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From: Nancy B. Miller, M.D.
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Subject: Final Clinical Review of Supplemental Biologics License Application for Hepatitis A vaccine, purified inactivated (STN 103606 VAQTA), manufactured by Merck & Co., Inc.

To: BLA STN# 103606/5049

Through: Antonia Geber, M.D., Team Leader
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cc: Gopa Raychaudhuri, Ph.D.
Gale Heavner, R.N.

1. **Title and General Information**

1.1 **Title:** Medical Officer's Review

1.1.1 **STN BLA** 103606/5049

1.1.2 **Related INDs:** -----

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

1.1.4 **Submission Date:** 10/31/03

1.1.5 **Review Completed:** 6/22/05

1.2 **Product Name**

1.2.1 **Proper Name:** Hepatitis A Vaccine, Purified, Inactivated

1.2.2 **Trade Name:** VAQTA

1.2.3 **Product Formulation:** VAQTA is an inactivated whole virus vaccine derived from hepatitis A virus (HAV) grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. It is formalin inactivated. One mL of the vaccine contains approximately 50 units of hepatitis A virus antigen, which is purified and formulated without a preservative. The 50U of VAQTA contains < 0.1 mcg of non-viral protein, < $4X10^6$ mcg of DNA, < 10^{-4} bovine albumin, and < 0.8 mcg of formaldehyde.

Pediatric/Adolescent Formulation: Each 0.5 mL dose contains approximately 25 units of hepatitis A virus antigen adsorbed onto approximately .225 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 35 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Adult Formulation: Each 1.0 mL dose contains approximately 50 units of Hepatitis A virus antigen adsorbed onto approximately 0.45 mg aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 70 mcg of sodium borate as a pH stabilizer in 0.9% sodium chloride.

1.3 **Applicant:** Merck & Co., Inc.

1.4 **Pharmacologic Category**: Vaccine

1.5 **Proposed Indication:** This supplement was submitted to support extension of the lower age limit for administration to 12 months (from 24 months).

1.6 **Proposed Population:** 12 months of age upwards

1.7 **Dosage Forms and Routes of Administration:**

VAQTA for Pediatric/Adolescent use is supplied as 25U/0.5 mL of hepatitis A virus protein in a 0.5 mL vial. It is also supplied as 25U/0.5 mL of hepatitis A virus protein in a 0.5 mL prefilled syringe, with a 5/8-inch needle.

VAQTA for Adult use is supplied as 50U/1mL of hepatitis A virus protein in a 1 ML single dose vial. It is also supplied as 50U/1mL of hepatitis A virus protein in a 1 mL single dose prefilled syringe, with a one-inch needle.

The vaccine is administered intramuscularly. In toddlers and older children, the vaccine may be administered in the deltoid or the anterolateral thigh. In adults, the vaccine may be administered in the deltoid.

Two doses are given at 0 and 6 months.

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3. **Executive Summary**

This BLA supplement proposes to expand the age indication for VAQTA down to 12 months of age from 24 months of age. The studies supporting this change in indication included Protocol 043, "A Study of the Safety and Tolerability of a 2-dose regimen of 25U/0.5 mL VAQTA in Healthy Children and Adolescents", and Protocol 057, "An Open, Randomized Multicenter of the Safety, Tolerability and Immunogenicity of VAQTA Given Concomitantly versus Nonconcomitantly with Other Pediatric Vaccines in Children app. 12 Months of age." Protocol 043 included 89 children 12-23 months of age in Monroe, NY, and Protocol 057 included 617 children 12-23 months of age at 14 centers throughout the US. Therefore, the total safety database included 706 children 12-23 months of age.

Clinical endpoint efficacy studies of VAQTA in children < 2 years of age were not conducted in support of this application. Instead, demonstration of efficacy was based on the evaluation of immunogenicity data obtained in clinical trials in subjects 12 months to 23 months of age. The presence of hepatitis A antibody was considered as a demonstration of protection and similarities of the immune response was established between 12 month old children and children 2-3 years of age (historical control).

For initial licensure in 1996, the protective efficacy, immunogenicity, and safety of VAQTA were evaluated in a randomized, placebo-controlled study involving 1037 susceptible children 2-16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). In this study, 99% of children who were initially seronegative, seroconversion within 4 weeks of vaccination after a single dose of VAQTA containing app. 25U/0.5mL. In subjects who were initially seronegative, the protective efficacy of a single dose of VAQTA was 100% (with 21 cases [$\geq$50 days after vaccination] of hepatitis A occurring in the placebo group and 0 cases in the vaccine group.) Further, 28 cases of hepatitis A occurred in the placebo group $\geq$30 days after vaccination and 0 cases in the vaccine group. In this study, the onset of seroconversion was shown to parallel the onset of protection against clinical hepatitis A disease. In a long term follow-up out to 9 years, there have been no cases of hepatitis A $\geq$ 50 days after vaccination. The continued long-term protection were supported by data published in: Werzberger, A. et al: Vaccine 20;1699-1701,2002. A reprint of this publication was provided within the current supplement. In combined clinical studies in children and adolescents 2 through 18 years of age, 97% (N=1230, 95% CI: 96%, 98%) and 100% (N=1057; 95% CI: 99.5%, 100%) of subjects seroconverted after the first and second doses with a GMT of 43 mIU/mL (95% CI: 40, 45) and 10,077 mIU/mL (95% CI: 9394, 10,801), respectively. The efficacy of VAQTA in older age groups was based on immunogenicity measured 4-6 weeks after vaccination for children up to18 years of age, and in combined clinical studies in adults 19 years and older.

For the new label indication, immunogenicity was studied in Protocol 057. In this study, children app. 12 months of age given VAQTA x 2 doses alone (6 months apart) had acceptable seropositivity rates to hepatitis A which were similar to those seen historically in children 2-3 years of age after dose 2. Since routine pediatric vaccines are administered in this age group, this study also included assessments of the effect of concomitant vaccinations. They also demonstrated that hepatitis A seropositivity rates 6 weeks postdose 1 are similar when VAQTA was given with MMRII + VARIVAX versus when VAQTA was given alone. It was also noted that postdose hepatitis A seropositivity

rates are similar when VAQTA is given with TRIPEDIA (+/- polio) versus when VAQTA is given alone. In addition, seroconversion rates for measles, mumps, and rubella at 6 weeks postvaccination with VAQTA + MMRII + VARIVAX were similar to rates seen historically when MMRII + VARIVAX are given without VAQTA. The Sponsor has not demonstrated that the percentage of children with $\geq$ 5gpELISA units for Varicella 6 weeks after MMRII + VARIVAX, when given with VAQTA, were similar to corresponding response rates historically when MMRII + VARIVAX were given without VAQTA. The immunogenicity results and assays used to assess immune responses following receipt of VARIVAX given concomitantly with VAQTA were reviewed by Dr. Philip Krause, M.D. Please refer to his review for an assessment of these responses. The clinical trial was not adequately designed to assess the responses to the pertussis components following receipt of TRIPEDIA. The sponsor failed to meet the pre-specified endpoint with regards to expected four-fold responses to PT based on historical data. However, the data were not interpretable because the children enrolled in the studies had not received four consecutive doses of TRIPEDIA and the assays were not adequately validated (assay reviews by Bruce Meade, Ph.D. Please refer to his review for an evaluation of the performance of the pertussis assays No studies were conducted with PREVNAR or Haemophilus influenza b- conjugate containing vaccines.
Safety was assessed in both protocols. The safety follow-up periods in Protocol 057 were 42 days for postdose 1 adverse events (because live vaccines were given in Groups 1 and 2 at either of these timepoints) and 14 days for postdose 2 adverse events. Postdose 1, Groups 3 and 4 received VAQTA alone. Injection site adverse events ranged from 2-9.5%. Systemic adverse events ranged from 54.4%-59.3%. When VAQTA was given with MMRII + VARIVAX, 8.1%-10.7% had injection site adverse events., and 56.1-62.2% had systemic adverse events. Postdose 2, Groups 2 and 4 received VAQTA alone. 6.1%- 7.4% had injection site adverse events, and 29.5% - 31.6% had systemic adverse events. Groups 1 and 3 received VAQTA dose 2 + TRIPEDIA +/- polio, and 13.3%-19.7% had injection site adverse events, and 35-37% had systemic adverse events. There were observationally more systemic adverse events noted after the first dose compared with the second dose.

The most common local adverse events after Dose 1 or Dose 2 included pain/tenderness/soreness, erythema, swelling and warmth. For subjects who received VAQTA alone at Visit 1 (Groups 2 and 4), the most common systemic adverse event were fever (23.1%), URI (15.6%), and rhinorrhea (7.5%). For subjects who received VAQTA alone at Visit 3, 8.1% had fever, 6.6% had URI, 5.1% had otitis media, and 5.1% had irritability. Therefore, the proportion of subjects experiencing systemic adverse events after either dose of VAQTA alone was small. At CBER's request. additional information relating to the severity of adverse events in tabular presentation was submitted in the first Complete Response letter. Most adverse events were noted to be mild to moderate. Only one subject discontinued due to an adverse events (crying, rhinorrhea).

Serious Adverse Events: There were 14 serious adverse events, and two were considered study vaccine related. One subject had a febrile seizure 9 days after MMRII and VARIVAX (and 51 days after VAQTA dose 1), which the investigator judged as related

to receipt of MMRII+VARIVAX (subject had vesicular rash at about the same time), and one subject had a febrile seizure 9 days after receiving MMRII + VARIVAX+VAQTA. This subject was being treated for an otitis media at the time of vaccination
.
In Protocol 043, a post hoc analysis was done to compare the adverse events in the 12-23 month old age group with the 2-16 year old age group, and although there was a slightly higher proportion of subjects in the younger age group with adverse events, the proportions were similar.

A post-hoc combined safety and immunogenicity analysis of studies 043 and 057 was performed as the methodology for collecting AEs were similar in both studies and the populations were similar. The safety profile in the combined analysis was similar to that observed in the two separate studies. Subjects 12-23 months of age exhibited high levels of responses following two doses of 25 U hepatitis A protein/0.5 mL dose of VAQTA given as a two dose regimen at 0 and 6 months.

The proposed dosing regimen will be the same dose given to children $\geq$ 2 years of age, i.e., 25U hepatitis A virus protein/0.5mL, to be given in 2 doses IM, at least 6 months apart.

The drug-drug interactions of concern include the other commonly administered pediatric vaccines in this age group. The conclusion is that this supplement is approvable and that VAQTA may be used in children down to the age of 12 months. VAQTA may be administered with MMRII without a negative impact on the immune response to any of the antigens. Post-marketing studies will be conducted to provide additional safety data in 3000 subjects 12-23 months of age in order to provide additional safety data in this age cohort. These post-marketing studies will also assess the concurrent administration of VAQTA, PedvaxHIB and DTaP, VAQTA and PREVNAR and PROQUAD (a varicella-containing vaccine with MMRII).

4. **Significant Findings from Other Review Disciplines**

4.1 **Chemistry, Manufacturing and Controls (CMC):** There were several reviews of the assays used in one of the studies for this supplement, Protocol 057. These included the use of two hepatitis A antibody assays. The review team members responsible for the hepatitis A antibody assays concluded that they were sufficiently similar and results from both assays could be combined in a single analysis of immunogenicity responses to VAQTA.

As noted above, responses to the VARIVAX administered concomitantly with VAQTA were lower than anticipated. The review team identified that the results of the assay for VARIVAX appeared variable over time. Reviewers assigned to this portion of the review could not definitively determine the reasons for the discrepant results and thus the data from this study with regards to VARIVAX response were assessed as being uninterpretable

In addition, the assays used for the anti-polio titers was deemed appropriate. Assays for measles, mumps and rubella was also noted to be appropriate. Because subjects did not receive TRIPEDIA but rather were enrolled with prior receipt of

three doses of any manufacturer's DTaP and/or DTP for their primary immunization vaccination, and some subjects had received DTP, further evaluation of the pertussis assays were not requested. Insufficient information was provided to assess the tetanus and diphtheria assays.

4.2 **Animal Pharmacology/Toxicology:** No additional data.

5. **Clinical and Regulatory Background**

5.1 **Disease Studied and Available Interventions:**

VAQTA 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.

HAVRIX is a U.S. licensed inactivated hepatitis A vaccine, manufactured by GSK. It is indicated for subjects 2 years and older and contains 2-phenoxyethanol as a preservative. HAVRIX is also approved as a component of the combination vaccine TWINRIX, which is indicated for those 18 years of age and older.

5.2 **Important Information from Pharmacologically Related Products, Including Marketed Products**

HAVRIX, as noted above, is another U.S. licensed vaccine for the prevention of Hepatitis A. It is indicated for subjects 2 years of age and above.

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

VAQTA has been licensed for use in subjects 2 years and above since 1996. Results of a clinical ednpoint study to assess the safety and efficacy of the product in subjects 2-16 years of age are described in the label. Efficacy in those over 16 years of age was evaluated by assessing the immunogenicity response after 2 doses of VAQTA. Safety data are also presented in the label for subjects 2 years and older. Adverse events identified in association with the administration of VAQTA from post-marketing safety reports include Guillain-Barre, cerebellar ataxia, and thrombocytopenia.

5.4 **Regulatory Background Information**

Initial licensure	3/26/96
Protocol 043 Submission Revision 01 Revision 02 Revision 03	 Sent 1/30/96 Sent 5/19/97 Sent 3/31/98 Sent 3/13/02
Protocol 057 Submission	 Sent 1/19/99
Supplement to lower age indication to 12 months Submission Deficiencies Identified letter sent Complete Response sent to Sponsor Sponsor Responses to Complete Response Letter Second Complete Response sent to Sponsor Sponsor Responses to Second Complete Response Letter	 10/31/03 1/15/04 8/13/04 12/1/04 5/27/05 6/15/05

Approval	

6. **Clinical Data Sources, Review Strategy and Data Integrity**

6.1 **Material Reviewed**

Two clinical study reports were submitted in support of lowering the age indication of this vaccine from 2 years to 12 months.

Protocol 043: A Study of the Safety and Tolerability of a 2-dose Regimen of 25U/0.5 mL of VAQTA in Healthy Children and Adolescents. This was an open, single center study in which the safety and tolerability of VAQTA (25U/0.5 mL) were evaluated in healthy children and adolescents 1-16 years of age. The study site was the Kiryas Joel community, a Hassidic Jewish community in upstate NY, and the principal investigator was Dr. Werzberger, who conducted the Monroe Efficacy Study used to support the initial licensure of this vaccine.

The number of subjects is shown below (Protocol 043, p. 10, Module 5, Volume 1/10):

	12-23 Months of age	2-16 years of age	Total
Entered	**89**	420	509
Male (age range)	**44 (12-23 months)**	206 (2-16 years)	250 (1-16 years)
Female (age range)	**45 (12-23 months)**	214 (2-16 years)	259 (1-16 years)
Completed	**81**	386	467
Discontinued (Total)	**8**	34	42
D/C due to Clinical AE	**0**	0	0
D/C due to deviation from protocol	**0**	5	5
Lost to follow-up	**8**	29	37

The number of subjects that would be used to assess safety in the population 12-23 months is 89, since that is the number of subjects who received at least one dose of vaccine.

Protocol 057: An Open, Randomized, Multicenter, Study of the Safety, Tolerability and Immunogenicity of VAQTA Given Concomitantly versus Nonconcomitantly with Other Pediatric Vaccines in Children Approximately 12 Months of Age. This was an open, randomized, multicenter study in which healthy children were assigned to one of four groups. The study was conducted at 14 study sites throughout the US. Treatments received for each group are shown in the table below.

Visit	Group 1	Group 2	Group 3	Group 4
V1 (D0) App. 12 months	VAQTA MMRII VARIVAX	VAQTA MMRII VARIVAX	VAQTA	VAQTA
V2 (Wk. 6) App. 13.5 months	No vaccine	No vaccine	MMRII VARIVAX	MMRII VARIVAX
V3 (Wk. 24) App. 18 months	VAQTA TRIPEDIA Optional IPOL or ORIMUNE	VAQTA	VAQTA TRIPEDIA Optional IPOL or ORIMUNE	VAQTA
V4 (Wk. 28) App. 19 months	No vaccine	TRIPEDIA Optional IPOL or ORIMUNE	No vaccine	TRIPEDIA Optional IPOL or ORIMUNE

The next table contains the number of subjects in each group.

Numbers	Group 1	Group 2	Group 3	Group 4	**Total**
Entered	156	153	156	152	**617**
Male (age range)	86 (11-13 months)	78 (11-13 months)	84 (11-13 months)	83 (11-13 months)	**331 (11-13 months)**
Female (age range)	70 (11-13 months)	75 (11-13 months)	72 (11-13 months)	69 (11-14 months)	**286 (11-14 months)**
Completed	127	124	125	127	**503**
Discontinued	29	29	31	25	**114**
Deviation	0	6	1	3	**10**
Refused further	9	9	6	5	**29**
Lost to f/u	20	13	23	16	**72**
Noncompliant	0	1	0	1	**2**

Clinical AE	0	0	1	0	**1**

Both tables are provided in Protocol 057, p. 21, Module 5, Volume 1/10.

6.1.1 **BLA Volume Numbers Which Serve as a Basis for the Clinical Review**
These include Module 2 (Volume 1) and Module 5 (Volumes 1, 2, 3, 4, 5, 6).

6.1.2 **Literature**
References from the Sponsor were included in Module 5.4, Volumes 7-10. The references cited in this review include the following:

CDC. Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the ACIP. MMWR 1999; 48(RR1-12):1-37
VAQTA Package Insert
Werzberger A et al. A Controlled trial of a formalin-inactivated hepatitis vaccine in healthy children. NEJM 327(7): 453-7, 1992
Werzberger A et al. Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' follow-up after the Monroe field trial of VAQTA. Vaccine 2002; 20:1699-1701

6.1.3 **Post-Marketing Experience**

A post-marketing safety study involving 42,110 people > 2 years of age who received 1 or 2 doses of VAQTA, which was conducted 4/1/97-12/31/98 at Kaiser Permanente Vaccine Study Center in Northern California, was resubmitted with this supplement (Module 5, Volume 6/10, Reference 12). This was previously reviewed. Multiple analyses were conducted for relative risks of adverse events collected before and after vaccination window time periods. The results have been previously incorporated into the label.

MARKED CONFIDENTIAL BY SPONSOR: Also included in the supplement in Module 5, Volume 6/10, Reference 11, is the MRL Worldwide Product Safety and Epidemiology Report: Periodic Safety Update Report #14 for VAQTA, dated 1/27/03 (covering the period 6/21/02 to 12/20/02. (The PSUR is noted to be confidential.) In this report, the Sponsor reported a 17- month old child who received VAQTA and typhoid vaccine. Within hours of receiving the vaccines, she developed a high fever to 105 ° F and developed febrile convulsions and was hospitalized. She recovered. Safety is monitored by the Sponsor on a continuing basis.

6.2 **Table of Clinical Studies**

Study	Countries	Trial Start	Trial End	Subject Age Range	N planned	N enrolled	Control	Follow-up duration	Formulation	Lot Numbers
043	US (Monroe, NY)	2/28/96	Primary - 4/4/97 Surveillance – through 2002	1-16 years	Initially 1000	509 (89 in 12-23 month olds; 420 in 2-16 years)	None	14 days after the 6 month dose 2, then yearly for 4 years surveillance for hepatitis A disease	**VAQTA** 25U/0.5 mL **VAQTA** 50U/1 mL	1339/C-Y552 1439/W-B692
057	US (multicenter)	12/29/98	5/7/01	12-23 months		617	Compared to historical controls	14 days after the 6 month dose 2	**VAQTA** 25U/0.5 mL (Merck) **MMRII** measles>=1000 TCID50, mumps>=20,000 TCID50 rubella >=1000 TCID/0.5 mL (Merck) Varuvax 3000pfu/0.5mL (Merck) **TRIPEDIA** 6.7Lf diphtheria toxoid, 5 Lf tetanus toxoid, 46.8 mcg pertussis antigens/0.5 mL (Aventis Pasteur) **IPOL** 40D Ag U of Type 1, 8D Ag U of Type 2, and 32D Ag U of Type 3/0.5 mL (Aventis Pasteur) **ORIMUNE** 10(5.4-6.4) infectivity titers of Type 1, 10(4.5-5.5) infectivity titers of Type 2, and 10(5.2-6.2) infectivity titers of Type 3/0.5 mL (Lederle)	1314J, 1110H, 0047J, 1315J, 0702K 0173K, 1171H, 1781H, 1979H, 1174H, 0625 0764K, 1802H, 1048H, 0425J, 1050H 0949260, 7387BA, UO299AB N1032-1, N0498-1, R1329-2 0792M, 466-604

6.3 **Review Strategy**

The review was based on the two protocols, 043 and 057, noted above.

For Protocol 043, only the safety data for the 89 children 12-23 months of age were reviewed and considered for inclusion in the package insert. The Sponsor had

done a post-hoc analysis comparing the safety profile of the VAQTA in 12-23 month old children with the safety in 2-16 year old children.
For Protocol 057, all safety and immunogenicity data were considered. It is noted that in this trial, the safety of VAQTA given concomitantly was compared with MMR+VARIVAX as compared with VAQTA given nonconcomitantly with those vaccines at 12 months of age, as well as the safety of VAQTA given concomitantly with DTaP+/-IPOL or ORIMUNE as compared with VAQTA given nonconcomitantly with those vaccines at 18 months of age. Immune responses were compared to historical controls. For VAQTA, 2-3 year olds were chosen as the historical control. The immune responses to MMR+VARIVAX as well as DTaP were compared to historical controls. The immune responses to polio (either IPOL or ORIMUNE) were analyzed in a post-hoc analysis, and because of the variation in the priming doses and lack of control, the data were not considered for full evaluation.
The methodology and populations included in both studies were similar and safety was analyzed in a combined analysis as well. Immunogenicity was analyzed from Protocol 057 (there was no immunogenicity data in Protocol 043.)

6.4 **Good Clinical Practices and Data Integrity** – No apparent problems.

6.5 **Financial Disclosures:**
This was provided in Module 1, Volume 2/2. None of the investigators or subinvestigators are Merck employees. The reporting appears appropriate.

7. **Human Immunogenicity**
Both VAQTA and HAVRIX are highly immunogenic in persons $\geq$18 years.

Anti-HAV concentrations are measured in comparison with a WHO reference immunoglobulin reagents 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 (< 20 mIU/mL) 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 >20 mIU/mL or 33mIU/mL as measured by using radioimmunoassays. Clinical studies of VAQTA have historically used levels >10 mIU/mL as measured with a modified radioimmunoassay (HAVAB). In this supplement, a new assay was used to measure app. 15% of the anti-hepatitis A antibody tests ----------.

A follow-up by the principal investigator of the Monroe Efficacy Study in 2002 indicates that there have not been any further hepatitis A epidemics after 1991 (when vaccination started) and there have been no hepatitis A cases among vaccines $\geq$ 50 days after vaccination over 9 years time. A publication by Werzberger A, Mensch B, Nalin DR, Kuter BJ. Effectiveness of hepatitis A vaccine in a formerly frequently affected community: 9 years follow-up after the Monroe field trial of VAQTA.

Vaccine 2002;20:1699-701, describing these data were submitted to the supplement and reviewed by this reviewer.

Simultaneous administration with other vaccines: As noted in the label, limited data from studies conducted among adults indicate that VAQTA may be administered concomitantly with typhoid and yellow fever vaccines with similar immune responses for these vaccines, and comparable hepatitis A immune responses after the booster dose of VAQTA.

