noted that participants visited the clinic for a variety of conditions, most commonly otitis media, rashes (e.g., eczema and diaper dermatitis), and respiratory illnesses (e.g., pneumonia and asthma). Medical records were reviewed by the DSMC and they concluded that these events were unlikely to be related to the hepatitis A vaccine. This assessment appears reasonable.

8.1.2.3 Reviewer's Comments-Conclusions Regarding Data for HAV-181: The data in this trial show that the vaccine at 720 EL.U + .25mcg/0.5mL is immunogenic in children at 12 months and 15 months born to seropositive mothers. There were lower immune responses in 6-month-old children born to seropositive mothers. HAVRIX was coadministered with other childhood immunizations during the course of the study, but the products varied over the years, and meaningful interpretation of these data is difficult.

The study also provides safety information on additional children. However, because these children received other variable vaccines with HAVRIX, it is difficult to state exactly what adverse event was related to HAVRIX. Nonetheless, safety data is provided for an additional 128 subjects after dose 1

and 121 subjects after dose 2. The safety data show that the most common solicited local adverse event was pain at the injection site in all groups, and slightly more after dose 2 compared with dose 1 overall, followed by redness and induration (slightly less overall incidences in dose 2 compared with dose 1).

For solicited general symptoms: Fussiness and sleepiness were the most common in all groups, followed by fever (mean T 100.7°F after Dose 1; mean T 101.3°F after Dose 2 in those with fever). The other solicited general symptoms included an approximate 10% incidence overall for decrease in appetite, and a 3.5% incidence of vomiting. Most adverse events lasted 1-2 days, although some persisted out to 3 days.

The serious adverse events reported in the 12-23 month age group within the 30-day period postvaccination were similar to the illnesses noted in the period > 30 days after vaccination. There was no clear temporal pattern for the development of SAEs.

8.1.3 TRIAL #3

8.1.3.1 Trial 208109/188 (HAV-188): Open study in healthy 2 month old infants to evaluate the immunogenicity and reactogenicity of SmithKlineBeecham's inactivated hepatitis A vaccine (720 El.U/0.5 mL) at ages 2, 4, and 6 months.

This was conducted in Israel under the direction of Dr. Ronald Dagan from 12/9/96 – 12/28/98.

Reviewer's Comment: There was a group of 12 month old children added to this trial, and the results of this group were considered as supportive of the present supplement.

8.1.3.1.1 Objective/Rationale

This study was conducted in Israel. Israel has a higher incidence of hepatitis A disease compared to the incidence in the US. Because of this higher incidence rate, it was anticipated that a number of the infants would be seropositive for hepatitis A prior to vaccination. Therefore, they also planned to study to see how maternal antibodies might affect the immune response to Hepatitis A vaccine. This study was done to see if the hepatitis A vaccine could be incorporated into the routine childhood immunization schedule.
The study sought to assess the immunogenicity and reactogenicity if SmithKlineBeecham's HAVRIX (720 EL.U/0.5mL) injected with DTaP, IPV, and HIB at 2, 4 and 6 months.

There was also a group of subjects who would be vaccinated once at 12 months of age (and enrolled at 10 months of age). This last group provided for review an additional 100 subjects in the 12-23 month old age group who received one dose of HAVRIX at 12 months.

8.1.3.1.2 Design Overview

Open label study with 300 healthy males and females at 2 months of age at time of the first dose of primary vaccine course and 100 healthy 12-month-old children previously unvaccinated with hepatitis A vaccine.

There were to be three groups: 2 month old children who were seronegative, 2 month old children who were seropositive, and children 12 months of age who were previously unvaccinated but could be seropositive. It is noted that the original protocol only had one group of subjects. The first amendment in 3/14/97 allowed the subjects to be stratified into two groups: those that were seronegative for hepatitis A vaccine and those who were seropositive for hepatitis A vaccine. The 12 month old age group was added in an amendment 7/3/97 because preliminary serology data indicated that maternally acquired antibodies might interfere with the immune response to hepatitis A vaccine administration at 2, 4, and 6 months of age. This interference was evidenced by low anti-hepatitis A virus titers in vaccinees who were initially seropositive. A booster dose at 12 months was allowed with this amendment, and the third group with 12 month old children who were previously unvaccinated with hepatitis A vaccine were enrolled as controls.

Seronegative was defined as an antibody level <33mIU/mL [assay cutoff].

Seropositive was defined as $\geq$ 33 mIU/mL. Again, a----------
as compared to HAV-210.

Table 46: Study HAV-188 Design

Group	N	Immunization
1	300	Hepatitis A vaccine at 2, 4, 6 months of age Booster at 12 months could be given if no response to earlier doses
2	100	Hepatitis A vaccine at 12 months of age

This review will focus on the results for the 12-month-old subjects who received their first dose of HAVRIX at 12 months of age.

The duration of the study for the 12 month olds was to be 3 months, and for the infants 13 months.

8.1.3.1.3 Population

Inclusion Criteria:

- Healthy children
- 12 month olds would be enrolled at 11-13 months of age and were previously unvaccinated with hepatitis A vaccine
- The younger infants were to be enrolled between 6 and 10 weeks of age and had not received previous diphtheria, tetanus, pertussis, or polio vaccination; informed written consent.

Exclusion Criteria:

- Allergy to neomycin and polymixin or allergic disease likely to be stimulated by vaccine
- Intercurrent diphtheria, tetanus, pertussis, polio, or hepatitis A disease

- Acute febrile illness at the time of planned vaccination warranted deferral until the subject recovered
- Major congenital defects or serious chronic illnesses
- Progressive neurological disease
- Any suspected or confirmed immunosuppressive condition (including HIV); immunosuppressive therapy (with exception of topical steroids)
- Simultaneous administration of vaccines not foreseen by the study protocol at the same study visit as study vaccines
- IG or administration of any blood products within 2 months before entering study or during the study period; administration of any other experimental or investigational drug within 30 days before entering the study or during the drug study period
- History of known hepatitis A infection in subjects in the 12 month group.

Concomitant vaccines: These included DTaP-IPV, HIB conjugate vaccine for all groups.

8.1.3.1.4 Products mandated by protocol

Hepatitis A inactivated, strain ----------: 720 EL.U + 0.25 mg aluminum /0.5 mL

DTaP-IPV vaccine: Lot 20711A9/M for the booster dose which contained diphtheria toxin 25Lf or $\geq$ 30 IU; tetanus toxoid 10 Lf or $\geq$ 40 IU; polio I=40D Ag units; polio 2=8D Ag units; polio 3 = 32D Ag units.

HIB conjugate vaccine: Lot HIB017A41/M for the booster which contained PRP=10 mcg; tetanus toxoid =20-40 mcg; with lactose.

2-month-old infants were given different lots with the same components.

2-month-old children who were initially seropositive were given an additional dose of hepatitis A vaccine at 12 months of age.

8.1.3.1.5 Endpoints

Primary Endpoint:

- GMTs of anti-HAV antibodies 1 month after the third vaccine dose in the 2 month old group.

