



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: December 5th, 2014

FROM: Dino Feigelstock

SUBJECT: Review Memo for STN 125563/0 ((b) (4) vaccine).

TO: Katie Rivers, DVRPA

THROUGH: Steven Rubin, Sara Gagneten, and Robin Levis, DVP, OVR.

Brief Description of Product:

((b) (4)) (referred to as PR5I in this memo) is a vaccine for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib). PR5I is a suspension for intramuscular injection in a single-dose vial for use as a three-dose series in children from 6 weeks through 4 years of age (up to the 5th birthday). PR5I is a hexavalent combination vaccine formulated with the following drug substances:

- 1) Diphtheria Toxoid Adsorbed
- 2) Tetanus Toxoid Adsorbed
- 3) 5-Component Acellular Pertussis Adsorbed, which is comprised of the following five antigens:
 - Pertussis Toxoid (PT) Adsorbed
 - Filamentous Haemagglutinin (FHA) Adsorbed
 - Pertactin (PRN) Adsorbed
 - Fimbriae Types 2 and 3 (FIM) Adsorbed
- 4) Inactivated Vero Trivalent Poliovaccine bulk (vIPV)
- 5) Haemophilus b Conjugate (PRP-OMPC)
- 6) Hepatitis B Surface Antigen (HBsAg).

The proposed proprietary name of the Drug Product is ((b) (4)). The Drug Product is manufactured by MCM vaccine Company (a partnership between Sanofi Pasteur Limited and Merck Sharp & Dohme Corp).

Description of Submission:

I was assigned to review the two assays used to measure anti-rotavirus antibodies: the Serum Anti-rotavirus Immunoglobulin A (IgA) Assay and the Serum Neutralization Assay

(SNA). These assays were used to evaluate the immune response to anti-rotavirus vaccines when administered concomitantly with the PR5I vaccine (as secondary objectives).

Serum Anti-rotavirus Immunoglobulin A (IgA) Assay

The serum anti-rotavirus IgA (b) (4)




Serum Neutralization (b) (4) for Serum Neutralizing Antibodies to Rotavirus


The rotavirus serum neutralizing antibody (SNA) (b) (4)



The operating characteristics of both assays were established in the (b) (4)



Validation documents for the Rotavirus Serum IgA (b) (4) were previously



submitted in the BLA for RotaTeq™ (Rotavirus Vaccine, Live Oral, Pentavalent) (BLA #125122).

Given that these assays were later transferred from the (b) (4), studies were performed to assess whether the (b) (4) is capable of producing results acceptably comparable to those derived by the Main Campus. Data from these studies were submitted previously (May 2014) by Merck under BLA 125122 supplements 1247 and 1250.

Anti-rotavirus Clinical Data (Protocols 005 and 008):

The immune response to each antigen in PR5I was evaluated in the context of concomitant administration of PR5I and RotaTeq in Protocol 005 using both assays. I reviewed the data pertaining to immune responses to Rotateq. The immune response to RotaTeq was evaluated by measuring GMTs of anti-rotavirus IgA at one month post-dose 3 (as a secondary end point). The results indicate that the GMT of anti-rotavirus IgA at one month post-dose 3 is similar (estimated GMT ratio 1.02, above the pre specified non-inferiority margin of 0.67) in subjects who received either PR5I or licensed component vaccine control (Annex 1, table 1). In addition, > 97% of subjects in each vaccination group seroconverted to anti-rotavirus IgA at one month post-dose 3 as indicated by the percent of subjects with ≥ 3 -fold rise from baseline titers (Annex 1, table 2). Finally, the GMTs for serum neutralization antibody were similar between vaccination groups for all serotypes tested (Annex 1, table 2). I noted a minor discrepancy between the data presented in table 1 and 2 (anti-rotavirus IgA GMT titers are 282.54 and 277.95 in one table versus 278.19 and 274.46 in the other).

Protocol 008 was designed to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with Rotateq or Rotarix (and Prevnar 13) vaccines. No data on the immunogenicity of Rotarix is presented in the submission. Of note, the final immunogenicity data for this study are not part of the pivotal data being provided in support of licensure in the U.S.

Reviewer's Comments:

The assays selected by the sponsor to evaluate the response to rotavirus were previously used to evaluate the response to RotaTeq vaccine in clinical trials. Validation documents for both assays were previously submitted in the BLA for RotaTeq (BLA #125122). The CMC reviewer of RotaTeq (BLA 125122) indicated in his review memo that these two assays were thoroughly reviewed by CBER staff for their appropriateness and use in clinical studies. In addition, those assays were also used to evaluate the response to RotaTeq when administered concomitantly with other vaccines. The potential interference of samples obtained from subjects vaccinated with PR5I with the performance of the assays was discussed with the sponsor in the corresponding IND and resolved (see my review memo for IND 14496 amendment 85 stamped April 9th, 2014).