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 043** – A Study of the Safety and Tolerability of a 2-Dose Regimen of 25U/0.5 mL of VAQTA (Formalin Inactivated, Alum Adjuvanted Hepatitis A Vaccine) in Healthy Children and Adolescents.

8.1.1.1.1 **Objective/Rationale**

The primary objective was to determine the safety and tolerability of a 2-dose regimen of 25 U/0.5 mL of VAQTA in healthy children and adolescents 1-16 years of age. Other objectives included following the vaccinees every 6 months for a total of 5 years to see if hepatitis A disease occurs. If any cases of hepatitis A were to occur (which would be confirmed by laboratory testing), they would explore the relationship between the titers of subjects within 1 week of exposure in order to determine if exposure of a vaccine recipient to a case of hepatitis A would result in an anamnestic booster response in hepatitis A antibody level without clinical disease. (It is noted that there was only one subject who was exposed to hepatitis A disease, but serum samples were not obtained within 1 week of exposure. No other cases were reported.)

8.1.1.1.2 **Design Overview**

This was an open, single-center (Kiryas Joel, NY) in which healthy children and adolescents 1-16 years of age received 2 doses of VAQTA at Day 0 and Month 6. The treatment duration of the study was 6 months and surveillance continued for 5 years. [Dates of primary therapy period 2/28/96-4/4/97; surveillance 1997-2002].

8.1.1.1.3 **Population:** Healthy children 1-16 years of age

Inclusion Criteria: 1-16 years of age; no evidence of liver disease or active infection; no clinical history of previous hepatitis A infection; written consent from parent/legal guardian.

Exclusion Criteria: Clinical history of hepatitis A; allergy to any vaccine component; moderate or severe febrile illness >= 100 °F or 38 °C at time of vaccination; previous receipt of hepatitis A vaccine; receipt of any vaccine within 15 days prior to either injection; receipt of IG or blood derived product within 6 months prior to the first injection or plan to receive such a product 13 months thereafter; receipt of immunosuppressives; severe thrombocytopenia or any coagulation disorder; pregnancy or plan to conceive during study period; and condition which in the opinion of the investigator might have interfered with the evaluation of the study objectives.

No concomitant vaccinations were to be administered.

8.1.1.1.4 **Products Mandated by the Protocol**

Product: VAQTA (25U/0.5 mL) IM (deltoid). No placebo. The vaccine was supplied in either single dose vials containing app. 25 U viral antigen/0.5 mL or single dose vials containing 50 U/1 mL volume.

Table with Lot numbers for products used (Protocol 043, p. 22 Module 5, Volume 1/10)

	Lot #	Bulk #	Fill #	Dosage	Package
VAQTA	1439/W-B692	2032601	0500478	50U/1mL	1.2 mL fill single dose vials
VAQTA	1339/C-Y552	2013933	0608173	25U/0.5 mL	0.7 mL fill single dose vials

8.1.1.1.5 **Endpoints**

The **primary objective** was assessment of safety and tolerability of the vaccine in 1-16 year old subjects. Also assessed, which was not a preplanned objective, was a comparison of the safety of the vaccine in children 12-23 months of age to that observed those children 2-16 years of age. Injection site adverse events were to be reported x 5 days (day of vaccination and 4 days after) on vaccine report cards. Grading was to be reported as mild, moderate or severe. No measurements of injection site redness or swelling was to be done. Temperatures were to be done once per day x 5 days after vaccination (but it is noted that temperatures were assessed "qualitatively" in 88% of subjects, 6.5% by axillary method, 2.4% by oral method, 0.8% by otic method, and 2.4% by rectal thermometer.)

The **secondary objective** was to assess whether those who were vaccinated and then were later exposed to hepatitis A disease would develop an anamnestic response after exposure. Surveillance was done to be done at 6 months intervals, but was performed yearly instead. In addition, parents/guardians were to call the investigator within 1 week of exposure to hepatitis A. Only 1 blood sample was taken 4-8 weeks post-exposure to hepatitis A. In Protocol 043-03, follow-up surveillance was curtailed by 1 year (to 4 years) because further surveillance was not thought to provide additional information.

8.1.1.1.6 **Surveillance/Monitoring**

Parents were given a Vaccine Report Card on which to record Temperatures and injection site adverse events (specifically pain, swelling, warmth or redness) for 5 days total (day of vaccination and 4 days after each vaccination). Injection site adverse events were to be graded as none (no signs or symptoms of intolerance), mild (easily tolerated), moderate (causes interference with usual activity), and severe (inability to do usual activity). No measurements were done on the size of the redness and swelling.

Clinical adverse events that occurred within 14 days after each vaccination were obtained by phone 2 weeks after each vaccination (week 2, week 26). The investigator was responsible for assessing causality. Severity was to be recorded on the Case Report Form.

The parent/guardian was to contact the study site immediately if there was a serious adverse event. (passive)

Active surveillance for hepatitis A disease was conducted by telephone contact. The subjects (parents) were contacted every year after vaccination #2 (instead of every 6 months). Active surveillance was terminated in Amendment 043-01, and restarted with Amendment 043-02. Subjects were subsequently surveyed for 4 more years. One serum sample was obtained from one vaccinee exposed to hepatitis A disease for anti-hepatitis A antibody. As noted above, the follow-up was terminated 1 year early at 4 years.

8.1.1.1.7 **Statistical Considerations**

The age groups were not specifically defined in the original protocol, but in the clinical study report, the data are summarized separately for the purpose of assessing the safety of VAQTA in children younger than the currently approved age indication $\geq$ 2 years.

The number in the original protocol was 1000 subjects. This was decreased to 511 when enrollment was halted, because VAQTA was licensed 3/29/96. The trial was originally designed to collect safety data and disease surveillance data every 6 months x 2 years for the population in Monroe, NY.

A 2-sided 95% CI on the true proportion of subjects who report an adverse event after any injection (one or both) were to be provided. If the upper limit of this CI was $\leq$ 37%, it would be concluded that the adverse event rate is not greater than the highest experienced in a pediatric population and the vaccine will be judged safe and well tolerated. In the Clinical Study Report, they did this for the group as a whole. It is not clear what was the basis for selecting this margin of difference as being clinically significant.

8.1.1.2 **Results**

8.1.1.2.1 **Populations Enrolled/Analyzed**

Population enrolled – 511 1-16 year old subjects in Kiryas Joel, Monroe, NY. Analysis was done on the entire population, and also on the 12-23 month olds and the 2-16 year olds. 509 actually entered the study.
Serostatus was not obtained. (Antibody level to hepatitis A would only be done if exposure to hepatitis A occurred.)

Comparability of study groups: Safety of the vaccine in 12-23 month old children were compared to 2-16 year old children. This was conducted as a post hoc analysis.

Number per group: There were 89 subjects 12-23 months of age and 420 in the 2-16 years age group. The age breakdown for the younger age group was as follows: 12 months: 6 (1 lost to follow-up); 13 months: 7 (2 lost to follow-up); 14 months: 7 (1 lost to follow-up); 15 months: 9

16 months: 7; 17 months: 10; 18 months: 7 (1 lost to follow-up); 19 months: 5 (1 lost to follow-up); 20 months: 7; 21 months: 6
22 months: 8; 23 months: 10 (2 lost to follow-up)

Demographics: All children were part of a homogeneous group and were members of Hassidic Jewish community in upstate NY where the initial efficacy trial for VAQTA was done. There were 44 males in the 12-23 month old group, and 206 males in the 2-16 years. There were 45 females in the 12-23 month old group, and 214 females in the 2-16 year old group.
The results for the younger age group are bolded in the tables provided below.
Table 7 Summary of Subject Characteristics by Age Group (Protocol 043, p. 31, Module 5, Volume 1/10)

	VAQTA 12-23 months N=89	VAQTA 2-16 year old N=420	Total N=509
Gender			
Male	**44 (49.4%)**	206 (49%)	250 (49.1%)
Female	**45 (50.6%)**	214 (51%)	259 (50.9%)
Age			
Mean	**17.7 months**	4 years	3.5 years
SD	**3.5 months**	2.8 years	2.8 years
Median	**17 months**	3 years	3years
Range	**12-23 months**	2-16 years	1-16 years
Male	**12-23 months**	2-16 years	1-16 years
Female	**12-23 months**	2-16 years	1-16 years
Race/Ethnicity			
Caucasian	**89 (100%)**	420 (100%)	509 (100%)

Concomitant medicines: none

Protocol violations: All subjects who received at least one injection and had follow-up data were included in the safety and tolerability summaries.
AN06004 received the first dose of VAQTA, but participated in another clinical study.
AN06011 was inadvertently assigned a second AN 06411 and received 1 extra dose of VAQTA during the study for a total of 3 vaccinations. All data was consolidated under AN 06011.
AN06059 received the first dose of VAQTA, but then it was revealed that the subject had a prior dose of VAQTA and a history of Hepatitis A disease.
AN06325 and **AN06406** had a prior dose of VAQTA and a history of hepatitis A disease. **AN06325** and **AN06406** received the first dose of VAQTA, but participated in other clinical studies.

Table 5 shows the number and reasons for patients who discontinued (Protocol 043, p. 29, Module 5, Volume 1/10).

	VAQTA 12-23 month olds N=89	VAQTA 2-16 year olds N=420	Total N=509
Entered	**89**	420	509
Completed	**81 (91%)**	386 (91.9%)	467 (91.7%)
Discontinued	**8 (9%)**	34 (8.1%)	42 (8.3%)
Clinical AE	**0**	0	0
Deviation from protocol	**0**	5 (1.2%)	5(1%)
Lost to follow-up	**8(9%)**	29 (6.9%)	37 (7.3%)

8.1.1.2.2. **Efficacy Endpoints/Outcomes:** No efficacy endpoints/outcomes were included in this trial.

8.1.1.2.3. **Safety Outcomes**

There was a post-hoc comparison made between the 12-23 month old group and the 2-16 year old group. Adverse events were collected for 14 days after each vaccination (Vaccination 1 and Vaccination 2). Clinical follow-up was obtained for 509 subjects following Visit 1 and 468 subjects following Visit 2. These are shown in tabular forms. I have provided the results from both age groups in this review as well as the overall rates. Observational comparisons were performed between both groups.

The **proportions of subjects with 1+ clinical adverse event** following any visit were **18%** in the 12-23 month old group and 13.8% in the 2-16 year old group, and 14.5% overall.

The incidence of **injection site adverse events** were **9%** in the 12-23 month old group and 6% in the 2-16 year old group, and 6.5 % overall.

For the time period of **0-14 days after any vaccination** visit, the proportion of subjects with 1+ **systemic clinical adverse event** were **11.2%** in the 12-23 month old group, 9.8% in the 2-16 year old subjects, and 10% overall.

The incidence of **vaccine related adverse events** was **13.5%** in the 12-23 month old subjects, 9.5% in the 2-16 year old subjects, and 10.2% overall.

The occurrences of **injection site vaccine related adverse events** were **7.9%** in the 12-23 month old subjects, 6% in the 2-16 year old subjects, and 6.3% overall.

The incidences of **vaccine related systemic adverse events** were **7.9%** in the 12-23 month old subjects, 4.5% in the 2-16 year old subjects, and 5.1% overall.

Therefore, there were slightly more frequent adverse events in the 12-23 month old age group as compared to the 2-16 year old age group. The above results are shown in Table 9 (p. 35, Protocol 043, Module 5, Volume 1/10) below.

Table 9: Clinical AE Summary (Days 0-14 Following Any Vaccination Visit)

	VAQTA 12-23 month old subjects N=89	VAQTA 2-16 year old subjects N=420	Total N=509
Subjects with f/u	**89**	420	509
Subjects with AE	**16(18%)**	58(13.8%)	74(14.5%)
Injection site AE	**8(9%)**	25(6%)	33(6.5%)
Systemic AE	**10(11.2%)**	41(9.8%)	51(10%)
Subjects with VR AE	**12(13.5%)**	40(9.5%)	52(10.2%)
VR injection site AE	**7(7.9%)**	25(6%)	32(6.3%)
VR systemic AE	**7(7.9%)**	19(4.5%)	26(5.1%)
SAE	**0**	0	0
Died	**0**	0	0
Discontinued due to AE	**0**	0	0
Discontinued due to SAE	**0**	0	0

Specific Adverse Events:

Injection Site Adverse Events (Shown in **Table 10**, p. 38, Protocol 043, Module 5, Volume 1/10)- Days 0-4

After **Dose 1**, **6.8%** of the 12-23 month old subjects, 3.9% in the 2-16 year old age group, and 4.4% overall had injection site adverse events. The most

common injection site adverse events after dose 1 were pain/tenderness/soreness, with 3.4% in each group and overall. Swelling was reported by 4.5% in the 12-23 month old age group, and 1.4% in the 2-16 year old age group, and 2% overall. In the 12-23 month age group, all were mild to moderate in severity (presented in the CR response).
After **Dose 2, 2.5%** in the 12-23 month old age group, 2.6% in the 2-16 year old age group and 2.6% of the total had injection site adverse events. Therefore, there were fewer subjects with injection site adverse events after the 2nd dose of VAQTA. The most common injection site adverse events after dose 2 were pain/tenderness/soreness, with 1.3% in the 12-23 month olds, 1.8% in the 2-16 year olds, and 1.7% overall. In the 12-23 month age group, all were mild (presented in the CR response).
After **any vaccine dose**, **9%** in the 12-23 month olds, 6% in the 2-16 year olds, and 6.5% overall had an injection site adverse event. The most common injection site adverse events after any vaccination were pain/tenderness/soreness, swelling, erythema and warmth.
Pain/tenderness/soreness occurred in 4.5% of the 12-23 month olds, 4.8% in the 2-16 year olds, and 4.7% overall. Most were mild/moderate in intensity. Swelling occurred in 4.5% of the 12-23 month olds, 1.7% of the 2-16 year olds, and 2.2% overall. Most were mild to moderate in intensity and lasted 1-2 days. Erythema occurred in 1.1% of the 12-23 month olds, 1.2% of the 2-16 year olds, and 1.2% overall. Warmth occurred in 2.2% of the 12-23 month olds, 1.0% of the 2-16 year olds, and 1.2% overall. By observational comparison, the most common injection adverse events occurred in similar proportions in both age groups.

Appendix 4.6 (Protocol 043, p. 214, Module 5, Volume 1/10) shows the numbers of subjects with **specific injection site AEs (>0%) Days 0-4 following any vaccination visit**.

Appendix 4.6: N(%) with Specific Injection Site AEs (>0%) Days 0-4 following any Vaccination Visit

	VAQTA 12-23 Month olds N=89	VAQTA 2-16 year old subjects N=420	Total N=509
N	**89**	420	509
N with f/u	**89**	419	508
N with IS AE	**8(9%)**	25(6%)	33(6.5%)
Discoloration	**1(1.1%)**	2(0.5%)	3(0.6%)
Erythema	**1(1.1%)**	5(1.2%)	6(1.2%)
P/T/S	**4(4.5%)**	20(4.8%)	24(4.7%)
Rash	**0**	1(0.2%)	1(0.2%)
Swelling	**4(4.5%)**	7(1/7%)	11(2.2%)
Warmth	**2(2.2%)**	4(1%)	6(1.2%)

Percentages were calculated based on the number of subjects with follow-up after any vaccination visit.
Although a subject may have had w or more IS AEs, the subject is counted only once in the overall total.

Systemic Adverse Events

The data after **Dose 1** for **systemic adverse events** are presented for Days 0-14. [Table 11 (Protocol 043, p. 40, Module 5, Volume 1/10)] After Dose 1, **5.7%** of the 12-23 month olds and 5.5% of the 2-16 year olds had systemic adverse events. The most frequent adverse event after Dose 1 was fever. Fever occurred in 2.3% of the 12-23 month olds, 1.7% of the 2-16 year olds, and 1.8% overall after Dose 1. In the 12-23 month age group, other systemic adverse events

after Dose 1 were irritability (2.3%), emotional changes (1.1%), and upper respiratory infection (1.1%). Again, all were mild to moderate in severity.
The data after **Dose 2** for **systemic adverse events** are presented. [Table 12, (Protocol 043, p. 41, Module 5, Volume 1/10)] After Dose 2, **7.4%** of the 12-23 month olds, 4.9% of the 2-16 year olds, and 5.3% overall had systemic adverse events. The most common systemic adverse event after Dose 2 was fever. Fever occurred in 2.5% of the 12-23 month olds, 2.8% of the 2-16 year olds, and 2.8% overall after Dose 2. Other systemic adverse events seen in > 1% in the 12-23 month age group included a rash (2.5%), lymphadenopathy (1.2%), irritability (1.2%), and upper respiratory infection (1.2%). All were mild to moderate in severity (from CR response).
The data after **any dose** for **systemic adverse events** are presented. [Table 13 (Protocol 043, p. 43, Module 5, Volume 1/10)] After any dose, **11.2%** of the 12-23 month olds, 9.8% of the 2-16 year olds, and 10% overall had systemic adverse events. The most common systemic adverse event after any vaccine dose was fever, which was mild to moderate and lasted 1-3 days. Fever occurred in 4.5% of the 12-23 month olds, 4% of the 2-16 year olds, and 4.1% overall. For the 12-23 month age group, other common systemic adverse events after any dose included irritability (3.4%), emotional changes (1.1%), upper respiratory infection (2.2%) and rash (2.2%).

The data for **elevated Temperatures >= 102 ° F, Days 0-4,** are presented. [Table 14, (Protocol 043, p. 45, Module 5, Volume 1/10)] Temperatures taken rectally were changed to oral by subtracting 1 °F; Temperatures taken by the axillary method were changed to oral by adding 1 °F; Temperatures taken by otic method were recorded as reported.
After **Dose 1**, such temperatures were seen in **2.2%** of the 12-23 month olds; 1.2% of the 2-16 year olds; and 1.4% overall.
After **Dose 2**, such temperatures were seen in **2.5%** of the 12 –23 month olds, 2.3% of the 2-16 year olds; and 2.4% overall.
After **any dose**, such temperatures were seen in **4.5%** of the 12-23 month olds, 3.1% of the 2-16 year olds and 3.3% overall.

CBER requested additional data regarding increased temperatures at 0-4 days after vaccination. The Sponsor provided this information in the CR response. After Dose 1, in the 12-23 month age group, 92.1% of subjects had normal Ts; 5.6% had Ts < 100.4°F; 1.1% had Ts 101.3°F to < 102.2 °F; and 1.1% were "febrile". After Dose 2, 91.3% of the children had normal Ts; 5% had Ts < 100.4 °F; 1.3% had Ts 100.4 – 101.3 °F; 1.3% had Ts T > 102.2; and 1.3% were "febrile". After any vaccination dose, 86.5% had normal Ts; 9% had Ts < 100.4 °F; 1.1% had Ts 101.3 to < 102.2 °F; 1.1% had T $\geq$ 102.2 °F; and 2.2% were "febrile". It is noted that in Protocol 043, 89.9% of the Ts were taken qualitatively; 6.7% were taken by the axillary method; 2.2% were taken rectally; and 1.1% were taken orally. Overall, the percent of 12-23 month old children with a Temperature $\geq$100.4 °F or "febrile" after any injection was 4.4%.

The sponsor assessed that the proportion of all subjects (1-16 years of age) who reported the first clinical adverse event was 14.5% (11.6, 17.9 95% CI). The upper bound of the CI was compared with the historical rate of 37% of the clinical adverse events in children and adolescents in other studies. Since the upper limit was not > 37%, the pre-specified endpoint with regards to safety was met in 1-16 year old children. This analysis was done for all subjects together, and not broken down by age group (i.e., 12-23 months or 2-16 years).

Serious Adverse Events:
There were 2 subjects with serious adverse events, but only 1 in the younger age group.
AN06170, a 1-year-old male, received Dose 1 of VAQTA and 236 days after, developed pneumonia. The pneumonia lasted 13 days, and was of moderate severity. The child recovered. The investigator judged the AE to be not related to the vaccine.
AN06363, a 3-year-old female, received Dose 1 of VAQTA and 229 days later, had ophthalmic surgery (2 days duration), of moderate severity. The child recovered. The AE was judged to be not related to the vaccine by the investigator. The nature and temporal relationship of the AE to vaccination support this conclusion.

8.1.1.3 **Comments – Reviewer's Conclusion Regarding Data for Protocol 043**

This study provided safety data on 89 subjects in the 12 – 23 month old age group. There were no immunogenicity (efficacy data). Eighteen percent of these subjects experienced an adverse event, and 9% had an injection site adverse events and 11.2% had a systemic event. These proportions were slightly higher in the younger age group when compared in a post-hoc analysis to the older age group (2-16 years of age).

When comparing post-Dose 1 and post-Dose 2 adverse events, the proportion of 12-23 month old children experiencing an adverse event after Dose 1 was slightly higher than the proportion experiencing an adverse event after Dose 2. (This was true for the 2-16 year old population as well).

The most common injection site adverse event was pain/tenderness/soreness in both the younger and older age groups. Also seen were swelling, erythema, and warmth. Most injection site adverse events were mild to moderate in severity.

In regards to the systemic adverse events, the proportion of 12-23 month old subjects experiencing such events was low (5.7%) and similar to the 2-16 year olds (5.5%) after Dose 1, as well as after Dose 2 (7.5% for the younger group as compared to 4.9% for the older group.) The most common systemic adverse event was fever in both age groups after both doses in a low percentage of subjects. Fever was described as mild to moderate in both age groups. It was noted that approximately 89% of temperatures were reportedly taken "qualitatively" rather than "quantitatively" (if the subject felt feverish and/or had an oral T $\geq$102 °F.)

As noted above, a combined analysis of the safety was conducted to include studies 043 and 057 once CBER had determined that the methods of collection of adverse events and populations studied were similar in both protocols.

Table 2.7.4.6: Clinical Adverse Experience Summary Following Any Dose of VAQTA Administered Nonconcomitantly at Both Visits Versus VAQTA Administered Concomitantly at Either Visit With Other Pediatric Vaccines (Days 0-14 Postvaccination)

	Protocol 043	Protocol 057		Combined Protocols
	Noncocnomitant Adminstration N=89	Noncocnomitant Administrtion N=152	Concomitant Administration N=465	Total N=706
Number of subjects	89	152	465	706
Subjects with follow-up	89	147	447	683
Subjects with 1+AE	16 (18%)	84 (57.1%)	285 (63.8%)	385 (56.4%)
Subjets with 1+ IS AE	8 (9%)	19 (12.9%)	79 (17.7%)	106 (15.5%)
Subjects with 1+ systemic AE	10 (11.2%)	75 (51%)	261 (58.4%)	346 (50.7%)
Subjects with SAEs	0	0	2 (0.4%)	2 (0.3%)
Subjects who died	0	0	0	0
Discintiunued due to SAE	0	0	0	0

In addition, no child in the 12-23 month old age group discontinued from the study due to an adverse event.

Regarding the post-hoc analysis which was conducted to compare the safety of the vaccine in 12-23 month old children as compared to children 2-16 years of age, there was no formal statistical comparison between the 2 age groups (i.e., 12-23 months and 2-16 years). The sponsor also compared the proportion of subjects with adverse events with "historical controls". As noted above, the sponsor used a value of < 37% as an acceptable cutoff as a comparison point with historical controls, without providing the exact rationale for this cutoff value.

Nonetheless, while the data are limited by the small number of subjects in the 12-23 month age group, the safety profile of the vaccine appeared similar in this age group as compared to older children and adolescents.