Secondary Endpoints:

- Anti-HAV antigen antibody titers and seropositivity at each timepoint
- Reactogenicity elicited by hepatitis A vaccine after each dose
- Antibody response to diphtheria, tetanus, polio, and HIB at each timepoint (in 2 month old subjects)
- Anti-HAV titers 1 month after booster at 12 months of age in children who were initially seropositive
- **Anti-HAV antibody titers 1 month after the first dose of vaccine given at 12 months of age in the previously unvaccinated group.** This is the endpoint of interest from this study for this BLA supplement.

8.1.3.1.6 Surveillance

Immunogenicity based on antibody levels after vaccination.

For the 12 month olds who were vaccinated for the first time, serum titers of anti-HAV were to be drawn 1 month after this dose of vaccine.
The assay used was the ---------- assay, and the cutoff was 33mIU/mL.

Safety

Systemic and local reactions were followed for 4 days after vaccination. A diary card was used, with grading and causality. The solicited general symptoms were rectal temperature, unusual crying (more than 1 hour), drowsiness, T $\geq$ 38°C, vomiting, diarrhea, any other general symptom. Local solicited adverse events included pain on pressure at the injection site, redness size, swelling size, and any other local reactions. Unsolicited symptoms were to be followed for 30 days after each vaccination.

8.1.3.1.7 Statistical considerations

The target size sample of 90 evaluable subjects in each of the infant groups was expected to provide 80% power with an alpha of 5% to reject the null hypothesis that the GMTs of anti-HAV were not different by more than 30% and to reject the null hypothesis that seropositivity rates are not different than more than 10% (2-sided).
There was to be an analysis of demographics with respect to age in weeks, sex, mean age, ratio of males: females by the Fisher exact test.

Analysis of immunogenicity

GMTs of the 95% CI for all vaccine antigen components (Diptheria, Tetanus, Pertussis, HIB, Polio, and Hrepatitis A) at each timepoint, by taking the log transformation of individual titers.
Student's t-test or Wilcoxon test was used to compare the GMTs of anti-HAV antibodies between the seropositive and seronegative subjects in the younger age group. Seropositivity rates (percentage of seropositive subjects) were compared using a Fisher's exact test.

Analysis of Safety

The incidence of local and general adverse events after each injection of DTPa-IPV and HIB + HAV and overall were evaluated.
The frequency and intensity of each individual solicited reaction was evaluated.
The duration of each adverse event $\leq$ 1 day or > 1 day was reported.
The incidence of adverse events was calculated using the number of symptom sheets, which corresponded tot the number of doses following which the investigator documented the assessment of solicited and unsolicited symptoms.
The incidence of unsolicited symptoms, grade 3 unsolicited symptoms, and those of probable or suspected relationship to vaccine were presented by group and overall.
Serious adverse events were listed for each group.
The number of subjects who received concomitant medications was presented per group and overall.

8.1.3.2 Results

8.1.3.2.1 Population enrolled/analyzed

The sites involved were Soroke Medical Center, Israel, and Schneider Children's Medical Center, Israel. Table 6 (p. 35, CSR HAV-188, not shown here) provides the number of subjects stratified according to prevaccination anti-HAV status and vaccinated at each center.

There were 100 subjects in Group 3 (those vaccinated for the first time with hepatitis A vaccine) were all seen at Center 2. There were 48 females and 52 males in this group. 12 of these subjects were seropositive.

Study Completion and Drop Out: All 100 subjects who were enrolled in Group 3 of the study completed the study.

Eligibility for analysis: Only one subject (Subject 332 in Group 3) was ineligible for immunogenicity analysis because blood sampling was outside the acceptable time limit. There were 47 females and 52 males included in this analysis. For the safety analysis, those who received at least one dose of vaccine with symptoms documented on the Adverse Event form in the CRF.

8.1.3.2.2 Immunogenicity endpoints

Table 47, below, shows the data for the pre- and post-dose 1 seropositivity rates and GMTs in all groups. One month following the vaccine dose in Group 3 (month 11), 93.9% of subjects were seropositive and the GMT was 120.3 mIU/mL. The Sponsor did a comparison between subjects in Group 1 at 11 months who had received 3 doses of hepatitis A vaccine at 2, 4, and 6 months and those in Group 3 who had only received one dose. There was a significant difference with those in Group 1 having a much higher GMT. However, this comparison was not valid in that the subjects in Group 1 received several additional vaccinations as compared to those in Group 3 who received one vaccination.

Reviewer's Comment: A better comparison would have been one between subjects who were seropositive initially in Group 3 and who received 2 doses of vaccine (not done in this study) with the subjects in Group 1 who were initially seropositive who received 2 doses of vaccine.

Table 47: Anti-HAV seropositivity rates and GMTs in subjects included in the ATP analysis of immunogenicity for Group 3 (1 month post vaccination)

Timing	N	N S+	% S+	LL,UL	GMT	LL,UL	Minimum titer	Maximum titer
Pre	99	12	12.1%	6.4, 20.2	52	39.7, 68	34	132
Post	98	92	93.9%	87.1, 97.1	120.2	106.1,136.1	36	1479

(From Table 14, CSR HAV-188, P. 44)

Supplement 8 (not shown here, from CSR HAV-188, p. 55) shows the same analysis for the total cohort. There is only one more subject in the N for the Pre (i.e., 100) and for the Post (i.e., 99), and the other numbers are similar.

Immune responses for the other vaccines post-administration were not obtained in Group 3. Overall, 92/98 in the ATP group (93.9%, 95% CI: 87.9,97.1) were seropositive 1 month after Dose 1 of HAVRIX, with a GMT of 120.2 mIU/mL (95% CI: 106.1, 136.1). When compared with the Total Cohort (Supplement 8, p. 55, CSR HAV-188, not shown here), 93/99 were seropositive 1 month after Dose 1 HAVRIX (93.9%, 95% CI: 87.3, 97.7) with GMTs 120.8 mIU/mL (95% CI: 106.7,136.6).

After the first dose, 93.9% of subjects had seroconverted. (Appendix Table IIIA, pp. 188-190, IR letter, Comment 10, not shown here). The mean antibody level of subjects who were initially seropositive (N=12, which included 11 responders) was 104 mIU/mL. 91.7 % had a seroresponse of these subjects. The mean antibody level in all subjects who were initially seronegative was 148.6 mIU/mL (N=86, 5 nonresponders after 1 dose). In all subjects, 94.1% of those who were initially seronegative had a seroresponse. In the ATP cohort, 100% who were initially seropositive were seropositive 1 month after 1 dose, and 93.9% of those who were initially seronegative had seroconverted at 1 month after dose 1.

Reviewer's Comment: The data appear to demonstrate that HAVRIX is immunogenic after the first dose of vaccine among children who received the vaccine for the first time at 12 months of age. Interpretation of these results is difficult due to: (1) lack of a true control group; (2) ----------; (3) immune responses to concomitantly administered vaccines were not available in the group immunized for the first time at Month 12; (4) lack of information regarding the primary series these children received for other vaccines; and (5) responses after dose 2 were not studied.