8.1.2 **Trial #2**

8.1.2.1 **Protocol 057:** An Open, Randomized, Multicenter, Study of the Safety, Tolerability and Immunogenicity of VAQTA Given Concomitantly versus Nonconcomitantly with Other Pediatric Vaccines in Children Approximately 12 Months of Age. This was an open, randomized, multicenter study in which healthy children were assigned to one of four groups. The study was conducted at 14 study sites throughout the US. Treatments received for each group are shown in the table below.

8.1.2.1.1 **Objective/Rationale**

This study was designed to assess the immune responses as follows:

1. Anti-Hepatitis A antibody when VAQTA is given alone at 12 months of age compared to when it is given with MMRII + VARIVAX.
2. Anti-Hepatitis A antibody when VAQTA is given alone at 18 months of age compared to when it is given with TRIPEDIA (+/- Orimune or IPOL).
3. The immune responses to MMRII + VARIVAX + VAQTA compared to historical controls when MMR II + VARIVAX are given without VAQTA.
4. The immune responses to TRI PEDIA + VAQTA (+/- Orimune/IPOL) compared to historical controls when TRIPEDIA is given without VAQTA.

The study was also designed to assess the safety for the above combinations.

8.1.2.1.2 **Design Overview**

Open, randomized, multicenter study where healthy children 12 months of age were assigned to 4 treatment groups. The table below shows these groups:

(Protocol 057, p. 21, Module 5, Volume 1/10).

Visit	Group 1	Group 2	Group 3	Group4
Visit 1, Day 0 (app. 12 months)	VAQTA MMRII VARIVAX	VAQTA MMRII VARIVAX	VAQTA	VAQTA
Visit 2, Week 6 (app. 13.5 months)	No vaccine	No vaccine	MMRII VARIVAX	MMRII VARIVAX
Visit 3, Week 24 (app. 18 months)	VAQTA TRIPEDIA IPOL or ORIMUNE	VAQTA	VAQTA TRIPEDIA IPOL or ORIMUNE	VAQTA
Visit 4, Week 28 (app. 19 months)	No vaccine	TRIPEDIA IPOL or ORIMUNE	No vaccine	TRIPEDIA IPOL or ORIMUNE

8.1.2.1.3 **Population:** healthy children 12 months of age

Inclusion Criteria: Subjects 12 months of age (-15 days/+40 days) at time of enrollment; parent/guardian sign informed consent; subjects received the following vaccines prior to study start-polio [2 or 3 doses of OPV or IPV by any manufacturer], DTP/DtaP [3 doses of DTP or DtaP by any manufacturer]; subjects had no history of vaccination with hepatitis A vaccine, MMRII vaccine or Varicella vaccine; subject had no history of hepatitis A, measles, mumps, rubella, varicella, diphtheria, tetanus, pertussis and polio disease; Subject had no evidence of active liver disease or any other disease that would preclude evaluation of study endpoints; subject in good health on basis of medical history; subject had received no routine pediatric vaccine within 30 days prior to entry into the study, and was not scheduled to receive them throughout the study (Day 0 through 14 days after the last scheduled visit, except as indicated in the protocol. [Hepatitis B or HIB vaccine could be given, if necessary, either > 30 days prior to enrolment, or between the end of the 42 days, after the week 6 visit, and >30 days prior to the week 24 visit].

Exclusion Criteria: Any known or suspected immune deficiency, neoplastic disease, or depressed immunity resulting from systemic corticosteroids or other immunosuppressive treatment; allergic to any vaccine component; on the day of any vaccination, immediately [prior to receiving vaccine, had moderate or severe febrile illness >= 102°F rectal, >=101 ° F oral or >= 100°F axillary; within 3 months prior to the first injection, received IG, a donor blood transfusion (not including self-donated blood products), or blood derived product, or planned to receive such a product during the course of the study; was anemic, had severe thrombocytopenia, or any coagulation disorder that would have contraindicated IM injection; any condition, that in the opinion of the investigator, might have interfered with the evaluation of study objectives.

Procedures Allowed: Concomitant vaccinations were to include either MMRII+Varivax at 12 months or TRIPEDIA +/- IPOL or ORIMUNE at 18 months. This is shown in Table 3, (Protocol 057, p. 44, Module 5, Volume 1/10 below.

Table 3: Concomitant Vaccinations Allowed

Vaccine	Route of administration	Group 1	Group 2	Group 3	Group 4
VAQTA MMRII TRIPEDIA	IM SC IM	DO, Wk 24 D0 Wk 24	D0, Wk 24 D0 Wk 28	D0, Wk 24 Wk 6 Wk. 24	D0, Wk. 24 Wk. 6 Wk. 28
IPOL or ORIMUNE (optional)	SC PO	Wk 24 Wk. 24	Wk 28 Wk. 28	Wk. 24 Wk. 24	Wk. 28 Wk. 28

8.1.2.1.4 **Products Mandated by Protocol** (Table 4, pp. 46-48, Protocol 057, Module 5, Volume 1/10)

VAQTA: 2 doses given IM 6 months apart (25 U/0.5 mL)- Merck & Co., Inc., Lots 1314J, 1110H, 0047J, 1315J, 0702K; 25 Units/0.5 mL [0.7 mL fill single dose vials].

MMRII: 1 dose subcutaneously – contains $\geq$ 1000 tissue culture infectious doses (TCID50), measles virus, $\geq$20,000 TCID50 mumps virus, and $\geq$1000 TCID50 rubella virus per 0.5 mL [0.7 mL single dose vials].- Merck & Co., Inc., Lots 0173K, 1171H, 1781H, 1979H, 1174H, 0625

VARIVAX: 1 dose subcutaneously – contains app. 3000 pfu/0.5 mL.[0.7 mL fill single dose vials]- Merck & Co., Inc., Lots 0764K, 1802H, 1048H, 0425J, 1050H

Sterile diluent for live virus vaccines, Merck & Co., Lots 0915K, 1121H, 0918K, 0197J

TRIPEDIA: 1 dose IM – contains 6.7 Lf diphtheria toxoid, 5 Lf tetanus toxoid, and 46.8 mcg pertussis antigens per 0.5 mL.- Aventis Pasteur, Inc., Lots 0949260, 7387BA, UO299AB

IPOL: 1 dose subcutaneously 40D antigen units of Type 1, 8D antigen units of type 2 and 32D antigen units of type 3 poliovirus per 0.5 mL.[single dose syringes] - Aventis Pasteur, Inc., Lots N1032-1, N0498-1, R1329-2

ORIMUNE: poliovirus infectivity titers of $10^{5.4} – 10^{6.4}$ for Type 1 antigen, $10^{4.5} – 10^{5.5}$ for Type 2 antigen, and $10^{5.2} – 10^{6.2}$ for Type 3 antigen in each 0.5 mL dose. [dispette].- Lederle Laboratories, Lots 0792M, 466-604

8.1.2.1.5 **Endpoints**

Primary Response Parameters

For **Hypothesis 1**, the endpoint of interest was the Hepatitis A SeroPositivity Rate (SPR) (proportion of subjects who develop anti-HAV titers $\geq$ 10 mIU/mL) 1 month after Dose 2 of VAQTA in Group 4. The analysis was performed on subjects who were seronegative at baseline. 10mIU/mL is the cutoff for seropositvity in both assays used in this study.

For **Hypothesis 2a,** the endpoint of interest was the hepatitis A SPR 6 weeks after Dose 1 of VAQTA. Groups 1 and 2 were combined and compared with combined Groups 3 and 4. The analysis was performed on subjects who were seronegative at baseline. [This was comparing Groups 1&2 who received VAQTA+MMRII+VARIVAX compared to Groups 3 & 4 who received VAQTA before MMR+VARIVAX].

For **Hypothesis 2b**, the primary endpoint for the MMR antigens was the seroconversion rates 6 weeks postinjection with MMRII. Only subjects who were seronegative at baseline were included in the analysis. For the Varicella antigen, the proportion of subjects with varicella zoster virus antibody titers

>= 5gp ELISA units 6 weeks after administration of VARIVAX was the primary endpoint of interest. Only subjects with a preinjection titer < 5 gp ELISA units were included. For these antigens, Groups 1 & 2 were compared with historical controls. If success was obtained for Hypothesis 2 (2a and 2b combined), then the analysis for hypothesis 3 (Hypothesis 3a and 3b combined) was to use Groups 1 and 3 combined in comparison with Groups 2 and 4 combined for **Hypothesis 3a**, and groups 1 and 3 combined in comparison with the expected response rate for **Hypothesis 3b**. If success was not obtained for hypothesis 2, then group 3 alone was to be compared with Group 4 alone for **Hypothesis 3a** and group 3 alone was to be compared with the expected response rates for **Hypothesis 3b. T**he original protocol (p. 40 Protocol 057-00, serial 333, submitted 1/19/99 to IND ------), indicated that success for all 5 antigens (measles, mumps, rubella, varicella, hepatitis A) in Hypothesis 2b in order to say that MMRII+Varivax+VAQTA could be coadministered. However, the Sponsor did indicate that a claim for administration of VAQTA to 12-23 month olds would still be pursued even if it could not be coadministered with MMRII+Varivax. MMRII was successfully coadministered with VAQTA without a change in immune response, but Varivax was not shown to be successfully coadministered with VAQTA. This failure for the coadministration of Varivax and VAQTA was ascribed by the sponsor to their having performed gpELISA assays for Varivax in two runs, and resulted in discrepant results between the two assay run dates (2000 and 2002). These results were assessed by Philip Krause, MD. Please refer to his review.

For **Hypothesis 3a**, endpoint of interest was Hepatitis A SPR 4 weeks after Dose 2 of VAQTA. This analysis was conducted on subjects who were seronegative at baseline.

For **Hypothesis 3b**, the endpoint of interest for diphtheria and tetanus were the percentages of subjects with titers for antibody to d and T >= 0.1 IU/mL 4 weeks postinjection of TRIPEDIA. Of note, participants who had received DTP and/or DTaP vaccines for their primary series were included in the study and no attempt was made to recruit subjects who had received three prior doses of TRIPEDIA. The pre-specified endpoint for pertussis FHA and PT was the percentage of subjects with >= 4-fold rise in anti-FHA and anti-PT for 18 weeks pre-injection to 4 weeks post-injection of TRIPEDIA. It is noted that Hypothesis 2 was not met, so for Hypothesis 3a, group 3 alone was to be compared with Group 4, and for Hypothesis 3b, Group 3 alone was to be compared with the expected response rates for Hypothesis 3b.

Secondary Endpoints

Safety of **VAQTA when given alone to children app. 12 months of age *(and at app. 18 months of age).*** The Clinical Report indicates the age at 12 months only, but this safety objective has to do with the safety analysis at 12 and 18 months of age (since Dose 1 is given at app. 12 months of age, and Dose 2 is given at app. 18 months of age.)

Safety of **VAQTA when given with MMRII + VARIVAX to children app. 12 months of age.**
Safety of **VAQTA when given with TRIPEDIA to children at app. 18 months of age.**

To assess the **1st safety objective** (VAQTA alone at 12 and 18 months), the overall safety profile was summarized after each and any of the visits when VAQTA was given (Visits 1 and 3) by treatment group and combined across all treatment groups. Summary was presented for Days 0-42 post-vaccination at Visit 1 and Days 1-14 post vaccination at Dose 2 of VAQTA, and Days 0-14 at either Visit 1 or 3 (combined dose 1 and 2 of VAQTA). Group 4 was of special interest because it was the only group who received both VAQTA doses without other vaccines (at visits 1 and 3).

To assess the **2nd safety objective**, the comparison was made of safety and tolerability of VAQTA given concomitantly and nonconcomitantly with MMRII+VARIVAX at app. 12 months. This analysis considers Groups 1 and 2 combined [concomitant] vs. Groups 3 & 4 combined in follow-up of study Visits at Day 0 (Visit1) and Wk. 6 (Visit 2). The safety evaluation shows overall adverse events: local and systemic adverse events $\geq$1% in one or more treatment groups of the subjects (Groups 1 and 2 combined, and Groups 3 and 4) at Day 0 and Wk 6.
To describe the **3rd safety objective**, the comparison was made of safety of VAQTA + TRIPEDIA (concomitant, nonconcomitant) + optional polio at 18 months of age. This analysis considers Groups 1 & 3 combined [concomitant] vs. Groups 2 and 4 combined [nonconcomitant] for follow-up of study visits at Week 24 (Visit 3) and Week 28 (Visit 4). The safety evaluation shows the overall adverse events: local and systemic adverse events $\geq$1% in one or more treatment groups of subjects [Groups 1 & 3 combined and Groups 2 & 4 combined following study visits at Weeks 24 and Week 28]. G1 and 3 received concomitant vaccines at week 24. G1 and 3 received no vaccine at week 28. G2 and 4 received VAQTA alone at week 24. G 2 and 4 received TRIPEDIA +/- polio vaccine only at week 28.
For the **2nd and 3rd safety objective**, analyses tables including risk differences between concomitant and nonconcomitant vaccine groups, their 95% CIs, and p-values were presented for injection site adverse events (erythema, pain/tenderness/soreness, swelling, warmth); rashes (measles-like, rubella-like, varicella-like); mumps symptoms; increased Temperature ($\geq$102°F oral equivalent, converted by adding 1°F to axillary, subtracting 1°F from rectal, leaving otic unchanged), all of which were prompted for on the Vaccine Report Card. Also, risk differences, along with their 95% CIs were provided for each comparison of concomitant vs. nonconcomitant vaccines with respect to other specific systemic adverse events at an incidence of >= 1% in one or more comparison groups.
For the **2nd safety objective** (VAQTA+MMRII+VARIVAX), the summaries and comparisons at Visits 1 and 2 involved 2 combined follow-up periods,

Days 0-42 (total of 86 days) with respect to specific systemic adverse events, and also 2 combined follow-up periods, Days 0-4 (10 days total) with respect to **Temperature**. With respect to injection site adverse events, the comparisons were made by vaccine injection site, and involved only one follow-up period, Days 0-4, after either Visit 1 or Visit 2, at which time the vaccine was administered.

For the **3rd safety objective**, the summaries and comparisons after VAQTA +/- TRIPEDIA and optional polio at Visits 3 and 4 involved 2 combined follow-up period, Days 0-14 each (a total of 30 days) with respect to the specific systemic adverse events, and also 2 combined follow-up period (Days 0-4, total of 10 days) with respect to Temperature. With respect to injection site adverse events, the comparisons were made by injection site, and involved only one follow-up period, Days 0-4, after either Visit 3 or Visit 4, at which time each vaccination was given.

There were 2 secondary immunogenicity objectives:
12-month-old children given VAQTA +/- other pediatric vaccines will develop anti-HAV titers after Dose 1 similar to those seen historically in children 2-3 years of age who received VAQTA.

12 month old children given VAQTA + MMRII+VARIVAX will develop anti-HAV titers after Dose 1 similar to those seen historically in children 2-3 years of age who receive VAQTA.

8.1.2.1.6 **Surveillance**

Table 5 (Protocol 057, p. 55, Module 5, Volume 1/10) shows the summary of lab measurements. (see below)

Study Time Period	Group	Hep A	MMR	V	DTP	Polio 1,2,3
Day 0 (Visit 1)	1	X	X	X		
	2	X	X	X		
	3	X				
	4	X				
Week 6 (Visit 2)	1	X	X	X	X	X*
	2	X	X	X		
	3	X			X	X*
	4	X				
Week 28 (Visit 4)	1	X			X	X*
	2	X				
	3	X			X	X*
	4	X				

*Testing for polio will have occurred only if poliovirus was coadministered, and if sample volume was sufficient after testing for other antigens listed.

Safety Parameters

Follow-up visits: Day 0 (Visit 1), Week 6 (Visit 2), Week 24 (Visit 3), Week 28 (Visit 4).

Subjects were followed for systemic adverse events x 42 days after Visits 1 and 2 (Day 0, Week 6), whether or not they received vaccine.

Subjects were followed for injection site adverse events x 4 days after each vaccination. These were listed on a Vaccine Report Card.

Subjects were followed for systemic adverse events x 14 days after Visits 3 and 4.

Subjects' parents reported to investigators symptoms/signs. The investigators graded the adverse events and assessed them for causality.

All Vaccine Related adverse events as assessed by the investigator, whether serious or not, were followed for outcome.
It is noted that those who did not seroconvert to VAQTA, MMR or VARIVAX were eligible for revaccination with the appropriate vaccine. Clinical follow-up of injection site adverse events and systemic adverse events was required in these subjects. (Injection site adverse events x 5 days after each vaccination for all; systemic adverse events x 42 days for MMRII and/or VARIVAX and 14 days for VAQTA.)

Adverse Event: ANY unfavorable or unintended change associated with the use of the product whether or not considered related to use of the product. This also includes worsening of a pre-existing condition.
Temperatures were followed as below:
Days 0-4, daily Temperature after each vaccination.
Days 5-42 after Visit 1 (Day 0) and Visit 2 (Week 6). Temperatures were to be recorded on the Vaccine Report Card only if $\geq$102°F or if the subject felt feverish.
Days 5-14 after Visit 3 (Week 24) and Visit 4 (Week 28) Temperatures were to be recorded on the Vaccine Report Card only if $\geq$ 102°F or if the subject felt feverish.
The Temperatures were reported as adverse events by the study personnel, and the investigator assessed increased Temperature by grading, seriousness, action taken, and relationship to test vaccine.
Serious Adverse Events
Subject were to contact study personnel immediately if any serious adverse events from the time of consent through 42 days after Day 0 and Week 6 visits, and for 14 days after Weeks 24 and 28 visits. Serious adverse events were to be reported whether or not they were vaccine related. Any serious adverse event outside the study follow-up periods that were possibly vaccine related, or if death occurred, were to be reported, if and when, brought to the attention of the investigator. All serious adverse events were to be followed for outcome.

Rashes/Exposure: All subjects with measles-like, rubella-like, or varicella-like rashes, or with signs of mumps were to be seen by study physician. The clinical finding and exposure were to be documented on the CRF.

Each **Vaccine Report Card** was reviewed with the parent if returned at a visit or at a time of return to identify any rashes or signs of mumps (to be seen by study personnel). If the Vaccine Report Card was received by mail, the parent was to be contacted. If a subject had a rash or signs of mumps or was exposed to measles, mumps, rubella, or varicella within 42 days after vaccination with MMRII + VARIVAX, the information was reported to the appropriate CRF.

8.1.2.1.4 **Statistical Consideration**

There are **five primary immunogenicity objectives**.

Hypothesis 1: Children approximately 12 months of age given **VAQTA x 2** (6 months apart) ALONE had acceptable seropositivity rates (SPR) to hepatitis A similar to that seen historically in children 2-3 years of age after Dose 2. [Group 4]

Postdose 2 seropositivity rate for Group 4 was provided with CI and p-value testing of the null hypothesis that the true SPR is <99% by 10% or more. The statistical criterion required that the lower bound of the 95% CI on the observed Postdose 2 SPR be >89%, or equivalent, the corresponding p-value $\leq$0.025.

Hypothesis 2a: Hepatitis A SPRs 6 weeks **postdose 1** of VAQTA are similar when VAQTA is given concomitantly with MMRII+VARIVAX (Groups 1 and 2 combined) versus when VAQTA is given without other pediatric vaccines (Groups 3 and 4 combined).

The estimate of Postdose 1 SPRs: The differences in SPRs for the two groups being compared (Groups 1 and 2 minus Groups 3 and 4) were provided. In addition, the 2-sided 95% CI for the difference and the corresponding p-value for testing the null hypothesis that the true SPR in the concomitant groups (1 and 2) is less than in the nonconcomitant groups (3 and 4) by 10% points or more is provided.

The statistical criterion requires that the lower bound of the 95% CI on the estimate of the difference (concomitant minus nonconcomitant) in the treatment groups exclude a difference of 10% points or more (i.e., be entirely above –10% points), or equivalently, the corresponding p-value be $\leq$0.025. If the statistical criterion was satisfied, then Hypothesis 2a would be met, and Postdose 1 SPR would be considered similar (non-inferior) between concomitant and nonconcomitant vaccine groups.

Hypothesis 2b: Seroconversion rates (SCRs) for Measles, Mumps, Rubella, and the percentage >=5gpELISA units for varicella at 6 weeks post-vaccination with MMRII and VARIVAX, when given concomitantly with VAQTA are similar to corresponding response rates seen historically when MMRII+VARIVAX are given concomitantly without VAQTA].

To address this, the response rates for children who received concomitant MMRII+VARIVAX+VAQTA (Groups 1 and 2) were provided along with their confidence intervals (CIs) and corresponding p-values for testing the null

hypothesis that the true response rates are less than historical control rates of 99% for MMR, and 90% for varicella by 10 percentage points or more.
The statistical criterion requires that the lower bound of the 95% CI on the observed rates be >89% for each of measles, mumps, rubella and >80% for varicella, or equivalently, the corresponding p-value be <= 0.025.
If the statistical criteria for each component of hypothesis 2b were satisfied, then Hypothesis 2b would be met and the response rates would be considered similar to their corresponding historical rates.
Hypothesis 2 would be met if 2a and 2b were met and then the general claim would be sought that VAQTA can be administered concomitantly with MMRII+VARIVAX to children app. 12 months of age.
What is different is that the Sponsor initially stated that they had to succeed on BOTH 2a **AND** 2b (not **OR**) in order to make a claim. Success was required for all 5 antigens. Instead, a post hoc analysis was performed (see below).
Hypothesis 3: In the protocol, it was specified that if success was not met on the 2nd primary hypothesis (2a and 2b above), the Hepatitis A SPR 4 weeks after Dose 2 VAQTA in Group 3 (concomitant with TRIPEDIA) alone would be compared with that in Group 4 (nonconcomitant) [Hypothesis 3a] and the primary antibody response to TRIPEDIA vaccine in Group 3 alone would be compared to their expected historical responses [Hypothesis 3b].
If success had been met in Hypothesis 2, then Hepatitis A SPR 4 weeks after the 2nd dose of VAQTA in Groups 1 and 3 concomitantly would be combined and compared with those in Groups 3 and 4 combined (nonconcomitantly) [Hypothesis 3a] and the primary antibody response rate to TRIPEDIA vaccine in Group 1 and 3 combined would be compared to their expected historical responses [Hypothesis 3b].
Hypothesis 3a: Postdose 2 hepatitis A SPRs are similar when VAQTA is given with TRIPEDIA (+/- polio) versus when VAQTA is given alone.
The estimate of SPR for VAQTA postdose 2 and the difference in SPRs for the 2 compared groups were provided along with the 2-sided 95% CI for the difference.
Also, the corresponding p-value for testing the null hypothesis that the true SPR in the concomitant group (Group 3 alone) is less than the nonconcomitant group (Group 4 alone) by 10% points or more.
The statistical criterion requires that the lower bound of the 95% CI on the estimate of the difference (concomitant minus nonconcomitant) in treatment groups which include a difference of 10% points or more (i.e., be entirely above –10% points), or equivalently, the corresponding p-value <= 0.025. If the statistical criterion was met, then Hypothesis 3a would be met, and postdose 2 SPR would be considered similar (non-inferior) between concomitant and nonconcomitant vaccine groups.
Merck selected their prespecified immunogenicity endpoints based on historical data obtained in clinical trials in which the relevant vaccines had been studied for Hypotheses 1, 2a, 2b, and 3b.
Hypothesis 3b: Responses to DT and pertusssis PT and FHA would be adequate when VAQTA was given concomitantly with TRIPEDIA and polio

vaccine (optional) versus historical controls when TRIPEDIA is given without VAQTA.
To address this, the response rates for children who received concomitant vaccination with TRIPEDIA with VAQTA (Group 3 alone) was compared along with their CIs.
The corresponding p-values were computed for testing the null hypothesis that the true response rates are < historical rate of 95% for diphtheria and Tetanus (percentage >=0.1 IU/mL) by 10% points or more, less than the historical rates of 85% and 80% for pertussis PT and FHA, respectively (percentage $\geq$ 4-fold rise from prevaccination to postvaccination) by 15% points or more.
The statistical criteria require that the lower bound of the 95% CI on the observed rates be >85% for each of d and T, > 70% for pertussis PT, and >65% for pertussis FHA or equivalent. The corresponding p-values would be <=0.025.
If the statistical criterion was met, Hypothesis 3b would be met, and the response rates would be considered similar to their corresponding historical rate.
Success was needed for all 5 antigens.

Possible successful outcomes included:
First primary hypothesis was met.
The first and second primary hypotheses (1, 2a, 2b) were met.
Combination of the first and third primary hypotheses (1, 3a, 3b) met.
All hypotheses met.

Two **secondary immunogenicity objectives** included:
1. Demonstrate that 6 weeks after the **first dose of VAQTA**, children who receive it with MMR+VARIVAX (Groups 1 & 2) will have an acceptable SPR for hepatitis A.
2. Six weeks after **Dose 1 VAQTA**, children who receive it without other vaccines (Groups 3 and 4) will have an acceptable SPR for hepatitis A.
For both secondary hypotheses, the expected SPR for children after the 1st dose of VAQTA was 97%. This was based on data from previous studies in which the serology timepoint was 4 weeks postdose 1 of VAQTA. No difference in immune response was measured 4 weeks postvaccination vs. 6 weeks postvaccination since SPRs at 4 and 24 weeks postvaccination are generally comparable. The SPR would be considered acceptable if the lower bound of the 95% CI on the observed population was >87% (<10% point decrease from the expected response). The corresponding p-values were also computed. A p-value <=0.025 would support the same conclusion of acceptable SPR.
While not prespecified, a comparison in hepatitis A GMTs postdose 1 and postdose 2 of VAQTA between initially seropositive and initially seronegative subjects was assessed. This was an observational assessment and compared the GMT and 95% CI by dose and serostatus.

Three **secondary safety objectives**
1. Safety in 12 month olds (and 18 month olds) without other vaccines
The overall safety profile was summarized after each and any visit when VAQTA was given (Visits 1 and 3) by treatment group and combined across all treatment groups.
A summary is presented (Days 0-42 postvaccination at Visit 1 (Day 1 of VAQTA). Days 0-14 postvaccination at Visit 3 (Dose 2 of VAQTA), Days 0-14 postvaccination at either Visit 1 or 3 (combined Doses 1 and 2 of VAQTA).
Group 4 served as an important control as VAQTA was given alone at both doses.

2. Safety of VAQTA with MMRII+VARIVAX to children at 12 months of age.

3. Safety of VAQTA with TRIPEDIA at 18 months of age.
For #2 above, they compared the safety of VAQTA given with and without MMRII+VARIVAX at 12 months of age. Groups 1 and 2 combined were compared to Groups 3 and 4 combined for Day 0 (Visit 1) and Week 6 (Visit 2).
For #3 above, they compared the safety of VAQTA with and without TRIPEDIA (and an optional dose of polio vaccine) at 18 months of age. Groups 1 and 3 combined were compared to Groups 2 and 4 combined at Week 24 (Visit 3) and Week 28 (Visit 4).
Both comparisons presented injection site adverse events and systemic adverse events >1%.

Analyses tables included risk differences between concomitant and nonconcomitant vaccine groups, and their 95% CIs and p-values were presented for injection site adverse events (erythema, pain/tenderness/soreness, swelling, warmth); rashes (measles-like, rubella-like; varicella-like); mumps symptoms; increased Temperature ($\geq$102°F oral and otic, and adding 1°F to axillary T and subtracting 1°F from rectal T). All of these were prompted for on the Vaccine Report Card. Also, risk differences along with 95% CIs were provided for each comparison of concomitant and nonconcomitant vaccine with respect to other specific systemic adverse events at an incidence in one or more comparison group.

Of note, there are 2 different time windows for post-vacination follow-up. Following receipt of VAQTA+MMRII+VARIVAX: Days 0-42 post-vaccination, systemic adverse events were collected. Days 0-4 post-vaccination, Temperature and injection site adverse events were collected. Following receipt of TRIPEDIA at Visits 3 and 4: Days 0-14 for systemic adverse events, Days 0-4 for Temperatures after Visits 3 and 4, and Days 0-4 for injection site adverse events after Visits 3 and 4.

Immunogenicity Analyses

With 135 subjects enrolled in each treatment group, and accounting for a dropout rate of 15%, the study was expected to have 115 evaluable subjects in each of 4 treatment groups. The expected seropositivity rates for VAQTA after Dose 1 and 2 are 97% and 99%, respectively. The rates were based on data obtained from previous clinical studies in which the immune response to VAQTA was assessed.

The anticipated rates of seroresponse for Measles, Mumps, Rubella and Varicella were based on response rates from another clinical study in which MMRII+VARIVAX and COMVAX were given concomitantly [2.2.3].

The anticipated rates for diphtheria, tetanus, pertussis PT and FHA were based on the product circular for TRIPEDIA. Of note, however, the assays were performed in a different laboratory and the priming history of children enrolled in this study differed from the cohort of subjects described in the TRIPEDIA package insert. This label shows the immune responses in 15-20 month olds when TRIPEDIA is combined with ACTHIB compared to the vaccines given separately in children who have received an initial three dose series of wDTP vaccine (whole cell).

With 115 expected evaluable subjects in Group 4, and assessing an expected response of 99%, the power was >99% for primary **Hypothesis 1** (comparison of responses to 2 doses of VAQTA) with historical controls. The power was calculated using exact methods.

With 230 subjects in concomitant groups (Groups 1 and 2 combined) and 230 in Groups 3 and 4 combined, with an expected response rate of 97%, there was >99% power to show similarity between the 2 treatment groups (Groups 1 and 2 concomitant and Groups 3 and 4 nonconcomitant) for **Hypothesis 2a** (comparison of response to 1 dose of VAQTA+MMR+VARIVAX compared with VAQTA alone). The assumption under the alternative hypothesis was that the true rates in the concomitant and nonconcomitant groups were equal. There would be decreased power if this was not true.

For **Hypothesis 2b** (response rate MMRII+VARIVAX+VAQTA compared with the historical responses to MMRII + VARIVAX given together. The power for each antigen was calculated using exact methods, assuming 230 expected evaluable subjects in Groups 1 and 2. The expected response rates were based on the results from study 009 for COMVAX (Synopsis, p.738-739, Module 5, Volume 3/10). The synopsis for this study was located in Appendix 2.2.3, and the study was published in 2004 (Hesley TM et al. Concomitant administration of a bivalent Haemophilus influenza type B- hepatitis B vaccine, MMRV vaccine: safety, tolerability and immunogenicity. Pediatric Infectious Disease Journal 2004; 23:240-5.)

If success was not achieved for Combined 1 and 2, Group 3 (concomitant) would be compared to Group 4 (nonconcomitant) for primary **Hypothesis 3a**,

and there would be app. 115 subjects per treatment group, and >99% power to show similarity of the hepatitis A SPRs between the 2 treatment groups.

For the primary **Hypothesis 3b** (diphtheria, tetanus, pertussis PT & FHA when TRIPEDIA given with VAQTA compared with historical responses when TRIPEDIA is given without VAQTA), the power for each antigen was calculated using exact methods, assuming 230 evaluable subjects (Groups 1 and 3) or 115 alone (from Group 3). In the analysis shown in the results, they compared to Group 3 alone.

Statistical Methods
Adjustment for Covariates: Two immunogenicity analyses were adjusted for study center.

Handling of Dropouts or Missing Data:
1. All immunogenicity analyses and summaries were based on a per-protocol approach.
2. Secondary immunogenicity analyses were based on "all subjects with serologies" (even if subject deviated)
3. All safety analyses were based on all subjects with safety data regardless of protocol violation.

Study Population
All immunogenicity analyses were performed on a per-protocol basis (i.e., those that received vaccine within the correct day ranges, completed follow-up, no protocol violations). Exclusion was based on prespecified criteria outlined in the Data Analysis Plan (wrong age; received IG or blood within 3 months; received immunosuppressives; history immunodeficiency; history of hepatitis A, measles, mumps, rubella, varicella, diphtheria, tetanus, or pertussis; previous vaccination with hepatitis A, MMRII or VARIVAX; received any vaccine within 30 days; assigned to the wrong group; missing baseline serologies; excluded if they are positive for hepatitis A, measles, mumps, rubella, varicella; those who did not have 3 doses of DTP or DTaP; did not receive full doses of study vaccines; vaccines were off schedule; received a vaccine that was not allowed).

Analysis for hepatitis A was based on those subjects who were seronegative at baseline and had valid serological measurements postvaccination.

Analysis for varicella was based on subjects with preinjection antibody titer <5 gpELISA units and valid serological measurements postvaccination within specified day ranges. A secondary population was based on subjects with prevaccination titers <1.25 gpELISA.

For hepatitis A, measles, mumps, rubella, immunogenicity results for those initially seropositive were summarized for each antigen separately and was based on the per protocol population.

No summary was performed for those initially seropositive for varicella (since only 2 subjects had prevaccination titers > 5gpELISA).

Immunogenicity Summary
All subjects with safety data were included.
No interim analysis was performed, and there were no multiplicity adjustments.

Four study centers with $\leq$ 20 subjects each were pooled into one center for the purposes of analyses.

The primary and secondary immunogenicity analyses of comparisons of response rates with historical or expected rates were based on observed values without adjustment for study centers.
All safety analyses were based on observed responses without adjustment for study centers.

Prior to the similarity analyses of the SPRs for VAQTA at 6 weeks postdose 1 and 4 weeks postdose 2 to address Hypothesis 2a and Hypothesis 3a respectively, the interactions between the compared treatment groups at each timepoint and pooled study center (study centers with <=20 subjects were pooled in one center) were investigated as in the Data Analysis Plan (pp. 956-958, Protocol 057, Module 5, Volume 4/10).

Multiple Comparisons (Protocol 057, p. 92, Module 5, Volume 1/10).
The **first primary hypothesis** used a 1-sided alpha =0.025.
If the primary hypothesis was met, they would proceed to hypotheses 2 and 3. They could declare success for Hypothesis 2 (2a **and** 2b) OR Hypothesis 3 (3a **and** 3b) but a multiplicity adjustment was required. They used the Bonferroni and testing for hypothesis 2 and hypothesis 3 would be performed at the 1-sided multiplicity adjusted, with an alpha of 0.025 significance level. Primary Hypothesis 2 (2a and 2b) and primary Hypothesis 3 (3a and 3b) each involved 5 antigens, and therefore had 5 comparisons. Success was needed on all 5 antigens in each set. Therefore the multiplicity adjusted error rate of alpha=0.025, 1-sided, controlled the overall error rate at 0.05 for primary Hypothesis 2 and 3.

Changes in the Conduct of the Study or Planned Analysis
Protocol 057-01 and 057-02 provide descriptions of **new assays** for detection of antibody to **hepatitis A, measles, mumps, and rubella** which were added to replace the assays that had been used. Assays were reviewed by product

reviewers and statisticians in CBER and deemed to be comparable, and results of different assays were able to be combined.

Changes in the Period Over Which increased Temperatures were compared.
Since Temperatures were taken sporadically (only if they felt feverish) after Day 4, direct comparisons were not performed. In the first CR letter, CBER requested additional analyses of these data in the first CR letter, and these are discussed in the results section.

Serology for Polio Types 1,2,3 antibody
These results were not available at the time of completion of the clinical study report. Polio vaccine was optionally administered to 428 subjects either as a dose of IPOL (N=365) or ORIMUNE (N=63). At CBER's request, serology results following receipt of IPOL or IPV were submitted. It is noted that prevaccination levels were obtained 4.5 months prior to vaccination with polio vaccine at 18 months and postvaccination levels were 1 week after IPOL or OPV. It is also noted that OPV is no longer recommended for the immunization against polio in the U.S. 157 subjects had post-vaccination results available (Groups 1 and 3). 99-100% were seropositive with titers $\geq$ after these doses. However, there were no control subjects and no comparisons made between those who had received polio concomitantly with VAQTA and nonconcomitantly with VAQTA. Additionally, as subjects may have received priming with IPV or OPV (as well as 2 or 3 prior doses of polio vaccine), the data were not viewed as relevant in support of the current recommended all IPV schedule in the US.

8.1.2.2 **Results**

8.1.2.2.1 **Populations Enrolled/Analyzed**

Table 11 (Protocol 057, p. 99-100, Module 5, Volume 1/10) provides a patient accounting.

	Group 1	Group 2	Group 3	Group 4	Total
Entered	N=156	N=153	N=156	N=152	N=617
Male (age range)	86 (11-13M)	78 (11-13M)	84 (11-13M)	83 (11-13M)	331 (11-13M)
Female (age range)	70 (11-13M)	75 (11-13M)	72 (11-13M)	69 (11-14M)	286 (11-14M)
Visit 1	156 (1005)	153 (100%)	156 (100%)	152 (100%)	617 (100%)
Visit 2	146 (93.6%)	145 (94.8%)	149 (95.5%)	146 (96.1%)	586 (95%)
Visit 3	138 (87.2%)	140 (91.5%)	139 (89.1%)	138 (90.8%)	555 (90%)
Visit 4	136 (87.2%)	132 (86,3%)	136 (87.2%)	137 (90.1%)	541 (87.7%)
Completed	127 (81.4%)	124 (81%)	125 (80.1%)	127 (83.6%)	503 (81.5%)
Discontinued	29 (18.6%)	29 (19%)	31 (19.9%)	25 (16.4%)	114 (18.5%)
Deviation	0	6(3.9%)	1(0.6%)	3(2%)	10(1.6%)
Refused	9(5.8%)	9(5.9%)	6(3.8%)	5(3.3%)	29(4.7%)
Lost to follow-up	20(12.8%)	13(8.5%)	23(14.7%)	16(10.5%)	72(11.7%)
Noncompliant	0	1(0.7%)	0	1(0.7%)	2(0.3%)
Clinical AE	0	0	1(0.6%)	0	1(0.2%)

AN01259 was considered to have deviated from protocol since post Visit 2 safety follow-up was not provided, but the subject returned for Visit 3 and completed safety follow-up for these visits. This subject was included as a protocol deviator.

Investigators: Table 17 (Protocol 057, p. 112, Module 5, Volume 1/10) lists the investigators and indicates the numbers of subjects in each group from each site.

Study #	Investigator/City	Group 1 N=156	Group 2 N=153	Group 3 N=156	Group 4 N=152	Total N=617
057 01	Block, S. /Berdstown, KY	11	11	10	10	42
057 02	Chartrand, S. /Omaha, NE	3	4	4	3	14
057 03	Reisinger, K. /Pittsburgh, PA	17	18	17	18	70
057 04	Walter, E. /Durham, NC	17	18	17	16	68
057 05	Werzberger, A. /Monroe, NY	21	21	22	21	85
057 06	Guerra, F. /San Antonio, TX	26	25	25	24	100
057 07	Santosham, M. /Baltimore, MD	11	9	10	10	40
057 08	Blumberg, D. /Sacramento, CA	12	12	12	18	49
057 09	Taylor, J. /Seattle, WA	14	13	13	13	53
057 10	Keyserling, H. /Atlanta, GA	4	4	4	4	16
057 11	Sperling, M. /Fountain Valley, CA	11	9	11	10	41
057 12	Bocchini, J. /Shreveport, LA	3	3	4	4	14
057 13	Murphy, D. /Ft. Worth, TX	5	5	5	5	20
057 14	Gooch, W.M./Salt Lake City, UT	1	1	2	1	5

Demographics: Table 18 (Protocol 057, p. 113, Module 5, Volume 1/10)

	Group 1	Group 2	Group 3	Group 4	Total
Gender					
Male	86(55.1%)	78(51%)	84(53.8%)	83(54.6%)	331(53.6%)
Female	70(44.9%)	75(49%)	72(46.2%)	69(45.4%)	286(46.4%)
Age (months)					
Mean	12.1	12	12	12	12
SD	0.3	0.3	0.3	0.4	0.4
Median	12	12	12	12	12
Range	11-13	11-13	11-13	11-14	11-14
Male	11-13	11-13	11-13	11-13	11-13
Female	11-13	11-13	11-13	11-14	11-14
Asian	1(0.6%)	0	0	0	1(0.2%)
Black	25 (16%)	17(11.1%)	21(13.5%)	25(16.4%)	88(14.3%)
White	83(53.2%)	87(56.9%)	90(57.7%)	90(59.2%)	350(56.7%)
Hispanic	27(17.3%)	30(19.6%)	28(17.9%)	23(15.1%)	108(17.5%_
Indian	0	0	1(0.6%)	0	1(0.2%)
Native American	11(7.1%)	10(6.5%)	12(7.7%)	10(6.6%)	43(7%)
Oriental	2(1.3%)	2(1.3%)	0	1(0.7%)	5(0.8%)
Other	7(4.5%)	7(4.6%)	4(2.6%)	3(2%)	21(3.4%)

The reasons for exclusion from the per protocol analysis for each group were presented in Tables 12 through 16, and the reasons listed appeared appropriate. (These tables were found in Protocol 057, p. 103-111).

There was a high degree of compliance in all groups (85-100%%) except for the receipt of polio vaccines (which were optional).

Table 18 (Protocol 057, p. 114, Module 5, Volume 1/10)
Initial Serostatus for Hepatitis A (Combined Assay Formats)

Initial Hepatitis A Serostatus	Group 1	Group 2	Group 3	Group 4	Total
Positive >=10mIU/mL	21(13.5%)	17 (11.1%)	17 (10.9%)	16 (10.5%)	71 (11.5%)
Negative < 10mIU/mL	128 (82.1%)	127 (83%)	127 (81.4%)	129 (84.9%)	511 (82.8%)
Unknown	7 (4.5%)	9 (5.9%)	12 (7.7%)	7 (4.6%)	35 (5.7%)

Most subjects were seronegative.

Table 19 (Protocol 057, p. 116, Module 5, Volume 1/10)
Summary of Initial Serostatus for Measles, Mumps, Rubella and Varicella at 12 months of age by treatment group (Combined Assay Formats)

Antigen	Initial Serostatus	Group 1 N=156	Group 2 N=153	Groups 1 and 2 N=309
Measles	Positive	18 (11.5%)	13 (8.5%)	31 (10%)
	Negative	131 (84%)	133 (86.9%)	264 (85.4%)
	Unknown	7 (4.5%)	7 (4.6%)	14 (4.5%)
Mumps	Positive	6 (3.8%)	6 (3.9%)	12 (3.9%)
	Negative	144 (92.3%)	140 (91.5%)	284 (91.9%)
	Unknown	6 (3.8%)	7 (4.6%)	13 (4.2%)
Rubella	Positive	1(0., 6%)	0	1(0.3%)
	Negative	148(94.9%)	146(95.4%)	294(95.1%)
	Unknown	7(4.5%)	7(4.6%)	14(4.5%)
Varicella	% gpELISA >=5U	1(0.6%)	1(0.7%)	2(0.6%)
	% gpELISA <5U	148(94.9%)	146(95.4%)	294(95.1%)
	% gpELISA >=1.25U	11(7.1%)	16(10.5%)	27(8.7%)
	% gpELISA < 1.25U	137(87.8%)	139(85%)	267(86.4%)
	Unknown	7(4.5%)	6(3.9%)	13(4.2%)

The results across the groups appear similar.

Protocol Violations

The following subjects were excluded from the per-protocol analysis.

52 deviated by receiving a vaccine other than those that were to be given within 30 days of entry through 42 days after the week 6 visit and/or within 30 days of the week 24 visit through the 14 day follow-up after the week 28 visit.

28 received off-schedule vaccines (during nonstudy visits) within 30 days of entry into the study or during the course of the study through the 14-day follow-up after the week 28 visit.

Personnel at two study sites (08 and 011) assigned Allocation Numbers to 2 potential subjects received study vaccines. No baseline bloods were obtained. AN01716 (Site 08) was a black female 12 months old (376 days) was randomized to Group 4. The consent was signed, then the parent refused participation prior to any vaccination. AN02060 (Site 011), a white male, 13 months old (405 days), was randomized to Group 2. Per the investigator, the subject would not have been able to be evaluated appropriately for study objectives. Therefore, he was excluded before getting the study vaccine.

One (AN01733, Site 09) received 4 doses of DtaP prior to the 1st visit of the study, so this subject did not meet the inclusion criteria of only receiving 3 previous doses of DtaP/DTP before entry. The subject's post-Visit 3 serology was excluded from the per protocol immunogenicity analysis. A listing of these subjects is provided in Appendix 3.

8.1.2.2.2 **Immunogenicity Endpoints/Outcomes**

Anti-HAV Response to VAQTA after each dose

The seroconversion rates for the four groups ranged from 92.5% - 98.3% seropositvity after dose 1 and 100% seropositvity after dose 2 of VAQTA in the per protocol population. The percent who were seropositive were similar in the all serology population, where 92.4% - 98.6% were seropositive after Dose 1 and 100% were seropositive after Dose 2.

Response after 2 doses VAQTA compared with Historical Controls

Primary Hypothesis 1: Group 4, which was the group that received VAQTA alone at Visits 1 and 3, would have acceptable SPR compared with children 2-3 years of age who received 2 injections of VAQTA who had SPR 99%. The SPR would be acceptable if the lower bound of the 2-sided 95% CI response of the observed proportion was >89%, which represents <10% point decrease for the expected response. A p-value <=0.025 supported the same conclusion indicating that the SPR was statistically significantly >89%. The Sponsor met this objective.
For the per protocol analysis, Group 4 [N=97] had 100% SPR (95% CI: 96.3%,100%) with GMT of 7336.1 (95%CI:6197.1,9162), giving a p-value <0.001.
For the all-serology group, Group 4 [N=132] had 100% serpositivity (95% CI: 97.2%, 100%) with GMT of 7925 (95% CI: 6607.3, 9507).

The Sponsor also presents the GMTs for subjects who were initially seropositive for Hepatitis A antibody as compared to those who were initially seronegative, by assay type. It is noted that although the GMTs were somewhat lower for those who initially seropositive, the levels of anti-hepatitis A antibodies were quite high 4 weeks postdose 2 for each group.

Table 27 (Protocol 057, p. 135, Module 5, Volume 2/10) shows the hepatitis A GMTs for those who were initially seropositive.

Hep A Assay	Time Point	Initially seropositive subjects			Initially seronegative subjects		
HAVAB		N	GMT mIU/mL	95% CI	N	GMT MIU/mL	95% CI
	D0	49	26.1	(21.8,31.3)	424	<10	-
	Wk 6 post V1	48	43.3	(34.2,55.1)	408	46.9	(43.2,5.1)
	Wk 4 post V2	40	6207.3	(4769.3,8078.9)	259	6809.6	(6131.6,7562.6)
----------	D0	13	33.8	(17.9, 63.9)	47	<10	-
	Wk 6 post V1	14	48.4	(29.6,679.4)	63	56.7	(42.5,75/7)
	Wk 4 post V2	10	4932.7	(1415, 17196)	84	7138.7	(5162,9872.2)

It is noted that there are 50 seropositive subjects with post-dose 2 results in the table above. Reviewing the sero-all data set, this reviewer found 60 seropositive subjects who had results of hepatitis antibodies after dose 2. In the all serology set, the lowest titer 6 weeks after Dose 2 in an initially seropositive subject was 177 mIU/mL, and the highest was 41,510 mIU/mL. At CBER's request, the Sponsor provided a table, which included the full 60 subjects and the results were very similar. The original table above included subjects from the per-protocol anlaysis. From review of the above table, those who were initially seropositive had a somewhat lower anti-hepatitis A antibody level than those who were initially seronegative when tested with the new assay ----------, whereas the titers in the seropositives are more similar to the seronegatives when tested with the original HAVAB assay.