8.1.3.2.3 Safety Outcomes

The overall incidence of solicited and unsolicited symptoms for 4 days after each vaccine dose and overall were provided in Table 10, p. 39, CSR HAV-188 (not shown here) For Group 3, 46/100 subjects had symptoms (46%). 39/100 (39%) had general symptoms and 6/100 (6%) had local symptoms with HAVRIX Dose 1. There were local symptoms at the DTPa-IPV site in 15/100 (15%) of these subjects.

For solicited local symptoms, the results are shown in Table 11 (CSR HAV-188, p. 40, not shown here). For Group 3, at the HAVRIX site, there were 4/100 (4%) with pain, 1/100 (1%) with redness, and 1/100 (1%) with swelling. None of the symptoms for subjects in Group 3 were Grade 3 severity for these local solicited symptoms. Supplement 3 (p. 52, CSR HAV-188, not shown here) provides the duration for the local solicited symptoms in Group 3. Of the 4 with pain, ¾ lasted $\leq$ 1 day, and 1 lasted > 1 day. For the one subject with redness, this symptom lasted > 1 day, and for the one with swelling, this symptom lasted $\leq$ 1 day.

Solicited general symptoms are presented in Table 12 (CSR HAV-188, p. 41, not shown here). For Group 3, 11/100 (11%) had diarrhea; 12/100 (12%) had

drowsiness, 3 (3%) which were Grade 3; 16/100 (16%) had fever, 5 (5%) were Grade 3; 12/100 (12%) had loss of appetite, 1 (1%) Grade 3; 21/100 (21%) had unusual crying, 2 (2%) Grade 3; and 2/100 (2%) had vomiting. Grade 3 symptoms were those that prevented normal activity, and Grade 3 fever was > 39°C. The Grade 3 symptoms were judged to be vaccine related by the investigator. Supplement 11 (p. 52, CSR HAV-188, not shown here) presents the duration of solicited general symptoms. Most were less $\leq$ 1 day duration, although some subjects had symptoms that persisted for $\geq$ 1 day. However, these children also received DTPa-IPV + HIB on the same day they received HAVRIX, so without a control, it is difficult to ascribe general symptoms to HAVRIX.

Unsolicited symptoms are presented in Table 13 (from CSR HAV-188, p. 42, not shown here). These occurred in the 30 days after vaccination. In Group 3, 15 doses were followed by at least one report of unsolicited symptoms. 12 subjects reported unsolicited symptoms. The number of unsolicited symptoms was 16. Supplement 5 (not shown here, from CSR HAV-188, p. 53) presents the number of doses followed by at least one report of unsolicited symptoms in the 30 days follow-up period after vaccination in the ATP cohort for reactogenicity. There were 15 such adverse events in Group 3. These included 9 cases of otitis media, and 1 case of fever, 1 case of gastroenteritis, 1 URI, 1 asthma, 1 rhinitis, and 1 rash.
Concomitant medications were given in 16 subjects in Group 3.

Serious Adverse Events: There were 9 serious adverse events in all groups, but one was noted in Group 3. This 13 month old male (subjects 386) received Hepatitis A vaccine with DTPa-IPV + HIB conjugate vaccine. 26 days after receiving the vaccines, the child was hospitalized after an asthma attack with fever and otitis media (from Appendix Tables IICi and IIDi, CSR HAV-188). It is not stated if the child had a history of asthma prior to vaccination.

8.1.3.3. Reviewer's Comments-Conclusions Regarding Data in HAV-188: This study provides additional safety and immunogenicity data for subjects 12 months of age after 1 dose of HAVRIX given with DTPa-IPV and HIB conjugate vaccine. In the 98 subjects in the ATP cohort, the vaccine was immunogenic in 93.9% of the subjects after 1 dose of HAVRIX. There were few local symptoms that appeared in the vaccinees in the four days after vaccination. General symptoms were seen in the 4 days after vaccination. A few were Grade 3 in intensity. These children also received concomitant vaccines, and there was no comparison to a control group who received HAVRIX alone. Therefore, we cannot discern which symptoms might have been related to HAVRIX, and which symptoms might be related to the other vaccines. In addition, the subjects were not given 2 doses of the vaccine (which is the recommended regimen). Also, the ----------. Nonetheless, the study does provide additional

supportive safety and immunogenicity information for the target age population for this supplement.

8.1.4 TRIAL #4

8.1.4.1 Protocol Title: 28109/204: Open clinical study to evaluate the immunogenicity and reactogenicity of SmithKline Beecham Biological's inactivated hepatitis A vaccine (HAVRIX) containing 720 ELISA units of hepatitis A per 0.5 mL dose administered according to 0, 6 month schedule in children 1-2 years of age. This was a Phase III trial that was conducted in Chile from 12/21/98 to 10/22/98.

8.1.4.1.1 Objective/Rationale: This study was to evaluate the immune response to vaccine and to evaluate the reactogenicity of the vaccine after each dose.

8.1.4.1.2 Design Overview: This was an open label, non-blinded study with one group. The duration of the study was approximately 7 months for each subject.

8.1.4.1.3 Population: There were 120 healthy male and female children between 1-2 years of age who were studied at 3 sites in Chile.

Inclusion Criteria:

- Male and female children between and including 1-2 years of age at the time of first vaccination; written informed consent
- Free of obvious health problems (by medical history and clinical examination).

Exclusion Criteria:

- Use of investigational or non-registered drug or vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period; administration of chronic (>14 days) immunosuppressive or other immune modifying drugs within 6 months of vaccine; any chronic drug reaction to be continued during the study period
- Planned administration/administration of vaccines not foreseen by the study protocol during the period starting for 30 days before each dose of vaccine(s) and ending 30 days after vaccination
- Previous vaccination against hepatitis A
- History of, or intercurrent, hepatitis A disease
- Any confirmed or suspected immunosuppressive or immunodeficiency condition, including HIV infection
- Family history of congenital or hereditary immunodeficiency
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine
- Major congenital deficits or serious chronic illnesses
- History of any neurological disorders or seizures
- Acute disease at the time of enrollment (but if minor illness, vaccine can be given)
- Administration if IG and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period

- Increased LFTs (ALT, AST > 2x ULN); hepatomegaly, RUQ pain or tenderness
- History of significant and persistent hematologic, hepatic, renal, cardiac or respiratory disease.

8.1.4.1.4 Products Mandated by the Protocol

Products: Inactivated hepatitis A strain HM175 (----------) with 720 EL.U ----------. Lot ----------.

Dose and Administration: This was given at Day 0/Month 0 followed by a second dose due at Month 6. There was no placebo.

8.1.4.1.5 Endpoints

Primary:

- Anti-HAV antibody titers at 1 month after dose 2 (Month 7)

Secondary:

- Anti-HAV antibody titer 1 month after the first vaccine dose (Month 1) and at time of the second vaccine dose at Month 6
- After each vaccination, the occurrence of solicited adverse events during the 4 day follow-up period after each dose
- Occurrence of unsolicited adverse events during the 30 days after each dose over the course of the study
- Occurrence of serious adverse events from the time of the first dose up to and including 30 days after dose 2.

8.1.4.1.6 Surveillance

Study Procedures are shown in Table 2 (not shown here, from CSR HAV-204, p. 22). Lab assays and time points are also shown. Screening blood was assayed for presence of anti-HAV in investigators labs using commercially available assay. Serum LFTs (ALT, AST) were also assayed in the investigators' lab. Blood was obtained at the time of 1 month after dose 1, at the time of the second dose, and 1 month after the second dose. Serum samples were tested in all subjects for anti-HAV using the commercially available ---------- test by ---------- which is an ELISA test. The cutoff for this test is 33 mIU/mL.

Diary cards were given to parents on the day of the vaccination to record local and general signs and symptoms (both solicited and unsolicited) occurring during the follow-up (days 0-3). These were to be completed and returned at the next visit. The parent was to contact the investigator if there were any serious signs or symptoms. Local solicited symptoms included pain, redness, and swelling. General solicited symptoms included Temperature, irritability, drowsiness, and loss of appetite. All were graded. For Temperature, Grade 0 < 38 deg°C; Grade 1 was 38 deg°C-38.5°C; Grade 2 was >38.5°C – 39.5°C; Grade 3 was > 39.5°C.

Causality was assessed by the investigator.

Concomitant medications were to be recorded if relevant (if given prophylactically in anticipation of reaction to vaccination, if given for existing symptoms, if it had impact on Inclusion/Exclusion criteria).

8.1.4.1.7 Statistical Consideration

Target sample size: In 100 evaluable subjects, it was hypothesized that there was a 95% probability that the real proportion of seroresponders in the study cohort would be 96-100%.

Cohorts:

The Total cohort included all those enrolled (i.e. vaccinated) subjects for whom data were available.

For the Total analysis of safety, this included all vaccinated subjects for whom safety data were available.

For the Total analysis of immunogenicity, this included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

The ATP cohort for analysis of safety included all who received at least one dose of study of vaccine; with sufficient data to perform an analysis of safety; for whom the administration site of study vaccine was recorded; who had not received a vaccine not specified or forbidden in the protocol.

The ATP cohort for analysis of immunogenicity included all subjects meeting all eligibility criteria; complying with procedures; and for whom data concerning immunogenicity measures were available.

Analysis of Demographics: Demographics (age, sex) tabulated. The mean age and range were calculated.

Analysis of Immunogenicity:

Based on the antibody response to vaccine antigen. Seronegative was defined as an antibody titer < 33mIU/mL, and seropositive was defined as an antibody titer $\geq$ 33mIU/mL.

Seroconversion was defined as the appearance of antibodies to hepatitis A in a serum sample from a subject with previously undetectable antibody (titer < LLOD).

Seropositivity rates (i.e., the percentage of seropositive subjects, with 95% CI) were calculated for anti-HAV at each blood sampling timepoint.

GMTs with 95% CI were calculated for the anti-HAV for each post-vaccination blood sampling timepoint. The GMT was calculated using the log-transformed of seropositive titers ($\geq$ 33mIU/mL) and taking the anti-log of the mean of these transformed values.

Analysis of Safety:

The incidence of local and general symptoms after each injection and overall were determined, in addition to the frequency, intensity, and relationship to vaccine of each individual solicited symptom. The incidence was calculated on the number of vaccine subjects who reported a symptom after at least one dose, and on the number of symptom sheets (specific pages in the individual case report form on to which the investigator transcribed diary card documentation on solicited symptoms reported for the subject). SAEs were described.

Unsolicited adverse events were coded by the WHO dictionary for adverse event reaction terminology.

Changes in planned analysis:
GMTs were also calculated giving the arbitrary value of ½ the cutoff (<33mIU/mL) to seronegative subjects, in order that the seronegative subjects were taken into account in the GMT calculation.
The duration (≤ or > 24 hours) of unsolicited symptoms was not analyzed as a result in the change in approach in reactogenicity analysis since the time of protocol development. Since the intensity and relationship to vaccine were analyzed, the Sponsor indicated that, in their opinion, assessment of duration does not contributive additional information.

8.1.4.2 Results

8.1.4.2.1 Populations Enrolled/Analyzed: 120 subjects were enrolled at 2 centers after serological assay confirmed anti-HAV seronegativity and normal AST and ALT.
As shown in Table 5 (not shown here, from CSR HAV-204, p. 30), two subjects dropped out of the study. One subject dropped out for a nonserious adverse event prior to any post-study vaccination. This subject, #22, dropped out due to the development of a rash on Day 1 after Dose 1. The mother noted palpebral edema but this symptom resolved by the third day when she was seen by the investigator. The child was found to have a maculopapular, erythematous, pruritic rash on the neck, face, and trunk, which was determined by the investigator to be an allergic reaction to the vaccine. The child was treated with hydroxyzine x 4 days and recovered b y Day 8. Another subject moved from the study area. 118 subjects completed the study.
The compliance for study completion was 98.3%. The compliance for blood sampling was 116/120 (96.7%). The compliance for study sheets completed was 236/239 (98.7%).
Demographics: In the Total cohort, there were 59 females and 61 males. The mean age overall was 17.2 months. In the ATP cohort for immunogenicity, there were 58 females and 58 males, with a mean age overall of 17.3 months. All 120 subjects were included in the safety analysis.
Four subjects were eliminated from the immunogenicity analysis (Table 6, not shown here, from CSR HAV-204, p. 32). As noted above, subject #22 was withdrawn before any post-vaccination blood was taken. This subject was initially seropositive or unknown antibody status. Three other subjects did not comply with the time interval (Subject #74 came 2 days early for the blood draw after Dose 1; #104 came 1 day early for the blood draw after Dose 1; and #97 came one day early for the Month 7 blood draw). One subject was initially seropositive or unknown antibody status.

8.1.4.2.2 Immunogenicity Endpoints
The analysis was based in the immune response to HAVRIX.
The data sets analyzed were the ATP and Total Cohorts

In the ATP cohort: The data from 116 subjects were eligible to be included in the ATP cohort. Seropositivity rates (the proportion of subjects with antibody ≥ 33 mIU/mL) and with GMTs with 95% CIs for anti-HAV are presented in Table 40. Also shown are the GMTs in seroconverters.

Table 48 -Seropositivity (S+) and GMT of anti-HAV antibody seroconverters (ATP analysis)

		Seropositivity		GMT mIU/mL		Min	Max
Timing	N	n(%)	95% CI LL, UL		95% CI LL, UL		
P1(M1)	116	115 (99.1%)	95.3, 100	161.7	137.3, 190.4	34	1373
P1(M6)	114	105. (92.1%)	85.5,96.3	112.9	98.2,129.7	36	852
P2(M7)	115	115(100%)	96.8,100	2939	2479.4,3483.7	353	21304

From Table 9, CSR HAV-204, p. 34

GMT data are also presented on all subjects (ATP analysis) where those who were seronegative were assigned an arbitrary value of ½ of the cutoff value of 33 mIU/mL.