However, the number of subjects tested with ---------- were small, CBER reviewers have assessed the assays to be comparable, and GMTs for the 95% CI were all well above the seropositivity cutoff. Therefore, clinically, subjects, whether initially seronegative or seropositive at this age would likely be protected against hepatitis A disease after receipt of VAQTA.

Hypothesis 2a: Hepatitis A Response when VAQTA was given concomitantly with MMRII + VARIVAX or followed 6 weeks later by MMRII + VARIVAX.
Groups 1 and 2 had VAQTA + MMRII +VARIVAX at Visit 1.
Groups 3 and 4 had VAQTA alone followed by MMRII + VARIVAX at a timepoint 6 weeks later.
The expected SPR for Hepatitis A was 97%, and the Sponsor needed to exclude a difference of 10% points or more, p-value $\leq$ 0.025.
The statistical measures for estimated SPR and GMT were computed based on the statistical analysis model adjusting for pooled study center (study center with <=20 subjects were pooled into 1 center).
For the per-protocol analysis, the SPR for concomitant groups (1 and 2 combined, N=237) was 95.5%, and the GMT was 47.3. The SPR for the nonconcomitant groups (3 and 4 combined, N=234) was 95.8%, and GMT was 50.1. The estimate difference in SPRs was -.3% points with a 2-sided 95% CI (-4.2,3.7), which excluded a decrease of 10% points or more. Therefore, the immune response to VAQTA when given with MMRII+VARIVAX was acceptable. The estimated fold difference was 0.94 (95% CI: 0.81, 1.11).
For the all serology analysis, the SPR for the concomitant groups (1 and 2 combined, N=286) was 95% and the GMT was 45.5. The SPR for the nonconcomitant groups (3 and 4 combined, N=284) was 96.3%. The estimated difference in SPRs was -1.4% (95% CI: -5%, 1.9%), which also excluded a decrease of 10% points or more. The estimated fold difference was 0.90 (95% CI: .78, 1.03).
Conclusion: The hepatitis A antibody response was not negatively impacted when VAQTA was given with MMRII+VARIVAX.

Hypothesis 2b: Responses to Measles, Mumps, Rubella and Varicella when given with VAQTA were to be similar to historical controls when MMRII+VARIVAX were given without VAQTA. The expected response to MMR was a 99% SCR. The expected response to VARIVAX was that 90% would have a gpELISA>5 units.
The primary analysis for MMR was based on those seronegative to MMR.
The primary analysis for Varicella was based on those with an initial level <5gpELISA units.

Measles, Mumps and Rubella antibody responses at 6 weeks postdose 1 were compared when given with VAQTA (Group 1) or when given without VAQTA (Group 2). The Sponsor first presented the results for measles,

mumps and rubella antibody responses broken down by assays (original, new). Most of the subjects were tested using the original assays. The changes in the assays were determined to be acceptable for use of all results in the present trial (see product review). The seroconversion rates were similar for the original and new assays for measles, mumps and rubella.
The per protocol analysis is shown in the table below.

Table 30 (Protocol 057, p. 145, Module 5, Volume 2/10) shows the statistical analysis of the response rates versus historical rates for MMR and Varicella at 6 weeks after Dose 1 (VAQTA+MMRII+VARIVAX concomitantly at 12 months) Hypothesis 2b-Per Protocol Analysis.

Antigen	Vaccine Response	Group 1 N=156	Group 2 N=153	Groups 1 and 2 N=309	
Measles ---------	Observed SPR +/Tested 95% CI	100% 118/118 (96.9%, 100%)	97.6% 120/123 (93%, 99.5%)	**98.8%** 238/241 (96.4%, 99.7%)	Similar to historical rate of 99% (i.e., LB>89%) P<0.001
Mumps --------	Observed SPR +/Tested 95% CI 95% CI	99.2% 130/131 (95.8%, 100%)	100% 132/132 (97.2%, 100%)	**99.6%** 262/263 (97.9%, 100%)	Similar to historical rate of 99%, i.e., LB > 89%, p<0.001
Rubella --------	Observed SPR +/Tested 95% CI	100% 134/134 (97.3%, 100%)	100% 136/136 (97.3%, 100%)	**100%** 270/270 (98.6%, 100%)	Similar to historical rate of 99%, i.e., LB > 89%, p<0.001
Varicella ----------	% gpELISA >=5 +/Tested 95% CI GMT 95% CI	80.7% 109/135 (73.1%, 87%) 10.2 (8.4,12.4)	77.2% 105/136 (69.2%, 84.6%) 9.5 (7.9,11.4)	**79%** 214/271 (73.6%, 83.6%) 9.8 (8.6,11.2)	**Failed to meet similarity with historical rate of 90% i.e., criterion of lower bound > 80% was not met, p = .696**

The acceptable response rate for each vaccine component corresponded to the lower 95% CI being <10% points below the expected response rate for each vaccine component. The p-value <0.025 would support that the response rate was significantly greater than 89% for MMR vaccine components and significantly greater than 80% for varicella vaccine. The sponsor was able to show that similar response rates were obtained following receipt of MMRII as compared to historical response rates for measles, mumps and rubella, but were not able to demonstrate similar response rates following receipt of varicella vaccine as had been historically observed. While not pre-specified, the study did meet more stringent criteria of success with regards to the responses to the MMRII vaccine components, as defined as demonstrating that the LB of the 95% CIs for measles, mumps, and rubella are all <5% than the expected 99% SCR. Similar results were obtained for the all serology population, with the LB of the 95% CIs for measles, mumps and rubella also show < 5% difference from the expected SCR of 99%.
In the per-protocol and all-serology analysis, the Sponsor did not meet the pre-specified criterion for success with respect to response rates to the varicella vaccine component.

The original Hypothesis 2b stated the Sponsor would fail if they did not show similarity of responses to all 5 vaccine components (measles, mumps, rubella, varicella, and hepatitis A). The Sponsor notes that different results were obtained for sera assayed for varicella antibody from sera assayed in two separate runs, 2000 and 2002, respectively. They delayed testing some sera for varicella antibody in order to preserve these sera for hepatitis A testing until the new hepatitis A assay was available. They noted that the lower bound of the 95% CI of the sample run in 2000 was 80.5% (which would have met their goal of achieving a response to be >80%), but did not achieve this response rate with the samples run in 2002.
For the 2000 run, the point estimate for the response rate was 85.8% (188/219) with a 95% CI (80.5%, 90.2%). For the 2002 run, the point estimate for the response rate was 50% (26/52) with a 95% CI (35.8%, 64.2%).
The Sponsor initially postulated that the difference observed following the two runs for varicella antibody was the result of incorrectly stored serum specimens, and also influenced by a difference in the Tissue Culture Control optical density values for the 2002 assay. CBER requested additional information regarding these sera which were reviewed by other committee members. As the exact reason for the lower response rates in a subset of subjects could not be definitively established, and no control group was available who had received VARIVAX without VAQTA, CBER concluded that the immunogenicity data submitted to support the concomitant use of VARIVAX and VAQTA were not interpretable. A post-marketing study to assess the concomitant administration of these vaccines will be conducted.

Because the Sponsor did not meet the primary endpoint for hypothesis 2b, they analyzed MMRII+VARIVAX separately from VARIVAX+VAQTA. They performed a multiplicity adjustment using a Bonferroni type of adjustment (0.025/2), which requires for any of the 2 hypotheses, all comparisons will be met at the 0.025/2 level. The p-value of <0.001 was adequate for MMRII+VAQTA to be administered together, even if this was not prespecified.
The Sponsor also performed a per protocol immunogenicity summary of GMTs at Day 0, and 6 weeks post-MMRII and the proportion of subjects with %≥ 4-fold rise from Day 0 for MMR in those who were intially seropositive. **Table 64** (Protocol 057, p. 268, Module 5, Volume 2/10) shows this data.

Antigen	Assay	Time	Group 1 N	Group 1 GMT	Group 1 %>4-fold rise	Group 2 N	Group 2 GMT	Group 2 %>=4-fold rise
Measles --------	Old	Day 0 Week 6	15 14	120.4 3419.7	- 100% (14/14)	11 10	121.4 1517.9	- 80%(8/10)
	New	Day 0 Week 6	2 3	174.4 1728.6	- 100% (5/5)	2 3	273.5 1887.5	- 100% (2/2)
Mumps --------	Original	Day 0 Week 6	5 5	5.2 139.7	- 100%(5/5)	4 4	5.8 93.9	- 75%(3/4)
Rubella --------	Original	Day 0 Week 6	1 1	3.9 81.9	- 100% (1/1)	- -	- -	

Conclusion: VAQTA may be co-administered with MMRII without interference on the immune responses to measles, mumps and rubella. There are insufficient data to assess the immune response to VARIVAX when the vaccine is given concurrently with VAQTA.

Hypothesis 3: VAQTA+TRIPEDIA+/-POLIO versus VAQTA followed 4 weeks by TRIPEDIA+/-IPOL
Hypothesis 2 failed to meet the prespecified success criteria. Therefore, Hepatitis A SPR Group 3 (concomitant) was to be compared with VAQTA alone (nonconcomitant, Group 4) for Hypothesis 3a.
The primary antibody response rates to TRIPEDIA in Group 3 were to be compared with their expected historical responses.

Hypothesis 3a: Hepatitis A Response when given with TRIPEDIA +/- polio vaccine or without TRIPEDIA +/- polio vaccine.
4 weeks after Dose 2 VAQTA, the Hepatitis A SPR of those who received VAQTA+TRIPEDIA (+/- polio) were to be similar to Hepatitis A SPR in those who received VAQTA alone, and then 4 weeks later received TRIPEDIA +/- polio.
The expected SPR after the second dose of VAQTA was 99%. The criterion for similarity corresponded to the lower bound of the 95% CI on the estimate of the difference (concomitant minus nonconcomitant) in treatment groups excluding a decrease of 10% points or more (CI >-10% points) or a p-value <0.025. Again, the SPRs and GMTs were computed from a statitiscal model adjusting for pooled study centers using sample size weights (and study centers with $\leq$ 20 subjects were pooled into 1 center).
In the per-protocol analysis, Group 3 (concomitant, N=86), the SPR was 100%, and the GMT was 6095.1. In Group 4 (non-concomitant, N=97), the SPR was 100% and the GMT was 7266. The estimated difference between the SPRs for Group 3 and Group 4 was 0 (95% CI: -4.6, 6.1), with a p-value <0.001. The estimated fold difference of the ratio of GMTs was 0.84 (95% CI: 0.63, 1.11).
A secondary analysis was performed on all serology, regardless of protocol violation. These results were consistent with the above. (The LB of the 95% CIs were also < 5%).
Conclusion: The immune response to VAQTA at dose 2 was not negatively impacted by coadministration with TRIPEDIA +/- polio vaccine.

Hypothesis 3b: Diphtheria, Tetanus, and Pertussis PT and Pertussis FHA Responses
4 weeks after the second dose of VAQTA+TRIPEDIA +/- polio, this concomitant group were to have response rates for antibodies to diphtheria, tetanus, pertussis PT and pertussis FHA that would be similar to historical controls when TRIPEDIA was given without VAQTA. The Sponsor compared Group 3 (concomitant) versus historical controls in this analysis.

The expected rate for pertussis PT and pertussis FHA, based on the % ≥ 4-fold rise were 85% and 80%, respectively. These response rates were based on those described in the TRIPEDIA package insert for the PT and FHA components of TRIPEDIA following three doses of wDTP (whole cell vaccine). The pre-specified acceptable response rates for pertussis PT and pertussis FHA correspond to the lower bound of the 95% CI on the observed proportion being > 70% and 65%, respectively (<15 % points decrease from the expected response).

The pre-specified expected response rate for both tetanus and diphtheria (%≥0.1 IU/mL) was 95%.

The acceptable response rates for diphtheria and tetanus correspond to the lower bound of the 95% CI on the observed proportion being >85% (<10% point decrease for the expected response) for both antigens. A p-value of <0.025 would support this.

Table 36 (Protocol 057, p. 165-168, Module 5, Volume 2/10) shows the statistical analysis of the response rates versus historical controls for diphtheria, tetanus, pertussis PT and pertussis FHA at 4 weeks after vaccination at Visit 3 (VAQTA+TRIPEDIA concomitantly at 18 months). Hypothesis 3b –Per protocol analysis.

Antibody Assay	Time Point	Vaccine Response	Concomitant Administration Group 3 N=156	Group 1 N=156	Groups 1&3 N=312	Similarity Conclusion
Diphtheria ---------- ----------	Pre-injection	%>=0.1IU/ml +/Tested 95% CI GMT 95% CI	25.3% (21/83) 0.048 (93) (0.037, 0.062)	26.2% (22/84) (17.2,36.9%) 0.047 (84) (0.037,0.062)	25.7% 43/167 (19.3,33.1%) 0.048(167) (0.04,0.057)	
Diphtheria ---------- ----------	Post-injection	%>=0.1IU/ml +/Tested 95% CI GMT 95% CI	100% (105/105) (96.5%, 100%) 2.64 105) (2.15,3.24)	97.1% 101/104 (91.8,99.4%) 2.8(104) (2.21,3.54)	98.6% 206/209 (95.9%, 99.7%) 2.72(209) (2.33,3.17)	Rate in group 3 similar to historical control rate of 95%, i.e., lower bound > 85%. P <0.001
Tetanus----	Pre-injection	%>=0.1IU/ml +/Tested 95% CI GMT 95% CI	90.4% (94/104) (83%, 95.3%) 0.62 (104) (0.49, 0.80)	93% 93/100 (86.1,97.1%) 0.45 (100) (0.30,0.55)	91.7% 187/264 (87,95.1%) 0.53 (204) (0.45,0.62)	
Tetanus----	Post-injection	%>=0.1IU/ml +/Tested 95% CI GMT 95% CI	100% (108/108) (96.6%, 100%) 10.98 (108) (9.27, 13.02)	100% 105/105 (96.5,100%) 11.41(105) (9.75,13.35)	100% 213/213 (98.3,100%) 11.19(213) 9.98,12.55	Rate in Group 3 similar to historical rate of 95%, LB > 85%, p < 0.001
Pertussis PT ----	Pre-injection	GMT 95% CI	7.51 (104) (6.02,9.36)	7.2(100) (5.8,8.9)	7.3 (204) (6.3,8.6)	
Pertussis PT ----	Post-injection	%>=4xrise +/Tested 95% CI GMT 95% CI	74% (77/104) (64.5%, 82.1%) 56.5 (104) (46.3, 69.1)	78% (78/100) (68.6,85.7) 53.6(100) (42.8,67.2)	76(155/204) (69. %, 81.7%) 55.1 (204) (47.5,64)	Rate in Group 3 failed to meet similarity to historical rate of 85% (i.e., stat. LB of > 70% not met), p = .216
Pertussis FHA	Pre-injection	GMT 95% CI	10.7 (104) (8.7, 13.2)	10.6(100) (8.7,12.9)	10.6 (204) (9.2,12.3)	
Pertussis FHA	Post-injection	%>=4xrise +/Tested 95% CI GMT 95% CI	82.7% (86/104) (74%, 89.4%) 105.7 (104) (86.4, 129.2)	84% 84/100 75.3,90.6% 103.7(100) (87.2,123.5)	83.3% (170/204) 77.5,88.2% 104.7(204) (91.8,119.5)	Rate in Group 3 similar to historical rate of 80%. I.e., LB>65% p <0.001

The prespecified criterion for similarity of pertussis PT antibody levels of hypothesis 3b was not met.
The sponsor performed a secondary statistical analysis for the all serology group, and again, the pre-sepcified criteria for pertussis PT antibody responses were not met.

The Sponsor investigated the lower than expected response for PT response. Prebooster blood was taken at 13.5 months (4.5 months before booster dose given) to fit in with blood drawing schedule. However, in the historical control studies used for comparison, the prebooster blood samples were taken immediately before the booster dose was given. The Sponsor provides a table showing the results of these studies (Table 37, Protocol 057, p. 170, Module 5, Volume 2/10) which present the Pertussis Toxin (PT) antibody titers before and after receipt of a booster dose of DTaP vaccine in published studies of DTaP vaccines.)

DtaP Vaccine Given	Time of Administration of booster	Prevaccination Blood		Postvaccination blood		%>=4-fold increase in antibody level	Reference
Bilken Connaught DtaP	15-20M	Age 15-20M	GMT 12.2, N=88	Age 16-21M	GMT 237 N=88	NA	1.2.14
SK DtaP	18-24M	Age 18-24M	GMT 4.5, N=25	Age 19-25M	GMT 66.7 N=25	100%	1.2.15
Tripacel+COMVAX	18M	Age 18M	GMT 1.5, N=112	19M	47 N=100	96.7%	2.3.7

The sponsor also presented evidence of decline in antibody titer to pertussis PT from the time the primary series was completed to the time of the booster at 15-20 months. They postulated that the lower seroresponse rate to the PT antigen which was observed in Study 057 may have been due to the earlier timepoint at which the pre-vaccination titers were obtained (13.5 months) with a somewhat higher pre-vaccination GMT than in the other study where pre-vaccination sera were collected just prior to administration of the booster (4^{th} dose). While this may have contributed to the lower than anticipated response rates, retrospectively this is difficult to assess without antibody decay data specific to this study. Furthermore, as noted elsewhere, a number of other variables were introduced into the study that make a comparison of results obtained to the pertussis antigens in Protocol 057 to those described in the TRIPEDIA package insert difficult to interpret. The two studies were performed at different times in different populations (thus not a randomized, controlled comparison), the assays were performed in different laboratories, and the priming history of children included in the two studies differed. show similarity for the pertussis PT.
Thus, in review of these data, it is difficult to assess the clinical relevance of the pertussis component immune responses obtained from Protocol 057.

CBER requested that the serology for polio vaccine recipients be run since these samples were available. There were 441 subjects in the study that received 2 or 3 doses of IPV prior to entry into the study, and of these, 221

were randomized into Group 1 or 3. Of the 221, there were 135 who received 2 doses of IPV prior to study entry and 1 dose of IPV concomitantly with VAQTA in the study. Other subjects received mixed regimens of OPV and IPV, received 3 doses of IPV prior to study entry, or had unknown polio vaccination. Even though there were high percentages with seroresponse and high GMTs, because of the various primary courses of polio vaccine given (including OPV which is no longer recommended for administration), the data are insufficient to assess the immune response to a third dose of IPV when given concurrently with VAQTA according to the current US recommended schedule of all IPV series.

Conclusion: The data submitted with regards to the assessment of TRIPEDIA and VAQTA are not adequate to assess whether the two vaccines can be given concurrently without diminishing responses to the pertussis components

Secondary Immunogenicity Hypotheses

Two secondary immunogenicity hypotheses were of interest in this study.

The first was that 6 weeks after the first dose of VAQTA, children who received VAQTA concomitantly with MMRII and VARIVAX (Groups 1 and 2) would have an acceptable SPR for hepatitis A.

The second was that 6 weeks after the first dose of VAQTA, children who received VAQTA without other pediatric vaccines (Groups 3 and 4) would have an acceptable SPR for hepatitis A.

For both secondary hypotheses, the prespecified point estimate of SPR for children after the first injection of VAQTA was 97%. The SPR was considered acceptable if the lower bound of the 95% CI on the observed proportion was >87% (less than a 10 percentage point decrease from the expected historical response.) A p-value $\leq$ 0.025 would support the same conclusion.

Results:

The per-protocol analysis showed that for Groups 1 and 2 (concomitant, N=309), the SPR was 95.4% (95% CI: 91.8%, 97.7%). The LB was > 87% and the p-value was <0.001. For Groups 3 and 4 (nonconcomitant, N=308), the SPR for hepatitis A antibody was 95.7% (95%CI: 92.3%, 97.9%). The LB was > 87% and the p-value <0.001.

Similar results were obtained in a secondary statistical analysis conducted for the all serology group.

Conclusion: Children in this age group had an acceptable SPR 6 weeks after receiving VAQTA with MMRII + VARIVAX or alone.

8.1.2.2.3 **Safety Outcomes**

All subjects who were vaccinated and had safety follow-up were included in the safety summaries. These were broken onto three sections.

1. Safety of VAQTA alone or with other pediatric vaccines at Months 12 and 18 (Visits 1 and 3).
2. Safety of VAQTA alone at 12 months versus VAQTA+MMRII+VARIVAX (Groups 1 and 2 versus Groups 3 and 4).

3. Safety of VAQTA alone at 18 months versus VAQTA + TRIPEDIA (+/- polio) (Groups 1 and 3 versus Groups 2 and 4).

The safety results post-vaccination at Months 12 and 18: VAQTA alone or with other pediatric vaccines (Dose 1 and Dose 2).
For adverse events postdose 1 or 2 Days 0-14 after Visits 1 or 3: This looks at any dose of VAQTA +/- other pediatric vaccines (Days 0-14 after Visit 1 or Visit 3) [Table 41, Protocol 057, pp. 184-5, Module 5, Volume 2/10]**,** most subjects had follow-up, and the percentage of adverse events was similar in the 4 groups (57.1-67.1%), with 62% overall.
Local adverse events ranged from 12.2%-20.8%, with 16.5% overall. There were similar rates across the groups.
Systemic adverse events ranged from 51-61.7%, with 56.6% overall.
There were few **serious adverse events** (2, 0.3% overall) and 1(0.2%) was considered vaccine related.
One subject (0.2%) discontinued from the trial secondary to a vaccine related adverse events overall.

For adverse events postdose 1 for VAQTA Days 0-42 after Visit 1, the following were noted. [Table 42, Protocol 057, p. 186-187. Module 5, V. 2/10]
Overall, 61.1% had an adverse event, 7.6% overall with injection site adverse events and 58.8% overall with systemic adverse events.
There were 6 serious adverse events overall (1%) and one of these (0.2%) was considered vaccine related.
One subject (0.2%) discontinued secondary to an adverse event which was considered to be vaccine related.

For **adverse events following Dose 2 of VAQTA Days 0-14 post Visit 3,** the following were noted. [Table 43, Protocol 057, p. 188-189, Module 5, V. 2/10]
Overall, there were fewer adverse events (38.5% overall postdose 2 versus 61.1% overall postdose 1).
Overall, there were slightly more injection site adverse events (11.7% postdose 2 compared with 7.6% postdose 1), but fewer systemic adverse events overall (33.3% postdose 2 vs. 58.8% postdose 1.)
There was one (0.2%) serious adverse event postdose 2 overall.

Injection site adverse events on VAQTA Days 0-4 postdose Visit 1 and Visit 3, with incidences >=1% are shown. [Table 68 (Protocol 057, p. 274-275, Module 5, Volume 2/10)**.]**
Pain/tenderness/soreness were the most common injection site adverse events (5.4% in Group 1, 6.1% in Group 2, 4% in Group 3, and 8.2% in Group 4) in all treatment groups at the injection site for VAQTA alone at Visits 1 and 3.
Most injection site adverse events were mild-moderate intensity, with a short duration.
Other injection site adverse events in the 4 groups included erythema (0.7-5.4%), swelling (1.3-4%), and warmth (0-2.7%).