Table 49-GMT of anti-HAV antibody on all subjects (ATP analysis)

		GMT Miu/mL		Min	Max
Timing	N		95% CI LL, UL		
P1(M1)	116	158.5	134.2, 187.3	<33	1373
P1(M6)	114	97	82.6,113.8	<33	852
P2(M7)	115	2939	2479.4, 3483.7	353	21304

From Table 10, CSR HAV-204, p. 34

The results for the Total cohort are presented in Supplement 1 (not shown here, from CSR HAV-204, p. 43.) These results are almost identical to the results shown in Table 49 above.

8.1.4.2.3 **Safety Outcomes:** There were no placebo controls.

The analysis included all who complied with the protocol defined procedures and for whom safety data were available (ATP)

There were 238 reports for 239 doses given.

Table 11 (not shown here, from CSR HAV-204, p. 35) showed the number of subjects who received vaccine. One subject (0.8% or 1/120) received only one dose. 119/120 (99.2%) received 2 doses.

Overall incidence of symptoms: Table 42 below provides the incidence of solicited and unsolicited adverse events (local and general) over 4 days after each dose and overall.

There were more general symptoms than local symptoms. General symptoms were reported with 39.5% of doses, and in 56.7% of subjects. Local symptoms were reported with 21.8% of doses, and in 37.5% of subjects. There were fewer symptoms reported after Dose 2 than Dose 1.

Table 50- Incidence and nature of symptoms during the 4-day follow-up period for each vaccine dose and overall: ATP analysis of safety

	N	Any Symptom		General Symptoms		Local Symptoms	
		n (%)	95% CI LL, UL	n (%)	95% CI LL, UL	n (%)	95% CI LL, UL
Dose 1	120	74 (61.7%)	52.4, 70.4	60 (50.0%)	40.7, 59.3	33 (27.5%)	19.7, 36.4
Dose 2	118	40 (33.9%)	25.4, 43.2	34 (28.8%)	20.8,37.9	19 (16.1%)	10, 24
Overall/dose	238	114 (47.9%)	41.4,54.4	94 (39.5%)	33.2, 46	52 (21.8%)	16.8, 27.6
Overall/subject	120	82 (68.3%)	59.2, 76.5	68 (56.7%)	47.3, 65.7	45 (37.5%)	28.8, 46.8

From Table 12, CSR HAV-204, p. 36

Solicited Local signs and symptoms: Table 51 gives the incidence of local injection site solicited reactions (pain, redness, swelling) in 4 days after vaccination and the symptoms grade as Grade 3.
Pain at the injection site was the most commonly reported local symptoms. This was reported in 28.6% of subjects and after 16.5% of all doses. Clinically significant or Grade 3 pain (crying with spontaneous limb movement) was noted in 4 subjects. There were 3 reports of the pain on one day only after Dose 1 (#29, 35, and 91). There was one report of pain on Days 0 and 1 after Dose 2 (#63).

Table 51 - Overall incidence of solicited local symptoms and those grade 3 in intensity over the 4-day follow-up period

Symptom	Parameter	Overall by Dose N=237		Overall by subject N=119	
		n(%)	95% CI LL, UL	n(%)	95% CI LL, UL
Pain	Total	39 (16.5%)	12, 21.8	34(28.6%)	20.7,37.6
	Grade 3	4 (1.7%)	0.5, 4.3	4 (3.4%)	0.9, 8.4
Redness	Total	18 (7.6%)	4.6, 11.7	16(13.4%)	7.9, 20.9
	Grade 3	0	0, 1.5	0	0,3.1
Swelling	Total	10 (4.2%)	2, 7.6	8 (6.7%)	2.9, 12.8
	Grade 3	0	0, 1.5	0	0,3.1

From Table 13, CSR HAV-204, p. 37

Supplement 3 (not shown here, from CSR HAV-204, p. 44) gives the incidence of solicited local symptoms after each dose. It is noted that there are fewer solicited local symptoms after Dose 2 as compared to Dose 1. All local symptoms were considered related to the vaccine.

Solicited general signs and symptoms: Table 52 presents the total incidence after vaccination for both doses for solicited general symptoms and those that are Grade 3.

Table 52- Overall incidence of solicited general symptoms over the 4 days after each injection

Symptom	Parameter	Overall by Dose N=236		Overall by Subject N=119	
		n (%)	95% CI LL, UL	n (%)	95% CI LL,UL
Fever	Total	13 (5.5%)	3, 9.2	13 (10.9%)	5.9, 18
	>39.5°F	2 (0.8%)	0.1, 3	2 (1.7%)	0.2, 5.9
Irritability/fussiness	Total	73 (30.9%)	25.1, 37.3	53 (44.5%)	35.4, 53.9
	Grade 3	2 (0.8%)	0.1, 3	2 (1.7%)	0.2, 5.9
Drowsiness	Total	26 (11%)	7.3, 15.7	25 (21%)	14.1, 29.4
	Grade 3	2 (0.8%)	0.1, 3	2 (1.7%)	0.2, 5.9
Loss of appetite	Total	51 (21.6%)	16.5, 27.4	42 (35.3)	26.8, 44.6
	Grade 3	3 (1.3%)	0.3, 3.7	3(2.5%)	0.5, 7.2

(From Table 14, CSR HAV-204, p. 38)

Supplement 4 (not shown here, from CSR HAV-204, p. 45) shows the incidence of solicited general symptoms by dose. Except for drowsiness, there are more solicited general symptoms after Dose 1 as compared to Dose 2.

Unsolicited adverse events

This is shown in Supplement 5 (not shown here, from CSR HAV-204, p. 46). During the 30-day follow-up period after each dose of the 2 dose series, a total of 120 unsolicited symptoms were reported. At least one unsolicited symptom was reported for 70 subjects. All unsolicited symptoms reported were general symptoms. One subject (#22) had a Grade 2 allergic reaction.

Out of 238 doses, there were 90 (37.8%, 95% CI: 31.6, 44.3) doses followed by at least one symptom. The most common unsolicited adverse events: URI and diarrhea (26/238, 10.9%, 95% CI: 7.3%, 15.6%); Pharyngitis (16/238, 6.7%, 95% CI: 3.9%, 10.7%); Bronchitis (13/238, 5.5%, 95% CI: 2.9%, 9.2%); Rhinitis (7/238, 2.9%, 95% CI: 1.2%, 6%); Otitis media (4/238, 1.7%, 95% CI: 0.5%, 4.2%); Fever, Gingivitis, Coughing, Laryngitis, Pneumonia (3/238, 1.3%, 95% CI: 0.3%, 3.6%); Infectious viral, erythematous rash (2/238, 0.8%, 95% CI: 0.1%, 3%); allergic reaction, syncope, abdominal pain, hematoma, bacterial infection, atelectasis, sinusitis, pustular rash, conjunctivitis (1/238, 0.4%, 95% CI: 0%, 2.3%).

Concomitant medications: 90 subjects received medications. No medications were given prophylactically. No subjects received concomitant vaccinations.

Serious Adverse Events: Two were reported.

Subject 102: 14 month old female developed cough and fever 31 days after the first dose of vaccine and was given clarithromycin. Two days later the child was hospitalized for **pneumonia** with a left base infiltrate on CXR. She was treated with penicillin and salbutamol inhaler. The child had a common cold prior to entering the study. After 4 days, the child was discharged. Three

days later, the child was readmitted with watery diarrhea and vomiting. The pneumonia had resolved. The child was treated with oral rehydration solution and was discharged 4 days later.

Subject #16: This **18-month-old** female with a history of recurrent otitis media developed fever, barking cough and inspiratory stridor 98 days after Dose 1. The child was hospitalized for 2 days with **croup** of probable viral etiology. A blood culture was negative. The child was treated with a single dose of dexamethasone, 24 hours of oxygen, and received racemic epinephrine. After 2 days, the child was discharged.

8.1.4.2 Reviewer's Comments-Conclusions Regarding Data in HAV-204: In this open trial, 120 children who were seronegative for Hepatitis A antibody and who were 1-2 years of age were included in this trial in Chile. 100% seroconverted at Month 1 post-dose 2 with a GMT of 2939 mIU/mL. Irritability was the most common general adverse event in the 4 days after vaccination. Pain at the injection site was the most frequently seen solicited local adverse event. Most of the adverse events were mild and moderate, and very few of these events were Grade 3 in intensity. The incidence of fever was relatively low in the 4 days after vaccination (approximately in 11% of subjects, with only 2% graded as severe). Even though this study was not controlled, the study provides an additional 120 children with safety data and 116 additional children with immunogenicity data for seronegative subjects who receive the vaccine starting at 12 months of age, which are supportive of the results for HAV-210. The vaccine formulation used in HAV-204 contained ---------- the formulation used in HAV-210, or in the currently U.S. licensed product. In addition, ---------- ---------- in HAV-210. The safety profile appears similar to that seen in HAV-210.

The next section includes other studies that were submitted with the supplement. Only a brief conclusion for each of these studies is included.

8.1.5 Trial #5 (A clinical study report was provided). **HAV-116**, **an open study of the immunogenicity and reactogenicity of SmithKlineBeecham Biological's inactivated hepatitis A administered to hemophiliac patients at 0, 1 and 6 months.** This was conducted in Italy from 6/92-7/94. There was one 17-month-old hemophiliac male who received a formulation of HAVRIX with 720 EL.U---- ---------- SQ at Months 0, 1, and 6. (The total number of subjects enrolled and vaccinated was 119). No AEs were reported for the 17 month old child, and he seroconverted after 3 doses. However, the dose was given SQ, was given in 1 mL, was given for 3 doses, and the formulation used had ---------- the present formulation as is given now to the pediatric age group.

8.1.6 **TRIAL #6** (A synopsis and case report form were provided). **HAV-118**, **an open study to evaluate the immunogenicity and reactogenicity of SmithKlineBeecham's inactivated hepatitis A containing 720 EL.U/0.5 mL given at 0, 12 months in healthy children.** This study was done in Lyon, France form 2/22/93 – 2/15/95. This study was considered a Phase III study. The one subject 12-24 months of age (total number of subjects was 54) received one dose of vaccine 6 days prior to the child's second birthday, and experienced mild headache and moderate vomiting within the first 2 days after Dose 1. He went on to receive the second dose at approximately 40 months of age. No anti-HAV levels were reported on the CRF provided. There were no SAEs reported in this subject.

8.1.7 **TRIAL # 7:** (A synopsis and case report forms for subjects 12-24 months of age were provided). **HAV –119**, **an open study of the immunogenicity and reactogenicity of SmithKlineBeecham's inactivated hepatitis A vaccine administered to hemophiliac subjects at 0, 1 and 6 months of age.** This was conducted in Bari, Italy from 9/92 -2/95. The study was considered a Phase IIIb study. There was to be a 24-month follow-up. Three subjects < 24 months of age were included in this study (total number of subjects was 91). Again, a ----------
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----------. There was variable drop-off in immune response at month 24. It is difficult to extrapolate the results of these three subjects to subjects in HAV-210, but there were no serious adverse events reported.

8.1.8 **TRIAL #8** (A synopsis and case report form were provided.) **HAV-132**: **A study to assess the immunogenicity and reactogenicity of SmithKlineBeecham's Hepatitis A vaccine administered subcutaneously to patients with congenital coagulation disorder using a single primary dose and booster dose of 1440 EL.U/1 mL in adults and 720 El.U/0.5 mL in children.** This was conducted in London, United Kingdom between 6/3/93-9/12/94. This was considered a Phase II study. One subject was 22 months old at the time of the first injection (total number of subjects 97), but received the dose SQ with ---------- that the formulation used in HAV-210 or in the currently U.S. licensed product. Nonetheless, the formulation was immunogenic and the subject had some mild to moderate local and general symptoms after vaccination.

8.1.9 **TRIAL #9:** ----------

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8.1.10.**TRIAL #10:** (A clinical study report was provided.) **HAV-126 – Open study to evaluate the immunogenicity and reactogenicity of SmithKlineBeecham's inactivated hepatitis A vaccine containing 720 EL.U of antigen per half mL dose injected according to a 0, 6 month schedule healthy infants in either anti-HAV negative or positive mothers.** This study was conducted in Naples, Italy from 5/30/93- 8/28/94. The infants were vaccinated at 5 and 11 months. There was a small number of subjects (total N=60), a small number of evaluable subjects for whom immunogenicity results were available after 1 dose (N=43) and after a second dose (N=33), and the subjects were 5 months of age at the time of the first dose of HAVRIX). The vaccine appeared immunogenic in all subjects, although less so in those infants born to seropositive mothers as compared to those infants born to seronegative mothers. There were no SAEs reported. The small number of subjects and the age at the first dose of HAVRIX preclude use of these data in extending use of the vaccine in an even younger age group (i.e., 5 months of age).

8.1.11 TRIAL #11: HAV-206 - An open multicenter post-marketing surveillance study of the inactivated hepatitis A vaccine (HAVRIX), injected according to the prescribing information enclosed, in healthy children and adults.

This trial was conducted in India and from 3/5/99-4/14/00, and was considered a Phase IV study. The total number of subjects enrolled was 502. The report provided did not separate out the children 1-2 years of age from older children, and some of the children received different formulations from the one studies in HAV-210. There were no adverse events that were considered serious.

9. **Overview of Efficacy (Immunogenicity)**

9.1 Indication: Extend use down to 12 months of age from 24 months of age

9.1.1 Methods: As noted in the Executive Summary, efficacy was based on the evaluation of immunogenicity data obtained in clinical trials in subjects 11-25 months of age. The pivotal protocol, HAV-210, provides the bulk of the immunogenicity data reviewed for this indication (632 subjects < 24 months of age). Protocols HAV-188, -181, and -204 provided supportive evidence for efficacy in children < 2 years of age. Together, these studies contributed immunogenicity data for 309 subjects after dose 1 and 264 subjects after dose 2 for those < 24 months of age.