Group 4 (VAQTA alone at Visits 1 and 3) had the highest proportion of subjects with injection site adverse events.
At CBER's request, additional information regarding the severity of the injection site reactions was submitted and most were noted to be mild to moderate in severity.

Injection site adverse events at all injection sites were presented for VAQTA+MMRII+VARIVAX in Groups 1 and 2 versus VAQTA alone in Groups 3 and 4 (Visit 1, Days 0-4 post-vaccination). [Table 69 (Module 5, p. 276-278, Volume 2/10)] Most groups have fairly low injection site adverse events (generally < 5%), although Group 4 had a slightly higher rate (9.5% rate) than the other groups. This is in comparison to Group 3 (who also had VAQTA alone) with a 2% injection site adverse event.
Injection site adverse events at all injection sites were presented for VAQTA + TRIPEDIA +/- IPOL in Groups 1 and 3 versus VAQTA alone in Groups 2 and 4 (incidences $\geq$ 0%), Days 0-4 post visits 1 and 3. [Table 73 (pp. 294-296, Module 5, Volume 2/10)] There was slightly more local injection site adverse events at the TRIPEDIA injection site (especially swelling). The injection site adverse event rates for VAQTA given alone (6-7.3%) or when given with the TRIPEDIA+/- IPOL (4.4-6.7%) were not observationally very different from each other.

Systemic adverse events after each dose of VAQTA were presented.
The number /% with **systemic adverse events >0% Days 0-42 post Visit 1** in one or more treatment groups by body system are presented [Table 71 (Module 5, p.281-287, Volume 2/10)].
The number/% with **systemic adverse events >0% Days 0-14 post Visit 3** in one or more treatment groups by body system are also presented. [Table 75 (pp. 299-304, Module 5, Volume 2/10)].
For subjects in Group 4, who were administered VAQTA alone at Visits 1 and 3, the most commons systemic adverse events post Visit 1 were fever (23.1%,), URI (15.6), rhinorrhea (7.5), and irritability (6.8). Other systemic adverse events noted Days 0-42 after VAQTA dose 1 were cough (6.1%), vomiting (4.1%, 1/6 VR) and diarrhea (4.1%).

The most common systemic adverse events after Visit 3 in Group 4 was fever (8.1); URI (6.6); otitis media (5.1); and irritability (5.1)

Elevated Temperatures are presented. [Table 77 (Protocol 057, p.310-312, Module 5, Volume 2/10)]. The number/% with increased temperatures **by Visits days** (Days 0-4 after each visit) are shown for all groups. The temperatures were presented for >=102°F or 38.9°C oral equivalent. All temperatures were converted to the oral equivalent by adding 1°F to an axillary reading, subtracting 1°F from a rectal Temperature, and leaving an otic reading unchanged. Per this definition, the % ranged from 2.7%-6.2%.

CBER requested additional analyses of fevers. As per the Brighton Collaboration Fever Working Group, fever is considered to be defined as >= 100.4°F. However, this protocol was submitted and conducted before the above recommendations were released. In the findings of this working group, it is concluded that there is probably no reliable accepted method to convert Temperatures from one reading method to another, and that no anatomic site for measuring fever in a clinical setting has been shown to be consistently superior to another.

In Protocol 057, there were noted to be a number of subjects with temperatures listed as "normal". For this reason, this reviewer went through the Temperature dataset (Day 0-4 after any vaccination) and pulled out any Temperature (by any method) $\geq$100.4°F (38°C).

There were 48 subjects who had an increased Temperature after VAQTA alone. Three groups (2, 3, and 4) received VAQTA alone. 10.9% (48/441) had T$\geq$100.4°F.

When VAQTA was administered with TRIPEDIA +/- polio (Groups 1 and 3), 22/297 (7%) had T$\geq$100.4°F.

When VAQTA was administered with MMRII+VARIVAX (Groups 1 and 2), 28/294 (app.10%) had T$\geq$100.4°F.

The Sponsor submitted further breakdown of the Temperatures noted after each dose in response to CBERs request. In Table 3 of Comment 19 of the first CR Response, the breakdown of Ts after each visit for each group is presented. The Ts for Visits 1 and 3 were reviewed in detail, when VAQTA was given with or without other vaccines. This table is shown below for only Visits 1 and 3 (when VAQTA was administered).

Table 3-Number (%) of Subjects in Protocol 057 with Temperature Data for Visits 1 and 3 (Days 0-4 Following Each Visit)

	Group 1 N=156	Group 2 N=153	Group 3 N=156	Group 4 N=152	Total N=617
	N(%)	N(%)	N(%)	N(%)	N(%)
Visit 1	VQ+M+VR	VQ+M+VR	**VQ**	**VQ**	
Number if subjects	156	153	156	152	617
Subjects with follow-up	148	146	149	146	589
Maximum T(oral equivalent)					
Normal	18(12.2%)	14(9.6%)	**18(12.1%)**	**19(13%)**	69(11.7%)
Grade 0[<100.4F]	117(79.1%)	117(80.1%)	**114(76.5%)**	**112(76.7%)**	460(78.1%)
Grade 1[100.4-<101.3]	6(4.1%)	6(4.1%)	**10(6.7%)**	**8(5.5%)**	30(5.1%)
Grade 2[101.3-<102.2]	4(2.7%)	4(2.7%)	**2(1.3%)**	**3(2.1%)**	13(2.2%)
Grade 3[>=102.2]	2(1.4%)	4(2.7%)	**5(3.4%)**	**1(0.7%)**	12(2%)
Febrile	1(0.7%)	1(0.7%)	**0**	**3(2.1%)**	5(0.8%)
Total >100.4+febrile	13(8.8%)	15(10.3%	**17(11.4%)**	**15(10.3%)**	60(10.2%)
Total>101.3+febrile	7(4.7%)	9(6.2%)	**7(4.7%)**	**7(4.8%)**	30(5.1%)
Total≥102.2+febrile	3(2%)	5(3.4%)	**5(3.4%)**	**4(2.7%)**	17(2.9%)
Visit 3	VQ+T+P	**VQ**	VQ+T+P	VQ	
Number of subjects	138	140	139	138	555
Subjects with follow-up	130	131	133	137	531
Maximum T(oral equivalent)					
Normal	33(25.4%)	**25(19.1%)**	23(17.3%)	**27(19.7%)**	108(20.3%)
Grade 0[<100.4]	84(64.6%)	**91(69.5%)**	93(69.9%)	**89(65%)**	357(67.2%)
Grade 1[100.4-<101.3]	7(5.4%)	**13(9.9%)**	9(6.8%)	**11(8%)**	40(7.5%)
Grade 2[101.3-<102.2]	4(3.1%)	**0**	2(1.5%)	**6(4.4%)**	12(2.3%)
Grade 3[>=102.2]	2(1.5%)	**2(1.5%)**	4(3%)	**2(1.5%)**	10(1.9%)
Febrile	0	**0**	2(1.5%)	**2(1.5%)**	4(0.8%)
Total>100.4+febrile	13(10%)	**15(11.5%)**	17(12.8%)	**21(15.3%)**	66(12.4%)
Total>101.3+febrile	6(4.6%)	**2(1.5%)**	8(6%)	**10(7.3%)**	26(4.9%)
Total≥102.2+febrile	2(1.5%)	**2(1.5%)**	6(4.5%)	**4(2.9%)**	14(2.6%)

As noted in the table above, the proportion of subjects with Ts > 102.2°F or febrile were 3.4% or lower for subjects who received VAQTA alone at either Visit 1 or 3. For those who received VAQTA with MMRII+Varivax, the proportion of those with T> 102.2°F or were febrile were also 3.4% or less. In Protocol 057, the axillary method was used most often (47-56%), followed by the rectal method (21-31%), the qualitative method (12-28%), and rarely the otic or oral methods.

The second safety evaluation assessed adverse events following receipt of VAQTA+MMRII+VARIVAX versus VAQTA alone at Visits 1 and 2 (ages 12-13 months)**.**

The overall clinical adverse events Days 0-42 after Visits 1 and 2 (total of 86 days of follow-up) for subjects who received VAQTA+MMRII+VARIVAX at Visit 1 (Groups 1 and 2) versus VAQTA at Visit 1 followed 6 weeks later by MMRII+VARIVAX (Groups 3 and 4) are presented**.** (Table 44, Protocol 057, p. 194, Volume 2/10) Groups 1 and 2 were compared to Groups 3 and 4. Of 617 subjects, 594 (96.3%) had safety data after Visits 1 and 2. Each of the combined groups had safety follow-up in 267 subjects. Approximately 75% in each of the combined groups had one or more adverse events. The percentage with any systemic clinical adverse event was slightly less than 75% in each of these groups, while the percentage reporting injection site adverse events in each of the combined groups was approximately 10%. There was a slightly higher percentage of subjects with injection site adverse events

in the nonconcomitant group (11.8%) compared with the concomitant group (9.4%).

The number/% of subjects with injection site adverse events (≥1% in one or more treatment groups) for concomitant Groups 1 and 2, versus nonconcomitant Groups 3 and 4 Days 0-4 after either Visit 1 or 2 is presented. [Table 45 (Protocol 057, p. 197-198, Module 5, Volume 2/10)] This table includes adverse events prompted for on the Vaccine Report Card and those spontaneously reported. The most common injection site adverse event was pain/tenderness/soreness ranging from 2.4%-4%. Most were mild-moderate and of short duration (1-3 days).The statistical comparisons for injection site adverse events between Groups 1 and 2 versus Groups 3 and 4 for VAQTA+MMRII+VARIVAX, respectively, for Days 0-4 after either Visit 1 or 2 are presented. [Table 46 (pp. 199-200), Table 47 (pp. 201-202), and Table 48 (pp. 203-204) in Protocol 057, Module 5, Volume 2/10]

The p-values are based on comparisons between the concomitant groups (1 and 2) and the nonconcomitant groups (3 and 4) with respect only to injection site adverse events prompted for by the Vaccine Report Cards. The injection site for each vaccine was assessed. There was no statistically significant difference between the concomitant and nonconcomitant groups with respect to any of the injection site adverse events for VAQTA. However, the percentages of subjects with erythema at the injection sites for MMR or VARIVAX were significantly higher (p-value of 0.009 and 0.028, respectively) when these vaccines were given without VAQTA as compared to when they were given with VAQTA. [Table 47 [Protocol 057, p. 201-202, Module 5, Volume 2/10 and Table 48 Protocol 057, p. 203-204, Module 5, Volume 2/10]]

The number/% of subjects with specific adverse events (≥1% in one or more groups) and risk differences for Groups 1 and 2 (VAQTA+MMRII+VARIVAX at Visit 1 and no vaccine at Visit 2) and Groups 3 and 4 (VAQTA at Visit 1 and MMRII+VARIVAX at Visit 2) for Days 0-42 after Visit 1 and 2 (total 86 days) is presented. [Table 49 **(**Protocol 057, p. 206-212, Module 5, Volume 2/10)] These data show the combined systemic adverse events for the group that received VAQTA concomitantly with the group that received VAQTA alone, then received MMRII+VARIVAX over this total 86 day time period. It shows that there is not much of a difference in systemic adverse events whether the vaccines are given alone or together over the entire 2 visit time period (D 0 through Day 42 after the second vaccination).
The most common systemic adverse events were fever (33.7% for Groups 1 and 2, 34.7% for Groups 3 and 4); URI (19.2% for Groups 1 and 2, 22.6% for Groups 3 and 4); Otitis Media (18.5% for Groups 1 and 2, 13.5% for Groups 3 and 4). Other AEs included diarrhea (14.8% for Groups 1 & 2 and 11.1% for Groups 3 & 4), vomiting (6.1% for Groups 1 & 2 and 7.7% for Groups 3 & 4), cough (12.5% for Groups 1 & 2 and 11.1% for Groups 3 & 4), rhinorrhea (10.4% for Groups 1 & 2 and 12.1% for Groups 3 & 4), rash (9.4% for Groups

1 & 2 and 5.7% for Groups 3 & 4. The rashes were possibly related to MMRII. The incidences of adverse events for Groups 1 and 2 and Groups 3 and 4 were similar, and the LB of the 95% CI for the percentage point risk differences for these events were usually <5% (with a few < 10%). Although fevers were defined as Ts $\geq$ 102°F, when further analyzed as requested by CBER, most fevers were noted to be mild to moderate in severity.

The number/% of systemic symptoms by body system in Days 0-42 after Visit 1 is presented. (Table 71, Protocol 057, Module 5, Volume 2/10, pp. 282-87) Here, it is noted that more rashes in the concomitant groups (1 and 2) than in the nonconcomitant groups (3 and 4). There were slightly more cases of otitis media in Groups 1 and 2 (concomitant) (12.1%) compared with Groups 3 and 4 (6.7%). Febrile seizures were rare – 1(0.7%) were described in Groups 1, Group 3 and Groups 4.

The number/% of systemic symptoms by body system in Days 0-42 after Visit 2 is presented. [Table 72 (pp. 288-293, Protocol 057, Module 5, Volume 2/10)] After Visit 2, fevers were distributed fairly evenly across all groups. Respiratory disorders were also fairly evenly distributed.

There were somewhat more rashes in Groups 3 and 4 (these subjects received MMRII+VARIVAX at 6 weeks after VAQTA). For groups 1 and 2 (VAQTA+MMRII+VARIVAX), Visit 2 was a nonvaccine visit. Group 2 had somewhat more respiratory symptoms and disorders of the special senses.

Rashes/Mumps Symptoms were specifically looked at because of administration of MMRII and VARIVAX. [Table 50 (Protocol 057, p. 214-215, Module 5, Volume 2/10) compares Groups 1 and 2 compared with Groups 3 and 4 for Days 0-42 after Visit 1 (concomitant) or Visit 2 (nonconcomitant).] The Vaccine Report Card prompted for these rashes. Rubella-like rash was not reported in the concomitant group, but there were 4 subjects (1.4%) in the nonconcomitant group who did report rubella-like rashes. The difference was small but was statistically significantly different, with a p-value of 0.041. Measles-like rash was seen in 11 (3.7%) of the concomitant group, and 8 (2.8%) of the nonconcomitant group. Varicella-like rash was seen in 9 (3%) of the concomitant group and 4(1.4%) in the nonconcomitant group. No subject reported mumps symptoms.

The number/% of subjects with temperatures $\geq$ 102 ° F oral equivalent or abnormal during Days 0-4 after Visits 1 and 2 and risk differences with 95% CI is shown. (Table 51, Protocol 057, Module 5, Volume 2/10, p. 217) The comparison is between Groups 1 and 2 combined (VAQTA+MMRII+VARIVAX at Visit 1, then no vaccine at Visit 2) versus Groups 3 and 4 combined (VAQTA at Visit 1 then MMRII+VARIVAX at Visit 2) for a total of 10 days. The same conversion was used as noted earlier in this review. In this table, the % of Temperatures was 5.1% in Groups 1 and 2, and 7.1% in Groups 3 and 4. The risk difference with 95% CI was –2.0 (-6.1, 1.9) and the difference was not statistically significant.

The **third safety evaluation** included an assessment of adverse events following concurrent administration of VAQTA+TRIPEDIA+/-polio compared to vaccination with VAQTA, followed 4 weeks later by TRIPEDIA +/- polio vaccination (at 18-19 months of age)**.** Here, Groups 1 and 3 received the vaccines concomitantly at Visit 3, and Groups 2 and 4 received VAQTA alone at Visit 3 and TRIPEDIA +/- polio vaccine at Visit 4. There were no significant differences between those that received VAQTA with TRIPEDIA +/- IPOL compared with those that received VAQTA alone, except there may have been slightly more cases of otitis media in the concomitant group (4%) compared with the nonconcomitant group (1.1%, combined visits 3 and 4). A summary of adverse events Days 0-14 after Visits 3 and 4 (total 30 days) for concomitant Groups 1 and 3 (VAQTA+TRIPEDIA+/-IPOL at Visit 3, followed by no vaccine at Visit 4) versus nonconcomitant groups 2 and 4(VAQTA at Visit 3, followed by TRIPEDIA+/-IPOL at Visit 4) at Visits 3 and 4 is presented. [Table 52 (pp. 222-3, Protocol 057, Module 5, Volume 2/10)] Of the 555 subjects at Visits 3 and/or 4, 543 (97.8%) had safety data Days 0-14 after each visit. There was safety follow-up in 272 in the concomitant group and 271 in the nonconcomitant group. There were slightly more than 50% in each group that had one or more adverse events. The % with systemic adverse events was approximately 50% in each group. There was a slightly higher percentage of injection site adverse events in the nonconcomitant group (19%) than in the concomitant group (16.5%).

There were no subjects who discontinued from the study due to an adverse event Days 0-14 after Visits 3 and 4. There were 2 serious adverse events in the concomitant groups and 0 serious adverse events in the nonconcomitant groups in Days 0-14 after Visits 3 and 4. None of these serious adverse events was considered vaccine related by the investigator. Summaries of these data are presented. [Table 52 (Protocol 057, p. 222-223, Module 5, Volume 2/10)] 54.8% had 1+ adverse event in Groups 1 and 3, and 53.5% had 1+ adverse events in Groups 2 and 4.

The number/% with injection site adverse events $\geq$1% in one or more treatment groups for combined Groups 1 and 3 (VAQTA+TRIPEDIA+/-IPOL at Visit 3, then no vaccine at Visit 4) and combined Groups 3 and 4 (VAQTA at Visit 3, followed by TRIPEDIA +/- IPOL at Visit 4) by individual vaccine during Days 0-4 after either Visit 3 or 4 is presented. [Table 53 (Protocol 057, p. 225-226, Module 5, Volume 2/10**]** Pain/tenderness/soreness was the most common injection site adverse event at both injection sites for VAQTA and IPOL. The incidence of pain/tenderness/soreness at the injection site for VAQTA was 2.6% in the concomitant group, and 4.1% in the nonconcomitant group. The incidence of pain/tenderness/soreness at the injection site for IPOL was 4.3% for the concomitant group and 2.4% for the nonconcomitant group. The most common injection site adverse events at the injection site for TRIPEDIA were swelling, erythema and pain/tenderness/soreness. In the concomitant groups, the incidences for the injection site adverse events were swelling (7.3%),

erythema (6.5%) and pain/tenderness/soreness (6.1%). In the nonconcomitant groups, the incidence for injection site adverse events were swelling (9.8%), erythema (9.4%) and pain/tenderness/soreness (9.5%). Most injection site adverse events were of mild to moderate intensity of short duration (1-3 days).

The comparison of groups 1 and 3 combined (VAQTA+TRIPEDIA+/-polio) versus Groups 2 and 4 combined (VAQTA followed 4 weeks later by TRIPEDIA +/- polio) injection site adverse events prompted for on the Vaccine Report Card during Days 0-4 after Visit 3 or Visit 4 are presented with risk differences and p-values. [Table 54 and Table 55 (Protocol 057, Module 5, Volume 2/10)] There were no statistically significant differences at either visit for injection site adverse events.

Table 54 presents the injection site adverse events and risk differences at the injection site of the 2nd dose of VAQTA. The lower bound of the 95% CI for percentage point risk difference between the concomitant and nonconcomitant groups is <5%, and there are no statistically significant differences in the concomitant versus the nonconcimtant group when one looks at the VAQTA injection site. Table 55 presents the number/% of subjects with TRIPEDIA injection site adverse events prompted for on the Vaccine Report Card among subjects who received VAQTA concomitantly with TRIPEDIA +/- IPOL (Groups 1 and 3 combined) versus subjects who received VAQTA at Visit 3 followed by TRIPEDIA +/- IPOL at Visit 4 for Days 0-4 after Visits 3 or 4. The LB of the 95% CI for the percentage point risk difference was < 9% for all solicited local adverse events, and were not statistically significantly different whether TRIPEDIA was given with or without VAQTA.

The number/% of subjects with injection site adverse events for each of the vaccines (incidence >0% in one or more groups) both prompted for on the Vaccine Report Card and spontaneously reported for each of the 4 treatment groups for Visits 3 (Table 73) and 4 (Table 74) is presented. [Table 73 (pp. 294-295) and Table 74 (pp. 297-298) Protocol 057 Module 5 Volume 2/10] There was observationallyslightly more pain/tenderness/soreness at the TRIPEDIA injection site when given nonconcomitantly with VAQTA as compared when given concomitantly with VAQTA.

Systemic Adverse Events are next reviewed for Visits 3 and 4.
The number/% of subjects with systemic adverse events $\geq$1% in one or more treatment group by body system and risk differences for combined Groups 1 and 3 (VAQTA+TRIPEDIA+/-IPOL at Visit3, no vaccine at Visit 4) and combined Groups 2 and 4 (VAQTA at Visit 3, TRIPEDIA +/- IPOL at Visit 4) for Days 0-14 after Visits 3 and 4 (for combined follow-up of 30 days) is presented. [Table 56 (Protocol 057, p. 232-235, Module 5, Volume 2/10)] The most common **systemic adverse events** were fever (15.8% in groups 1 and 3, 16.6% for groups 2 and 4); URI (8.5% for groups 1 and 3, 8.9% for Groups 2 and 4); irritability (8.1% for groups 1 and 3, 7.4% for Groups 2 and 4); otitis media (5.9% for groups 1 and 3, 7.7% for Groups 2 and 4). The incidences

appeared similar for the concomitant and nonconcomitant groups, and the LB of the 95% CIs for the percentage point risk differences were all <10% (most < 5%) . Although fevers were defined as Ts ≥ 102°F, when further analyzed as requested by CBER, most fevers were noted to be mild to moderate in severity. Most fevers were described as mild to moderate, and lasted 1-5 days.

The number/percentage of subjects with adverse events (incidence >0% in one or more treatment group) for each of the 4 treatment groups for 15 days after Visits 3 (Table 75) and 15 days after Visit 4 (Table 76) is presented**.** [Table 75 (pp.299-304) and Table 76 (pp. 305-309), Protocol 057, Module 5, Volume 2/10]
Incidences were similar across the 4 groups.

Elevated Temperature was next examined for the VAQTA+/-TRIPEDIA.
The comparison of Groups 1 and 3 combined (VAQTA+TRIPEDIA+/-polio) versus Groups 2 and 4 combined (VAQTA followed 4 weeks later by TRIPEDIA +/- polio) with respect to the number/% of subjects with increased Temperature (maximum Temperatures >=102°F oral equivalent) during the Days 0-4 after Visits 3 and 4 combined is presented. [Table 57 (Protocol 057, p. 237, Module 5, Volume 2/10]
In groups 1 and 3 (concomitant), increased temperature was seen in 5.7% after Visits 3 and 4. In groups 2 and 4 (nonconcomitant), increased temperature was seen in 8.6% after Visits 3 and 4. The percentage point risk difference was –2.9 and the LB of the 95% CI was –7.5). The difference was not statistically significant (p=0.194).