The supportive studies also demonstrated that the vaccine was immunogenic in children down to 12 months of age, and specifically, these studies also demonstrated that antibody levels were elicited that were expected to be protective against hepatitis A disease even in children who were initially seropositive. However, the ----------for HAV-210, and there were differing amounts of ---------- in the product used in some of these studies.

The other trials provided additional subjects for safety only.

Overall, these studies taken together provide evidence that nearly 100% of subjects in the 12-23 month old age group will attain seropositivity (and therefore expected protection) if they receive 2 doses of HAVRIX at a 6-month interval. The subjects who were initially seropositive had somewhat lower GMTs at 1 month after the second dose of HAVRIX when compared to those who were initially seronegative, but most had antibody levels that would be expected to provide protection against hepatitis A disease. The duration of the immune response in this population is not known at this time.

There were also data provided to support the coadminstration of HAVRIX with Haemophilus influenzae b PRP-T vaccine at 15 months, but further studies will be necessary to provide data on the coadministration with other commonly administered pediatric vaccines.
Several studies are ongoing that should provide additional data to assess whether MMRII, VARIVAX, PREVNAR, or DTaP may be coadministered with HAVRIX without a negative impact on the immune responses to any of the antigens in these vaccines. One of these studies will also provide additional data on the coadministration of HAVRIX with HIB vaccine.

10. Overview of Safety

10.1 **Safety Database:** Number of Subjects, Type of Subjects, Extent of Exposure
In HAV-210, there were 1028 subjects in the ATP cohort for reactogenicity/safety from 11 months – 25 months. There were 935 children between 11-24 months of age.

In HAV-181, there were 121 children postdose 2 (variable coadministrations without control).
In HAV-188, there were 100 children with postdose 1 data only (coadministration with no control).
In HAV-204, there were 120 children with postdose 2 data (seronegatives), although 67 of these children were < 2 years of age at the time of the second dose of HAVRIX (and all were < 2 years of age at the time of the first dose of HAVRIX).
In these studies, solicited local and systemic adverse events were followed for approximately four days after vaccination and were similar. Unsolicited adverse events were followed for approximately 31 days after each vaccination, and serious adverse events were generally reported for the duration of each study.

The major safety evaluation comes from HAV-210. There are safety data for any dose in 100% of all groups (N=1084), and from 935 subjects , 24 months of age. For HAV-210, the 11-13 month old age group had a higher incidence of solicited general symptoms compared with those in the 15-18 month old age group and the 23-25 month old age group in the 4 days after each vaccination. This was true for Dose 1 and Dose 2. In all groups, there was a lower incidence of general symptoms postdose 2 as compared with posstdose 1. Incidences of solicited local symptoms were similar after each dose for all groups.

Of the solicited local adverse events (pain, tenderness, and swelling), pain and redness were the most common specific solicited local adverse events, but the vast majority were mild to moderate in intensity, and very few subjects ($\leq$ 1.7% in any group) experienced a Grade 3 local adverse event.

Of the solicited systemic adverse events (drowsiness, irritability, loss of appetite, temperature), the most common systemic adverse event was irritability. The majority of systemic symptoms were mild to moderate in intensity, and very few of the subjects ($\leq$ 5.2% in any group) experienced a Grade 3 systemic adverse event. The majority of fevers were mild to moderate, and $\leq$ 5.2% of subjects experienced a Grade 3 Temperature ($\geq$ 39.5 deg C), and $\leq$ 1.9% of doses were followed by a Grade 3 Temperature.

There was statistically more drowsiness and loss of appetite when Hib-PRP-T and Infanrix were administered with HAVRIX as compared to when Hib-PRP-T and Infanrix were administered without HAVRIX in children 15-18 months of age. There was statistically more drowsiness, irritability, and loss of appetite when Hib-PRP-T and Infanrix were administered with HAVRIX, as compared to when HAVRIX was administered alone to children 15-18 months of age. There are no data to compare adverse events when Hib-PRP-T is given with HAVRIX (without Infanrix) as compared to when HAVRIX is administered alone in children 15-18 months of age. Most of these systemic adverse events were mild to moderate in intensity.

Local and systemic adverse events in the three supportive trials, HAV-181, -188, and -204, were similar in nature. Duration of the adverse events in one trial was 1-2 days, and most were mild to moderate in intensity.

There was no identifiable pattern the occurrence of serious adverse events noted in HAV-210, or in the three supportive trials. In HAV-210, one subject experienced a febrile seizure within 4 days of vaccination, but that child was being treated for otitis media at the time of vaccination, and was diagnosed with a viral illness at the time of the seizure. The two children who experienced their first episode of asthma after vaccination after a vaccination had these episodes occur some time after the dose was administered, and each of these children had a family history of asthma. There was no clear relationship to vaccine with the episodes of insulin dependent diabetes mellitus and Kawasaki's disease.

The most common unsolicited symptoms within 4 days of vaccination were upper respiratory infection, otitis media, diarrhea, rhinitis, viral infection, fever, vomiting, injury and coughing. Others included injection site reactions, rash, toothache, contact dermatitis, allergy, eczema, constipation, pneumonia, moniliasis, sinusitis, stridor and bronchitis.

The most common Grade 3 unsolicited AEs included conjunctivitis, otitis media, viral infection, fever, vomiting, diarrhea, stridor, pharyngitis, bronchitis, and injection site reactions. These all had incidences $\leq$ 3.3% (and for most were $\leq$ 2.3%).

10.3.1 Deaths: There was one death from accidental ---------- in HAV-210 some time after receipt of HAVRIX. There was no apparent relationship to vaccination. (The one death in HAV-181 occurred after enrollment, but before the child received any vaccines).

10.3.2 Other Significant Events: none others.

10.3.3 Dropouts: see HAV-210

10.4 Other Safety Findings: none others.

10.4.1 ADR Incidence Tables: see HAV-210

10.4.2 Lab Findings, Vital Signs, EKGs, Special Diagnostic Studies: These were not collected in most of the studies, except for Temperatures for the 4 days after each vaccination.

10.4.3 Product-Demographic Interactions: No interactions that might predict greater risk of adverse effects in certain demographic parameters with this product were detected.

10.4.4 Product-Disease Interactions: The subjects in the pivotal trial were healthy, and there were no apparent product-disease interactions.

10.4.5 Product-Product Interactions: The efficacy of concomitant administration of commonly administered childhood vaccines is discussed in HAV-210. HAVRIX does not appear to interfere with the immune response to the Hib-PRP-T when

given together at 15-18 months of age. There are insufficient data at the present time to support coadministration of HAVRIX with DTaP containing vaccines.