The number/% with increased Temperature after each visit by treatment group (shown post each visit**)** is presented. [Table 77**,** Protocol 057, Module 5, Volume 2/10, pp. 310-11] The most common Temperature method used to record in Days 0-4 after Visit 3 was the axillary method (53.7%) followed by rectal (22.4%), and Days 0-4 post Visit 4 were axillary (49.3%) followed by qualitative (26.8%). The distribution of Temperature methods was consistent between Treatment groups for Visitors 3 and 4. These results were discussed for Visits 1 and 3 above (when VAQTA was given). At Visit 1, those with Ts ≥ 102°F were 2.7% for Group 1 (VQ+M+V), 6.2% for Group 2 (VQ+M+V), 4 % for Group 3 (VQ) and 3.4% for Group 4 (VQ). At Visit 2, those with Ts ≥ 102 ° F were 1.4% for Group 1 (None), 0% for Group 2 (None), 4.8% for Group 3 (M+V) and 2.1% for Group 4 (M+V). At Visit 3, those with Ts ≥ 102°F were 2.3% for Group 1(VQ+T+/-I), 1.5% for Group 2 (VQ), 4.5% for Group 3 (VQ+T+/-I) and 4.4% for Group 4 (VQ). At Visit 4, those with Ts ≥ 102 ° F were 1.7% for Group 1(None), 5.8% for Group 2 (T+/-I), 4.2% for Group 3 (None) and 6.5% for Group 4 (T+/-I).
There were 2 subjects who reported serious adverse events in the concomitant groups and none in the nonconcomitant group Days 0-14 after Visits 3 and 4 (Table 52).

Serious Adverse Events are presented. [Table 58 (Protocol 057, p. 240-242, Module 5, Volume 2/10)] This is reproduced below.

There were 14 serious adverse events during this study. AN01339 suffered a febrile seizure 9 days after receiving VAQTA+MMRII+VARIVAX . This child was on treatment for otitis media at the time of the vaccinations. AN01323 suffered a febrile seizure 9 days after vaccination with MMRII+VARIVAX. Neither of these subjects were discontinued from the study.

Serious Adverse Evenets

AN	Study#	Sex	Race	Age 1st vax	Dose	Days post vax	AE	Duration	Severity	Cause	Outcome
Treatment Group 1											
01339	57004	M	Cauc	13M	1MMR 1VAQTA 1VAR	9	Seizure, febrile	25 min	Severe	Possibly	Recovered
01556	57006	F	Hisp	12M	NONVAX	13	Accidental ingestion	1 day	Mild	Definitely Not	Recovered
01582	57007	M	NatAm	11M	NONVAX	3 5	Pneumonia Asthma	34days 10days	Mod Mild	Def Not DefNot	Recovered Recovered
01962	57010	M	Black	12M	1MMR 1VAQTA 1VAR	31	Ingestion, FB	2days	Mod	Definitley Not	Recovered
Treatment group 2											
01535	57006	M	Hisp	12M	NONVAX 2VAQTA	24 24	Seizure, febrile Seizure, febrile	.3 min 1 min	Severe Severe	Prob Not Prob Not	Recovered Recovered
01867	57006	F	Hisp	12M	2VAQTA	24	Seizure, febrile	2min	Severe	Probably Not	Recovered
01579	57007	M	NatAm	11M	1MMR 1VAQTA 1VAR	38	Acidosis Dehydration Gastroenteritis Vomiting	5days 5days 5days 1day	Mod Mod Mod Mod	Definitely Not	Recovered
Treatment Group 3											
01323	57004	F	Black	12M	1MMR 1VAQTA 1VAR	9	Seizure, febrile	10min	Mod	Possibly	Recovered
01342	57004	M	Black	12M	1VAQTA	17	Seizure, febrile	1day	Mod	Probably Not	Recovered
01554	57006	M	Hisp	12M	1IPOL 1TRIP 2VAQTA	9 9 9 9	Bronchiolitis Fever URI Laryngotracheo-Bronchitis	11days 1day 5days 11days	Severe Severe Severe Severe	DefNot DefNot DefNot DefNot	Recovered Recovered Recovered Recovered
01801	57009	M	NatAm	12M	1MMR 1VAR	2 2	Infection viral Seizure, febrile	6days 2min	Severe Severe	DefNot DefNot	Recovered Recovered
Treatment group 4											
01511	57006	F	Hisp	12M	1VAQTA	21	Seizure, febrile	7min	Severe	Probably Not	Recovered
01571	57006	M	Hisp	12M	2VAQTA	17 20	Rotavirus Dehydration	6days 3days	Severe Severe	ProbNot ProbNot	Recovered Recovered
02269	57013	M	Black	12M	1VAQTA	29	Asthma	3days	Severe	Definitely Not	Recovered

Serious Adverse Events

AN01323: A 12 month old black female (Durham, NC)-VAQTA was administered Day 0 (----------) (Lot 1110H), and then MMRII Lot 1781H, and VARIVAX Lot 1048H 6 weeks later (----------). Concomitantly, the child received Tylenol. Nine days after MMRII+VARIVAX, the child suffered a Left sided febrile seizure. She was brought to the ER. The subjects also had a rash (which started on the same day), and she vomited x 1. The rectal

Temperature was 103.6°F. Laboratory results revealed that serum chemistries and urinalysis were within normal range. She was discharged that day on Tylenol or Motrin. The child was seen 1 day later in the doctor's office and had a chickenpox like rash at the injection site (ten days postvaccination). Two vesicles were on the right arm at the injection site and 10 vesicles were on the trunk. She had had the vesicles on the face the day before per the family. An EEG performed seventeen days after vaccination was normal (sleep, awake). The child recovered. Eighty-one days after vaccination, the subject had a cold and fever x 2 days. She was given zithromax. Later that day, she had a febrile seizure x 2 minutes. She was treated with Rocephin. Serum chemistries, CSF values, and urinalysis were all normal. She was discharged the same day. She subsequently received VAQTA dose 2, TRIPEDIA and IPOL on 2/24/00.

AN01339: A 13 month old white male (Durham, NC)-VAQTA (Lot 1110H)+MMRII (Lot 1171H)+VARIVAX (1048H) was administered Day 0 (----------). The subject was teething and had a history of otitis media. Concomitant treatment at the time of vaccination included Tylenol and Motrin for teething and amoxicillin for otitis media prophylaxis. Nine days postvaccination, the child had 3 febrile seizures over a 25-minute period. The temperature (rectal) was 104°F. Laboratory values were normal, including a CBC, WBC, U/A, urine culture, drug screen and lumbar puncture. The CXR was abnormal and he was felt to have a possible bronchitis and fluid behind the tympanic membranes. In the ER, he was treated with Rocephin 750mg IV for otitis media and questionable bronchitis, and lorazepam 1 mg pr suppository for the seizure, and Tylenol 120 mg suppository for fever. He was discharged. The next day in the doctor's office, he was diagnosed with otitis media and possible bronchitis. He was given Rocephin 750 mg IM. He subsequently recovered. He was seen again two days postvaccination. The tympanic membranes looked normal, and he then diagnosed with pharyngitis and treated with Augmentin 200 mg po bid x 10 days. Nineteen days after vaccination, he was seen by the doctor, and had recovered. The subject subsequently received VAQTA dose 2, TRIPEDIA and IPOL on 3/1/00 and completed the study.

AN01342: A 12-month-old black male (Durham, NC)- This child received VAQTA (Lot 1110H) on Day 0 (----------). Seventeen days after vaccination, the child was taken to the ER with a febrile seizure (shaking of the upper extremities). The Temperature was 104°F. The CSF showed a glucose of 88 mg/dL (increased), an increased RDW (11.5-14.5% normal), WBC 14.5 (4.5-11 normal) with 21% bands (0-5% normal), blood glucose 150 (normal 70-140), Hct 32 (normal 32-42), segmented neutrophils 20.8 (normal 27-35), MCV 61 (normal 80-101), blood culture negative, CSF culture negative without any WBC or organisms, U/A hazy blood. He was treated with Rocephin, Motrin and Tylenol. He was discharged the same day and subsequently recovered. The next day, he had a temperature of 100.2 ° F, and

was diagnosed with a viral illness. The following day, he developed a non-pruritic rash around the neck going up and down the body. He was diagnosed with a viral exanthem and resolving viral illness. The subject subsequently recovered. He received MMRII and VARIVAX on 11/19/99 and VAQTA dose 2, TRIPEDIA and IPOL on 4/18/00.

AN01511: A 12-month-old Hispanic female (San Antonio, TX)- VAQTA (Lot 1110H) was administered at Day 0 (---------). Twenty-one days after vaccination, her Temperature was 99.8°F, and she was given Tylenol. That same day, she had a febrile seizure that lasted 6-7 minutes. She was brought to the ER. She was noted to have body posturing for 10-15 minutes. Her Temperature was 103°F rectal. In the ER, her Temperature decreased to 101°F (otic method). She was given Rocephin and Motrin. Laboratory tests showed a normal urinalysis and normal blood tests. Approximately 2.5 hours later, her Tympanic Temperature was 98.7°F. The subject was diagnosed with Right Otitis media and a possible UTI. She was given Motrin and Bactrim, and discharged. Bactrim was discontinued when the urinalysis was determined to be normal. The otitis media persisted until twenty-three days postvaccination and Motrin was given twenty-two to twenty-four days postvaccination. Subsequently, she recovered. She went on to receive MMRII and VARIVAX on 7/29/99, VAQTA dose 2 on 12/6/99, and TRIPEDIA and IPOL on 1/4/00.

AN01535: A 12-month-old Hispanic male (San Antonio, TX)-This subject received VAQTA (Lot 1110H)+MMRII (Lot 1781H)+VARIVAX (Lot 1048H) on Day 0 (----------). At the time of vaccination, he received benadryl, bromfed, amoxicillin, motrin, predicare, and Genepap for congestion, allergies and fever. Sixty-three days postvaccination, the child was diagnosed with scarlet fever. Sixty-six days postvaccination (twenty-four days post Visit 2, nonvaccine visit), the patient was taken to the ER after a febrile seizure. His rectal Temperature was 104°F. Laboratory tests showed a normal urinalysis. He was given Tylenol. Prior to discharge, his otic Temperature was 98°F. At week 24, he received VAQTA dose 2. Twenty-two days after vaccination, the subject was given motrin and Tylenol. Twenty-three days after the Week 24 vaccination, his temperature was 103.5°F. Twenty-four days after the Week 24 visit, the subject was taken to the ER with an axillary Temperature of 103.2°F and was diagnosed with otitis media. He was given ear drops to relieve ear pain and Augmentin, which he vomited. On the same day he had a febrile seizure x 1 minute, and brought back to the ER. His Temperature was 104.6°F. He was given xylocaine to numb the injection site and Rocephin. He was also given Tylenol for fever. The subject was discharged from the ER and Augmentin was discontinued. He was also given TussiOrganidin for a runny nose. The subject recovered.

AN01554: A 12 month old Hispanic male (San Antonio, TX): This subject received VAQTA Day 0 (---------) (Lot 1110H), then received MMRII (Lot

1781H) + VARIVAX (Lot 1050H) 6 weeks later (---------). At week 24 of the study (----------) , the subject received Dose 2 of VAQTA (Lot 1110H) and TRIPEDIA (Lot 7387B) + IPOL (Lot N0498-1). Nine days postvaccination at Week 24, the subject was taken to the ER and was diagnosed with fever, acute croup, acute bronchiolitis, and URI. His Temperature (rectal) was 105.6°F, and he received one dose of Motrin. The CXR showed poor inspiration and perihilar atelectasis. The subject was discharged from the ER on the same day and was given zithromax, prednisolone, and pseudephedrine-codeine. The subject subsequently recovered after 11 days. He received all vaccines, but did not complete the study because he was lost to follow-up.

AN01556: A 12 month old Hispanic female (San Antonio, TX)-This child received VAQTA (Lot 1110H)+MMRII (Lot 1781H) + VARIVAX (Lot 1048H) on Day 0 (----------). At week 24 (----------), VAQTA (Lot 0047J) +TRIPEDIA (Lot 7387BA) + IPOL (Lot N0498-1) were administered. Forty-eight days post vaccination at week 24 (thirteen days after Visit 4, no vaccine), the subject took potassium pills. The subject was taken to the ER, and had gastric lavage and an EKG, and received charcoal and IV fluids. The subject was discharged the next day, recovered and completed the study.

AN01571: A 12 month old Hispanic male (San Antonio, TX)-This child received VAQTA (Lot 1110H) on Day (--------), then 6 weeks later (---------) was given MMRII (Lot 1781H) + VARIVAX (Lot 1050H). At Week 24 (----------), the subject received Dose 2 of VAQTA (Lot 0047J). Eighteen days after the Week 24 vaccination, the subject was brought to the ER for diarrhea. His rectal Temperature was 100.3°F. The subject was discharged that day and administered Pedialyte for 1 day. Twenty days after the Week 24 vaccination, the child was brought back to the ER for diarrhea again (not improving). The subject was admitted for dehydration due to diarrhea. Laboratory tests were as follows: a blood culture was negative, a blood glucose of 122 (60-140), BUN 19 (5018), Cl 113 (96-106), Cr 0.6 (0.8-1.4), Potassium 4.4 (3.7-5.2), Sodium 143 (135-145), CO2 13 (20-29). The low serum bicarbonate was indicative of lactic acidosis due to dehydration and the subject was found to be positive for rotavirus. Laboratory values 1 day later were as follows: glucose 82, BUN 6, Chloride 114, Creatinine 0.4, Potassium 3.3, Sodium 140, and CO2 15. The patient was given IV hydration and antibiotics and was discharged 2 days after admission.

AN01867: A 12 month old Hispanic female (San Antonio, TX)- This child received VAQTA (Lot 1110H) + MMRII (Lot 1781H) + VARIVAX (Lot 1048H) at Day 0. At Week 24, the subject received Dose 2 VAQTA (Lot 0047H). Twenty-four days after the Week 24 visit, the subject was taken to the ER after experiencing 2 febrile seizures lasting app. 3 minutes and 2 minutes, respectively. Her rectal Temperature was 104°F, and the subject was diagnosed with bilateral otitis media, febrile seizures, and tonsillitis. The subject was treated with 1 dose Amoxicillin and discharged from the ER. The

subject was continued on Amoxicillin and Tylenol prn. The subject recovered and finished the study (was due to receive TRIPEDIA +/- IPOL).

AN01579: An 11 month Native American male (Baltimore, MD)-This child received VAQTA (Lot 1110H) + MMR (Lot 1171H) + VARIVAX (1048H) on Day 0 (----------). Concomitant treatment included pseudephedrine and guaifenisin for a URI. Thirty-eight days after vaccination, the subject was admitted to the hospital for gastroenteritis, loss of appetite, runny nose, cough and vomiting. The subject also had metabolic acidosis and dehydration. The subject received Tylenol for fever and IV fluids 0.9 normal saline, Ceftriaxone, and Clindamycin for gastroenteritis. The subject was discharged 3 days later and recovered. He subsequently received VAQTA dose 2 on 11/30/99, and TRIPEDIA and IPOL on 1/25/00, and completed the study.

AN01582: An 11 month old Native American male (Baltimore, MD)-This child received VAQTA (Lot 1110H) + MMRII (Lot 1171H) + VARIVAX (Lot 1048H) on Day 0 (----------). Forty-six days after the vaccination (and three days after Visit 2, no vaccine), the subject was hospitalized for right lower lobe pneumonia, with symptoms including congestion, wheezing, green exudates, and fever. The subjects was given Pediazole, Motrin, PedePred, and Albuterol. The wheezing (asthma) lasted for 10 days and the pneumonia was resolved after 34 days. The patient recovered, received VAQTA dose 2, TRIPEDIA and IPOL on 11/20/99, and completed the study.

AN 01801: A 12 month old Native American Male (Seattle, WA)- This child received VAQTA (Lot 1314J) on Day 0 (----------), and then 6 weeks later (----------) received MMRII (Lot 1171H) + VARIVAX (Lot 1802H). Two days after the vaccination at Week 6, the subject was taken to the ER for a febrile seizure that lasted 2 minutes. Seven days after the vaccination at Week 6, the subject was diagnosed with hand, foot, mouth disease, and the onset was determined to be the day of the febrile seizure. The subject recovered. The subject subsequently received VAQTA dose 2 and TRIPEDIA on 9/19/00.

AN01962: A 12 month old black male (Atlanta, GA)- This child received VAQTA (Lot 0047J) + MMRII (Lot 1979H) + VARIVAX (1802H) on Day 0 (----------). Thirty-one days after vaccination, the subject ingested a penny and was hospitalized. During hospitalization, the subject underwent a procedure to remove the penny. He was discharged 1 day later from the hospital, and recovered after 2 days. He subsequently received VAQTA dose 2, TRIPEDIA and IPOL on 4/17/00, and completed the study.

AN02260: A 12-month-old black male (Fort Worth, TX)- This child received VAQTA (Lot 110H) on Day 0 (----------). Concomitant treatment included cromolyn sodium (Intal) qid and Albuterol qid. Twenty-nine days after vaccination, the subject had asthma exacerbation. Thirty days after

vaccination, the subject was hospitalized for asthma and increased respiratory distress. The subject was given albuterol, lorazepam, terbutaline, and breathing treatments. The subject was also given IV prednisolone. The child was released from the hospital 1 day later and given prednisolone. The patient subsequently recovered. He subsequently received MMRII and VARIVAX on 8/1/00, VAQTA dose 2 on 12/5/00, and TRIPEDIA and IPOL on 1/4/01. He completed the study.

Subjects Who Discontinued from the Study Due to an Adverse Event
One subject discontinued due to an adverse event.
AN02061: An 11 months old Hispanic female – This child was discontinued from the study due to crying and rhinorrhea four days after vaccination, and fever and crying five days after vaccination with Dose 1 VAQTA. The rhinorrhea lasted 3 days, the fever lasted 2 days, and the crying lasted 1 hour on each of day 4 and 5.

AN	Study#	Sex	Race	Age 1st Vax	Dose # Vax	Day of Onset	AE	Duration	Date D/C	Severity	Relation
02061	057011	F	Hisp	11 M	1VAQTA	4 4 5 5	Crying Rhinorrhea Crying Fever	1 hour 3 days 1 hour 2 days	13 13 13 13	Severe Mild Severe Mod	Possibly Possibly Possibly Possibly

No labs were taken on this subject.
No other Vital signs were collected. No actual temperature was taken for this subject (temperatures were to be taken Days 0-4) since the "feverish" feeling occurred on Day 5. This adverse event was reported as a fever.

Also provided is R13 (Module 5, Volume 6/10) which is the worldwide adverse events **(WAES Reports: Listing of spontaneous reports of misuse of hepatitis A vaccine inactivated VAQTA from consumers and health care professionals.)** The time period was 12/19/95-7/1/03.
There were 73 inadvertent administration of VAQTA.
Two of these subjects who were in the 12-23 month old age group had slight fever. One was a 16 month old who received Hepatitis A and HIB and DPT-polio, and this subject had mild fever and roseola. One subject was a 5 week old who received Hepatitis A and had a slight fever.
One 18-month-old child had biliary atresia and received Hepatitis A vaccine and Bactrim. Increased LFTs, rash, increased bilirubin, mononucleosis, jaundice, increased WBC, and decreased platelets were noted.

8.1.2.3 **Comments & Conclusions Regarding Data (Reviewer's Opinion)**
VAQTA 25U/0.5mL given IM at Day 0 and Month 6 appears to be immunogenic in children as young as 12 months of age. Children who received VAQTA alone at 12 and 18 months of age had seropositvity rates similar to historical controls (children 2-3 years of age). The use of historical controls

and comparison to an older age group who did not receive the vaccine at the same time provide imperfect comparators for the assessment of the data. A better comparison of the GMTs would have been possible had more appropriate control groups been included in the evaluation of the data. The GMTs were presented for those who were initially seropositive and compared to those who were initially seronegative. The GMTs were similar in both groups, although they were slightly higher in those who were initially seronegative, especially when assessed with new hepatitis A assay, ----------. However, since the GMTs were all indicative of seroprotection, and the seropositivity after two doses was 100% in the younger age group (even in the all-serology group), this would seem to indicate that the subjects as young as 12 months have a protective antibody level after 2 doses of the vaccine.

VAQTA 25U/0.5mL given at 2 doses approximately 6 months apart also appears to induce an adequate immune response even when it is given with or without concomitant pediatric vaccines (i.e., MMRII and VARIVAX at age approximately 12-13 months, and TRIPEDIA +/- polio vaccine at app. 18-19 months.) The immune responses of those who received VAQTA alone was compared with those that received it concomitantly with the other pediatric vaccines noted above. The SPRs were statistically compared for those who received VAQTA alone to those who received VAQTA with and without other pediatric vaccines. The GMTs were provided for the concomitant and nonconcomitant groups, and appear observationally similar.

MMRII when given with VAQTA (and VARIVAX) at 12 months appears to induce a similar immune response when compared to historical controls. Again, the use of historical controls is not the preferred trial design method. In addition, a post-hoc analyses of the responses to measles, mumps, and rubella were conducted (because the initial data analysis plan stipulated that to be successful, the sponsor would have had to show success for measles, mumps, rubella, varicella and hepatitis A immune responses). Nonetheless, the seroconversion rates in the two groups who received VAQTA with MMRII was 98.8% to measles (95% CI: 96.4,99.7); 99.6% for mumps (95% CI: 97.7, 100), and 100% for rubella (95% CI: 98.6, 100) as compared to the expected historical rates of 99% for each of the three virus antigens.

The immunogenicity data were insufficient to support the coadministration of VAQTA with VARIVAX , TRIPEDIA, or polio vaccine. There were no data provided regarding the coadministration of VAQTA with PREVNAR or Haemophilus influenza b-conjugate vaccine in this age group. The Sponsor has committed to conduct post-marketing studies to assess immune responses for a varicella containing vaccine (PROQUAD), a Hib-conjugate vaccine, and a DTaP vaccine when given with or without VAQTA.

While the number of subjects 12-23 months of age enrolled in clinical trials submitted to support the lower age indication is limited to 706 subjects, there

were no major safety concerns from the data presented in this application. Most of the adverse events were mild to moderate in severity. The most common local reactions included pain, tenderness, and soreness. Fever, again mostly mild to moderate in severity, was the most common systemic adverse event. However, there were reports of serious adverse events that occurred during the course of Protocol 057, including subjects with febrile seizures. Most of the febrile seizures occurred with medical events that may themselves be associated with fever (e.g., otitis media, tonsillitis). One of the febrile seizures occurred after administration of VARIVAX and MMRII, and one occurred after administration of VARIVAX, MMRII and VAQTA. All of these subjects received both doses of VAQTA, and all but one completed the study (lost to follow-up).

9. **Overview of Immunogenicity (Efficacy) Across Trials** – Only Protocol 057 was used to assess immunogenicity and therefore efficacy. Available data appear adequate to support the efficacy of VAQTA in those 12-23 months of age. See discussions in protocol 057 and Section 8.1.2.3 above for a synopsis.

10. **Overview of Safety (Across Trials)**

VAQTA was studied for safety in both Protocols 043 and 057. VAQTA has been licensed in the U.S. since 1996 for those 2 years and older. Millions of doses have been administered. The size of the overall safety database in the 12-23 month old age group is somewhat limited. However, there is substantial safety data available in subjects from the ages of 2 years and older in this previously licensed product.

In the 12-23 month old population, Protocols 043 and 057 provided safety data in approximately 683 subjects with follow-up (and involved a total of 706 subjects). It was noted in the analyses that the proportion of subjects in Protocol 043 had a lower rate of adverse events compared to the proportion of subjects in Protocol 057. The reasons for this difference were not entirely clear. In Protocol 043, a homogeneous population was studied by one group who had conducted earlier efficacy trials for children 2 years and older. On the other hand, Protocol 057 was a multicenter trial. However, since the methods of recording adverse events were similar across the two studies, the adverse events from the two studies were able to be combined.