10.4.6 Immunogenicity: See HAV-210 for a full discussion.

10.4.7 Human Carcinogenicity: HAVRIX has not been evaluated for its oncogenic potential.

10.4.8 Withdrawal Phenomena/Abuse Potential: Not relevant.

10.4.9 Human Reproduction and Pregnancy Data: HAVRIX is classified as a Pregnancy Category C pharmaceutical. Animal reproduction studies have not been conducted with HAVRIX. HAVRIX should be given to a pregnant woman only if clearly related. There are no data on breastfeeding with this product.

10.4.10 Assessment of Effect on Growth: HAVRIX has not been tested for its effect on growth.

10.4.11 Overdose Experience: There are no data to address overdose experience.

10.4.12 Person-to-person transmission, shedding: This is not relevant since this is an inactivated product.

10.5 Safety Conclusions

No major safety concerns were identified from the available safety data in 12-23 month old children for HAV-210. Supportive data for this conclusion is provided for HAV-188, HAV-181, and HAV-204. The total safety database for this cohort submitted in support of the new indication includes app. 935 children who are < 24 months of age who received 2 doses of HAVRIX (and 1084 children which include children who are up to 25 months of age). The ability to detect AEs that occur infrequently and are specific for the age group is limited. There are several ongoing coadministration studies which are expected to provide additional subjects < 2 years of age, and the sponsor has agreed to provide safety data for approximately 3000 subjects < 24 months of age (total includes subjects in the ongoing coadministration studies). These additional studies will assess coadministration of HAVRIX with PREVNAR, HAVRIX + MMRII+ VARIVAX, and HAVRIX + DTaP+OmniHIB.

11.Additional Clinical Issues

A major clinical issue for this age group involves coadministration of HAVRIX with other commonly administered childhood vaccines. In Protocol HAV-210, it was demonstrated that HAVRIX may be given with OmniHIB in 15-18 month old age group without negatively impacting the immune response to either antigen (i.e., PRP or hepatitis A).

As noted above, there are three ongoing studies which will assess the immunogenicity and safety when HAVRIX is given with other pediatric vaccines, including PREVNAR, DTaP+HIB and MMRII+VARIVAX.

11.1 Directions for Use

For children and adolescents 12 months through 18 years of age: A primary dose of 720 EL.U/0.5 mL is given at Month 0, and a booster dose of 720 El.U/0.5 mL is given at IM at Month 6 or 12. The vaccine is provided in a single dose vial or prefilled disposable vial.

In HAV-210, HAV-188, HAV-181 the subjects were given 0.5 mL IM. In HAV-204, the vaccine was given 0.5 mL IM deltoid. In HAV-127, HAV-119, HAV-145, the dose was given SC. In HAV-118 and HAV-206, the dose was given IM.

11.2 Dose Regimens and Administration

In the pivotal study, HAVRIX was given IM in the thigh. In the supportive studies HAV-188, HAV-181, HAV-204, HAVRIX was given IM as well. The proposed dosage and administration describes only intramuscular use.

In several of the other studies (HAV-116, 119, 132) the doses were given SC.

In one study (HAV-206), different doses were given than what is administered in the pivotal trial and what is recommended n the label.

In several studies, the formulation used includes a ---------- compared to 0.25 mg/dose in the present formulation.

In HAV-118, one subject received the IM dose 6 days before the subject's second birthday.

11.3 Special Populations

The pivotal study and main supportive studies included healthy children 11-25 months of age.

Individual subjects with hemophilia were studied in the other protocols, but these subjects received vaccine SC, and safety in children 11-23 months of age with this disease cannot be assessed from the very limited number of subjects.

11.4 Pediatrics

The supplement presents data to support the administration to children as young as 12 months of age. The vaccine's reactogenicity appears acceptable. The vaccine has been shown to be immunogenic down to 12 months of age.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new drug regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless the requirement is waived or deferred. The data provided in the BLA is sufficient to assess the safety and effectiveness for the claimed indication in individuals 12 months and older. Studies demonstrating safety and effectiveness in individuals < 12 months of age are deferred ----------. The status of the post-marketing commitments will need to be reported annually according to 21 CFR 601.70.

12.Conclusions – Overall

Available data appear adequate to support the safety and efficacy of HAVRIX in the 12-23 month old age group. The conclusion about efficacy is based on the immunogenicity data, in which subjects with detectable anti-HAV antibodies are expected to be protected against hepatitis A disease. There was an approximately 100% seropositvity rate in the target age group after two doses of the vaccine. Of interest, subjects with evidence of seropositvity at the time of first vaccination (presumably related to transfer of maternal antibodies) were shown to develop anti-HAV antibodies after two doses of the vaccine at a rate near 100%, although the GMCs were somewhat lower (not statistically different) compared to children who were initially seronegative. Also, the main study demonstrated that HAVRIX may be

coadministered with Hib vaccine (PRP-T) at 15 – 18 months of age without negatively impacting on the seroprotection against HIB disease at one month after vaccination, and without negatively impacting on the response to hepatitis A antigen after two doses of HAVRIX. There were insufficient data for assessing the immunogenicity for coadministration of HAVRIX with a DTaP-containing vaccine.

The safety data demonstrate that the most common solicited local symptoms in this age group were pain and redness, and the most common general solicited symptom was generally irritability/fussiness. The incidence of grade 3 fever (defined as $\geq$ 103.1° F rectally) was < 2% after any dose in the 4 days after vaccination. Unsolicited adverse events included commonly seen illnesses in this age group, including URI, otitis media, diarrhea, rhinitis, viral infections, and vomiting. The children with a serious adverse event after vaccination most often had an associated illness. The adverse event rates were somewhat higher when HAVRIX was administered with INFANRIX and OmniHIB.

The size of the overall safety database is somewhat limited, although the pivotal study provides safety data in 935 subjects in this age group. The supportive studies provide safety information in 341 additional subjects between the ages of 1-2 years of age after any dose of HAVRIX, although approximately 220 of these children were given variable coadministered vaccines without comparison to controls who received HAVRIX alone. Additional safety data and immunogenicity data will be obtained from the ongoing coadministration studies, which will bring the total number of children in this age group to app. 3000. CBER has received a letter regarding the Sponsor's agreement to complete the ongoing coadminstration studies (Amendment 3, submitted 10/11/05).

13. Recommendations

13.1 Approval Recommendations

The clinical data provided supports approval of HAVRIX down to 12 months of age.

13.2 Recommendations on Post-Marketing Actions: continuation and completion of ongoing coadministration studies.

13.3 Labeling

The label was changed to achieve consistency with CBER's current guidance on the intent and format of package inserts, and to include the new indication for 12-23 month old children. Language was clarified regarding the coadministration of HAVRIX with other pediatric vaccines. The final clean label was reviewed and found acceptable. It is noted that a rare adverse event, thrombocytopenia, which has been noted in previous reports (not in studies submitted with this supplement), has been added to the label as well. Changes were added to the Geriatric Subsection included in a separate supplement to the BLA (103475/5100), and in accordance with guidelines provided in the CFR (21 CFR 201.57(f)(10).

14. **Comments and Questions for the Applicant**

CBER requests that the ongoing coadministration study reports and postmarketing commitments be submitted to IND ------ when completed.