Overall, local adverse events most often included pain, tenderness, and soreness. No measurements were taken of the local reactions however, but most were reported to be mild to moderate in intensity. Systemic adverse events most often reported were fever, URI, and irritability. Also seen were diarrhea, cough, and vomiting. There were no significant differences in adverse events whether the vaccines were administered with other pediatric vaccines or alone.

Only 1 subject discontinued from the study due to an adverse event (crying, rhinorrhea, irritability), which occurred 4-5 days after vaccination with VAQTA.

10.1 **Safety Database** – Number of Subjects, Types of Subjects, and Extent of Exposure

Module 2 provides the overall safety tables.

There were a total of 706 children involved in Protocols 043 (N=89) and 057 (N=617). Of these, 241 received VAQTA concomitantly with other pediatric vaccines (MMRII, VARIVAX, TRIPEDIA, +/- optional polio vaccines).

Table 2.7.4.3 (Module 2, p. 21 Clinical Summary) is reproduced below and shows the overall extent of exposure in clinical studies to support the safety of VAQTA in 12-23 month old children.

Vaccine	Dose Volume	Protocol 043 N	Protocol 057 N
Dose 1 VAQTA (25U)	0.5 mL	89	617
Dose 2 VAQTA (25U)	0.5 mL	81	555
MMRII	0.5 mL	NA	603
VARIVAX	0.5 mL	NA	603
TRIPEDIA	0.5 mL	NA	521
IPOL	0.5 mL	NA	365
ORIMUNE	0.5 mL	NA	63

Table 2.7.4:4 (Module 2, p. 22, Clinical Summary) is reproduced below and presents a subject accounting for both protocols.

	Protocol 043	Protocol 057		Combined Protocols
	Nonconcomitant administration N=89	Nonconcomitant administration N=152	Concomitant administration N=465	Total N=706
Entered Male (age range mos.) Female (age range, mos.)	89 44(12 - 23) 45 (12 - 23)	152 83(11 - 13) 69(11 - 14)	465 248(11-13) 217(11-13)	706 375(11-23) 331(11-23)
VAQTA Dose 1 VAQTA Dose 2	89 (100%) 81 (91%)	152 (100%) 138 (90.8%)	465 (100%) 417 (89.7%)	706 (100%) 636 (90.1%)
Completed	81 (91%)	127 (83.6%)	376 (80.9%)	584 (82.7%)
Discontinued Deviation from protocol Refused further participation Lost to follow-up Subject nooncompliant Clinical AE-discontnued test vaccine	8 (9%) 0 0 8(9%) 0 0	25 (16.4%) 3 (2%) 5 (3.3%) 16 (10.5%) 1(0.7%) 0	89 (19.1%) 7 (1.5%) 24 (5.2%) 56 (12%) 1(0.2%) 1(0.2%)	122 (17.3%) 10 (1.4%) 29 (4.1%) 80 (11.3%) 2 (0.3%) 1(0.1%)

Table 2.7.4:5
Summary of Subject Characteristics – Protocols 043 and 057

	Protocol 043 Nonconcomitant Administration N=89	Protocol 057 Nonconomitant Administration N=152	Protocol 057 Concomitant Adminstration N=465	Combined Protocols N=706
Gender				
Male	44(49.4%)	83(54.6%)	248(53.3%)	375(53.2%)
Female	45(50.6%)	69(45.4%)	217(46.7%)	331(46.8%)
Age (Months)				
Mean				
SD	17.7	12	12	12.7
Median	3.5	0.4	0.3	2.3
Range	17	12	12	12
Male	12-23	11-14	11-13	11-23
Female	12-23	11-13	11-13	11-23
	12-23	11-13	11-13	11-23
Race/Ethnicity				
Asian	0	0	1(0.2%)	1(0.1%)
Black	0	25(16.4%)	63(13.5%)	88(12.4%)
Caucasian	89(100%)	90(59.2%)	260(55.9%)	439(62.2%)
Hispanic	0	23(15.1%)	85(18.3%)	108(15.3%)
Indian	0	0	1(0.2%)	1(0.1%)
Native American	0	10(6.6%)	33(7.1%)	43(6.1%)
Oriental				
Other	0	1(0.7%)	4(0.9%)	5(0.7%)
	0	3(2%)	18(3.9%)	21(3%)
Initial Hepatitis A serostatus (Vombined Assays)				
Positive (≥10mIU/mL)	0	16(0.5%)	55(11.8%)	71(10%)
Negative (<10mIU/mL)	0	129(84.9%)	382(82.2%)	511(72.4%)
Unknown	89(100%)	7(4.6%)	28(6%)	124(17.6%)

Table 2.7.4:6 – Clinical Adverse Experience Summary Following Any Dose of VAQTA Administered Nonconcomitantly at Both Visits Versus VAQTA Administered Concomitantly at Either Visit With Other Pediatric Vaccines (Days 0-14 Postvaccination)

	Protocol 043 Nonconcomitant Administration N=89	Protocol 057 Nonconcomitant Administration N=152	Protocol 057 Concomitant Administration N=465	Combined Protocol N=706
Number of subjects	89	152	465	706
Subjects with follow-up	89	147	447	683
N(%) with one or more				
AE	16(18%)	84(57.1%)	285(63.8%)	385(56.4%)
Injection site AE	8(9%)	19(12.9%)	79(17.7%)	106(15.5%)
Systemic AE	10(11.2%)	75(51%)	261(58.4%)	346(50.7%)
With SAE	0	0	2(0.l4%)	2(0.3%)
Deaths	0	0	0	0
Discontinued due to an AE	0	0	1(0.2%)	1(0.1%)
Discontinued due to SAE	0	0	0	0

10.2 **Safety Assessment Methods**

These were reviewed in the CR response. It was noted that follow-up was similar of both studies. The Table provided by the Sponsor in the CR response in Comment 15 which shows the duration of follow-up for adverse events after each visit in Protocol 043 and Protocol 057. This is reproduced below.

	Duration of AEs after each follow-up visit			
	Visit 1 (Day 0)		Visit 2 (Week 24)	
Protocol 043				
Injection Site AEs	5 days		5 days	
Temperatures	5 days		5 days	
Systemic AEs	15 days		15 days	
	Visit 1 (Day 0)	Visit 2 (Week 6)	Visit 3 (Week 24)	Visit 4 (Week 28)
Protocol 057				
Injection Site AEs	5 days	5 days	5 days	5 days
Temperatures	5 days	5 days	5 days	5 days
Systemic AEs	43 days (MMRII and Varivax administered)	43 days (MMRII and Varivax administered)	15 days	15 days

10.3 **Significant/Potentially Significant Events**

Overall 15.4 % had local reactions and 50.7% had systemic reactions. The local reactions included most often pain/tenderness/soreness; other local adverse events noted were erythema, swelling and warmth. The systemic adverse events most often seen were events commonly encountered in this age group, including irritability, fever. otitis media, upper respiratory infection, and diarrhea. It is noted that fever, when seen, was predominantly mild, and very few were grade 3 severity ($\leq$3.4%).

14 serious adverse events were reported in Protocol 057 and one in Protocol 043. The SAE in Protocol 043 in the 12-23 month old age group occurred over 200 days after the first dose of VAQTA (pneumonia).

As noted above, there were reports of serious adverse events that occurred during the course of Protocol 057, including subjects with febrile seizures. Most of the febrile seizures occurred with medical events that may themselves be associated with fever (e.g., otitis media, tonsillitis). One of the febrile seizures occurred after administration of VARIVAX and MMRII, and one occurred after administration of VARIVAX, MMRII and VAQTA. All subjects who experienced and SAE received both doses of VAQTA, and all but one completed the study (lost to follow-up).

Other serious adverse events are noted in Section 10.4.

10.3.1 **Deaths:** There were no deaths in either study.

10.3.2 **Other Significant/Potentially Significant Events**: None were noted.

10.3.3 **Dropouts**

Table 2.7.4:4 shows the reasons for subjects dropping out in each groups overall (shown in Section 10.1 above). In addition, additional information was provided in the CR response in Comment 20.

Summary of Subjects Lost to Follow-up in Protocols 043 and 057

Protocol	Number of Subjects	Reason for Discontinuation
Protocol 057 N=72		
	63	Never returned a VRC to study site after the prior visit and did not return for any remaining visits
	3	Moved and could not be contacted
	3	Missed scheduled appointments and was then outside the acceptable windowm of time for the visit.
	2	Family problems occurred such that the subject could not continue in the study
	1	Parents withdrew the child without excplanation
Protocol 043		
	9	Unavailable to return for the second dose of VAQTA with no further reason provided

Summary of Subjects Who Refused Further Participation in Protocol 057

Protocol	Number of Subjects	Reason for Discontinuation
Protocol 057 N=29		
	13	Parents withdrew consent for no specific reason
	9	Parents refused further blood draws
	2	Parents could no longer attend study visits
	2	Study appointments were missed and the child would be behind on routine immunizations with continued study participation
	1	Moved
	1	Parent felt there was too much paperwork
	1	The VRC was not returned

10.4 **Other Safety Findings**

Other serious medical events which occurred after vaccination with VAQTA in this population included accidental ingestion, pneumonia, asthma,, gastroenteritis with dehydration , bronchiolitis, fever, URI, laryngotracheobronchitis, rotavirus infection, and asthma exacerbation 20 days after vaccination

10.4.1 **ADR Incidence Tables (Local and Systemic Events)**

Table 2.7.4:7 – Number (%) of 12-23 month old subjects with injection site adverse events (Incidence ≥% in One or More Treatment Groups) at the Injection Site for VAQTA Among 12-23 month old subjects who received VAQTA alone at both visits or VAQTA administered concomitantly at any visit with other pediatric vaccines (MMRII, Varivax, TRIPEDIA, or IPOL) by Protocol
(Days 0-4 Following Each Vaccination Visit in Which VAQTA was administered)

	Protocol 043tion	Protocol 057	Protocol 057	Combined Protocols
	Nonconcomitant Administration	Nonconcomitant Administration	Concomitant Administration	Total
	Injection Site Of VAQTA N=89	Injection Site of VAQTA N=152	Injection Site of VAQTA N=465	Injection Site of VAQTA N=706
Number of subjects	89	152	465	706
Subjects with follow-up	89	147	447	683
N(%) with one or more SAEs	8(9%)	19(12.9%)	77(17.2%)	104(15.2%)
Discoloration	1(1.1%)	0	0	1(0.1%)
Ecchymosis	0	1(0.7%)	6(1.3%)	7(1%)

Erythema	1(1.1%)	8(5.4%)	31(6.9%)	40(5.9%)
Pain/tenderness/soreness	4(4.5%)	12(8.2%)	43(9.6%)	59(8.6%)
Swelling	4(4.5%)	6(4.1%)	25(5.6%)	35(5.1%)
Warmth	2(2.2%)	4(2.7%)	16(3.6%)	22(3.2%)

Table 2.7.4:14 – N(%) of Subjects with Systemic Clinical AEs (Incidence ≥1% in One or More Treatment Groups) Among 12-23 month old subjects who received VAQTA alone or VAQTA Administered Concomitantly at any Visit with Other Pediatric Vaccine (MMRII, VARIVAX, TRIPEDIA, IPOL or Orimune) by Protocol
(Days 0-14 Following any Vaccination Visit in which VAQTA was administered)

	Protocol 043	Protocol 057	Protocol 057	Combined Protocol
	Nonconcomitant Administration N=89	Nonconcomitant Administration N=152	Concomitant Administration N=465	Total N=706
Number of subjects	89	152	465	706
Subjects with follow-up	89	147	447	683
Subjects with one or more AEs	10(11.2%)	75(51%)	261(58.4%)	346(50.7%)
Body as Whole	4 (4.5%)	29 (19.7%)	101 (22.6%)	134(19.6%)
Fever	4 (4.5%)	26 (17,7%)	90 (20.1%)	120(17.6%)
Warm sensation	0	2 (1.4%)	0	2(0.3%)
Digestive System	0	19 (12.9%)	57 (12.8%)	76(11.1%)
Anorexia	0	4 (2.7%)	4 (0.9%)	8(1.2%)
Diarrhea	0	8 (5.4%)	32 (7.2%)	40(5.9%)
Vomiting	0	7 (4.8%)	20 (4.5%)	27(4%)
Hematologic and Lymphatic System	1(1.1%)	1(0.7%)	1 (0.2%)	3(0.4%)
Lymphadenopathy	1(1.1%)	0	0	2(0.3%)
Metabolic/Nutritional/Immune	0	2(1.4%)	5(1.1%)	7(1%)
Nervous System and Psychiatric	4(4.5%)	22(15%)	69(15.4%)	95(13.9%)
Crying	0	3(2%)	9(2%)	12(1.8%)
Emotional Changes	1(1.1%)	0	0	1(0.1%)
Insomnia	0	4(2.7%)	1(0.2%)	5(0.7%)
Irritability	3(3.4%)	14(9.5%)	57(12.8%)	74(10.8%)
Somnolence	0	2(1.4%)	3(0.7%)	5(0.7%)
Respiratory System	2(2.2%)	35(23%)	104(23.3%)	141(20.6%)
Asthma	0	3(2%)	2(0.4%)	5(0.7%)
Congestion, nasal	0	1(0.7%)	7(1.6%)	8(1.2%)
Congestion, respiratory	0	1(0.7%)	10(2.2%)	11(1.6%)
Cough	0	9(6.1%)	26(5.8%)	35(5.1%)
Infection, upper respiratory	2(2.2%)	22(15%)	45(10.1%)	69(10.1%)
Laryngotracheobronchitis	0	1(0.6%)	7(1.6%)	8(1.2%)
Rhinorrhea	0	9(6.1%)	30(6.7%)	39(5.7%)
Sneezing	0	2(1.3%)	1(0.2%)	3(0.4%)
Skin and Skin Appendage	2(2.2%)	11(7.5%)	72(16.1%)	85(12.4%)
Miliaria rubra	0	1(0.7%)	5(1.1%)	6(0.9%)
Rash	2(2.2%)	2(1.4%)	27(6%)	31(4.5%)
Rash, diaper	0	1(0.7%)	5(1.1%)	6(0.9%)
Rash, measles, mumps, rubella-like	0	0	7(1.6%)	7(1%)
Rash, varicella-like	0	0	6(1.3%)	6(0.9%)
Viral exanthema	0	1(0.7%)	6(1.3%)	7(1%)
Special Senses	0	14(9.5%)	61(13.6%)	75(11%)
Conjunctivitis	0	1(0.7%)	8(1.8%)	9(1.3%)
Otitis	0	2(1.4%)	10(2.2%)	12(1.8%)
Otitis media	0	10(6.8%)	42(9.4%)	52(7.6%)

Table 2.7.4:15 – Number(%) of 12-23 month old subjects in Protocol 043 and Protocol 057 Combined with Specific Systemic Clinical AEs (Incidence ≥1% in One or More treatment groups) by Body system following each dose of VAQTA Following each dose of VAQTA for subjects receiving VAQTA alone (Days 0-14 postvaccination)

	Dose 1	Dose 2
Number of subjects	241	219
Subjects with follow-up	236	218
Subjects with one or more AEs	55(23.3%)	49(22.5%)
Body as Whole	21(8.9%)	14(6.4%)
Fever	19(8.1%)	13(6%)
Digestive System	10(4.2%)	12(5.5%)
Anorexia	2(0.8%)	3(1.4%)
\Diarrhea	4(1.7%)	5(2.3%)
Vomiting	4(1.7%)	4(1.8%)
Nervous System and Psychiatric	17(7.2%)	11(5%)
Crying	3(1.3%)	0
Insomnia	2(0.8%)	2(0.9%)
Irritability	11(4.7%)	8(3.7%)
Respiratory System	21(8.9%)	21(9.6%)
Asthma	1(0.4%)	2(0.9%)
Cough	4(1.7%)	5(2.3%)
Infection, upper respiratory	15(6.4%)	10(4.6%)
Rhinorrhea	6(2.5%)	4(1.8%)
Skin and Skin Appendage	6(2.5%)	7(3.2%)
Rash	1(0.4%)	3(1.4%)
Special Senses	4(1.7%)	10(4.6%)
Otitis Media	3(1.3%)	7(3.2%)

10.4.2 **Laboratory Findings VS, ECGs, Special Diagnostic Studies:** No laboratory studies (except for immunogenicity assays and assessment of adverse events) were obtained. Ts were followed. No other studies were conducted.

10.4.3 **Product-Demographics Interactions:** There is no evidence from the data included in Protocols 043 and 057 that there were specific safety concerns for specific populations.

10.4.4 **Product-Disease Interactions:** In the population of 12-23 month old children, no apparent product-disease interactions were identified. There was one case outside of the studies (from the WAES reports) of a child (18 months of age) with increased LFTs after vaccination with VAQTA. However, this child had a history of biliary atresia, received Bactrim, and was subsequently found to have mononucleosis.

10.4.5 **Product-Product Interactions (Concomitant Administration of Vaccines)** These results have been reported in Section 8. In summary, VAQTA does not appear to interfere with immune responses to MMRII when given together (as per a post-hoc analysis with historical controls). There are insufficient data at the present time to support coadministration with a varicella containing vaccine, DTaP, and IPV. There are no data to support coadministration with PREVNAR or a Hameophilus influenza b-conjugate vaccine.

10.4.6. **Immunogenicity (Therapeutic Proteins) (if relevant)** not applicable.

10.4.7. **Human Carcinogenicity** – There have been no studies on the carcinogenicity to date.

10.4.8. **Withdrawal Phenomena/Abuse Potential** – not applicable

10.4.9. **Human Reproduction and Pregnancy Data** - No studies have been conducted to assess administration of VAQTA to women who are pregnant, and the vaccine is labeled as Category C. There are no data on breast feeding with this product.

10.4.10 **Assessment of Effect on Growth** – not assessed

10.4.11 **Overdose Experience** – one subject in Protocol 043 received three doses of VAQTA instead of two without apparent ill effect.

10.4.12 **Person –to-Person Transmission, Shedding** – not applicable, as this is an inactivated product.

10.4.13 Post-Marketing Experience

A post-marketing safety study involving 42,110 people > 2 years of age who received 1 or 2 doses of VAQTA, which was conducted 4/1/97-12/31/98 at Kaiser Permanente Vaccine Study Center in Northern California, was resubmitted with this supplement (Module 5, Volume 6/10, Reference 12). This was previously reviewed. Multiple analyses were conducted for relative risks of adverse events collected before and after vaccination window time periods. The results have been previously incorporated into the label.

10.5. Safety Conclusions

No major safety concerns were identified from the available safety data from the 12-23 month old age population enrolled in Protocol 043 and 057. However, the total safety database for this cohort submitted in support of the new indication includes 706 children and thus, the ability to detect adverse events that occur infrequently and are specific for this age group is limited. CBER has requested that an additional 3000 subjects in the 12-23 month old age group be studied in post-marketing studies. The sponsor has agreed to conduct these studies. Additionally, post-marketing adverse events will be collected and analyzed through the VAERS system.

11. **Additional Clinical Issues**

A major additional clinical issue for this age group involves coadministration of VAQTA with other commonly administered childhood vaccines. In Protocol 057, it was demonstrated that MMRII may be given with VAQTA without an negative impact on the immune response to either vaccine.

The Sponsor has agreed to conduct three post-marketing studies, two of which will study immune responses when VAQTA is administered with other pediatric vaccines. One of these studies will involve administration of VAQTA + PREVNAR + PROQUAD, and one will involve administration of PEDVAXHIB + VAQTA + DTaP. A third study will involve a safety study of VAQTA and PROPQUAD.

11.1. **Directions for Use**

The pediatric formulation is used in the 12-23 month age group, and contains 25U hepatitis A virus protein in 0.5 mL in a single dose vial or prefilled syringe (with a 5/8 inch needle).

The vaccine is to be stored at 2-8 ° C (36 ° F-46 ° F).
The material used in Protocol 057 was to be stored as noted, and vaccine was provided in a single dose vial or prefilled syringes.
In Protocol 043 (which took place earlier), the vaccine was supplied in either single dose vials containing 25U/0.5 mL or single dose vials containing 50U/1 mL. Subjects were all given 0.5 mL so received 25U of hepatitis A virus protein. Vaccines were to be stored at 2-8 ° C (no freezing).

11.2. **Dose Regimens and Administration**

For administration of VAQTA to children and adolescents ≥12 months to 18 years, the deltoid muscle can be used if muscle mass is adequate. The needle size can range in size can range from 22-25G and from 7/8 to 1 ¼ inches, on the basis of the size of the muscle. For toddlers, the anterolateral thigh can be used but the needle should be larger, usually 1 inch.
All the VAQTA injections were given imtramuscularly in the studies, and are to be given IM.

11.3. **Special Populations**

Only healthy children were immunized in the studies reviewed.

11.4. **Pediatrics**

This supplement presents data to support administration of VAQTA to children as young as 12 months. This vaccine is safe and immunogenic down to 12 months of age.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this 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 of age and older. Studies demonstrating safety and effectiveness of VAQTA vaccine in individuals less than 12 months of age are deferred as the clinical development in this age range, to include an assessment of the efficacy of the safety of VAQTA administered with routinely recommended US licensed vaccines given to children less then 12 months of age, is under development. . The status of the required post marketing commitments will need to be reported annually according to 21 CFR 601.70.

12. **Conclusions – Overall**

Available data seem adequate to support the efficacy of VAQTA in the 12 – 23 month old age group. The vaccine was immunogenic in this age group, with 100% showing seroconversion in those initially seronegative after two doses of vaccine, whether given with or without other pediatric vaccines.
The size of the overall safety database in this age group is somewhat limited. Additional safety data will be collected in post-marketing studies. However, there is substantial safety data available in subjects from the ages 2 and older in this previously licensed product. There were no major safety concerns evident from the available data. There were expected local reactions, with pain, tenderness, soreness most commonly seen, in addition to swelling and erythema.

The most common systemic adverse event was fever, but the majority of the temperature elevations were mild to moderate.

There were reports of serious adverse events during one of the trials, including febrile seizures. Most of the febrile seizures were associated with other medical events (e.g., otitis media), and one occurred after the subject received MMRII and Varivax along with VAQTA.

Regarding the concomitant vaccines administered with VAQTA, only MMRII was shown to be equally immunogenic compared to historical controls who had received MMRII without VAQTA as when given with VAQTA during the study. No major safety concerns were identified from the available data.

Further post-marketing studies will be conducted including administration of VAQTA with a varicella-containing vaccine, PREVNAR, a Haemophilus influenza b conjugate vaccine, and DTaP to attempt to determine if these other vaccines may be given with VAQTA. These studies will contribute a total of an additional 3000 subjects for the safety database.

13. **Recommendations**

13.1. **Approval Recommendations**

CBER recommends approval of VAQTA down to 12 months of age.

13.2. **Recommendations on Postmarketing Actions**

CBER recommended an additional safety database of 3000 children with coadministration studies to include VAQTA + HIB, VAQTA + PREVNAR, VAQTA + DTaP and VAQTA + varicella-containing vaccine (PROQUAD). We have reviewed the concept protocols and have made recommendations (to follow in a separate review).

13.3. **Labeling**

The label was changed to achieve consistency with CBER's current guidance on the intent and format for various sections of package inserts, and to include the new indication for 12-23 month old age group and supporting data. In addition, language was clarified regarding coadministration of VAQTA with other pediatric vaccines. The final clean label was reviewed and appears acceptable.

14. **Comments and questions for the applicant**

The Sponsor has been supplied with comments regarding the post-marketing commitment studies.