I reviewed the studies performed in order to assess whether the (b) (4) is capable of producing results acceptably comparable to those produced by the Main Campus. In these studies, up to (b) (4) samples having different anti-rotavirus antibody titers were assayed in the two laboratories. Analysis of the data included comparison of titers, assessment of concordance slopes, agreement in serostatus, and assay precision. Although I observed

differences between sites, I consider that the (b) (4) laboratory is acceptable for performing the Rotavirus assays, especially bearing in mind that the obtained results are secondary objectives and that all samples are run using the same assay.

Regarding the clinical studies, I consider that the data presented show that the immune response to RotaTeq was non-inferior in subjects who received RotaTeq concomitantly either with a 3-dose infant series of PR5I or with a licensed control vaccine regimen. No anti-rotavirus immunogenicity data when Rotarix was concomitantly administered with PRI5 were presented in the submission (note that these data are not part of the pivotal data being provided in support of licensure in the U.S).

Importantly, in a previous communication (IND 14496, November 01, 2010), CBER stated that “in the absence of an identified serological measure that can be used to infer vaccine-induced protection for rotavirus vaccines, CBER does not currently require an evaluation of immune responses to rotavirus vaccine in concomitant immunization studies. While CBER does not object to exploratory evaluation of immune responses to RotaTeq, CBER currently does not consider the results from the analyses proposed by the sponsor to be adequate to support a labeling claim that PR5I does not interfere with immune responses to RotaTeq.” In response to CBER’s comment, the sponsor proposed (IND 14496, amendment 2, response 12) that the current study design will allow them to claim that PR5I may be given concomitantly with rotavirus vaccines.

We noted a minor discrepancy in the anti-rotavirus IgA GMT titers reported (282.54 and 277.95 according to table 2.7.3 Prophylaxis: 16, page 59 of 130, and 278.19 and 274.46 according to table 2.7.3 Prophylaxis: 17, page 60 of 130). Given this is a minor difference that will not affect the interpretation of the results and could have occurred due to minor variations in calculations, a request for clarification was not issued to the sponsor.

Reviewer’s Recommendation:

In conclusion, both assays [serum anti-rotavirus IgA (b) (4)] and rotavirus serum neutralizing antibody (SNA) (b) (4)] are adequate to evaluate the immunogenicity of rotavirus vaccines when administered concomitantly with PR5I.

Annex 1: Anti-rotavirus Immune Responses

Table 1: Analysis of Non-Inferiority Regarding GMT for RotaTeq at One Month Post-dose 3 When Administered Concomitantly with PR5I/Control (Protocol 005)

Antigen	Endpoint	PR5I (N=924)		Control (N=460)		Estimated GMT Ratio [1] (95% CI)	NI Margin	One-Sided P-Value [1]	Conclusion: Non-inferiority Criterion Met/Not Met
		n	Estimated Response [1]	n	Estimated Response [1]				
Rotavirus IgA	GMT	522	282.54	274	277.95	1.02 (0.83, 1.24)	0.67	<0.001	Met

[1] The estimates for GMT, GMT ratio (PR5I group/Control group), and p-value were based on an ANCOVA model with natural log-transformed postvaccination titer as the response variable, and vaccination group, natural log-transformed prevaccination titer, actual brand of birth dose of hepatitis B vaccine (RECOMBIVAX HB™ or Other/Unknown) as explanatory variables. The missing prevaccination titers are imputed by a multiple imputation method and used in the ANCOVA analysis.
PR5I group received PR5I + Pevnar 13™ + RotaTeq™ at 2, 4, 6 mos; DAPTACEL™ + PedvaxHIB™ + Pevnar 13™ at 15 mos.
Control group received PENTACEL™ + Pevnar 13™ + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB™ at 2, 6 mos; DAPTACEL™ + ActHIB™ + Pevnar 13™ at 15 mos.
ANCOVA = Analysis of Covariance, CI = Confidence interval, GMT = Geometric mean titer, mos = Months, N = Number of subjects vaccinated, n = Number of subjects included in the analysis, NI = Non-inferiority, PP-RW = Per-protocol-Revised Window (defined as vaccination window Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose).

Table 2: Summary of Anti-Rotavirus Response by Time and Vaccination Group (Protocol 005)

Time Point	Endpoint	Vaccination Group			
		PR5I		Control	
		n	Observed Response (95% CI) [1]	n	Observed Response (95% CI) [1]
Antigen: Anti-rotavirus IgA					
Pre-Vaccination 1	GMT	784	0.80 (0.75, 0.84)	391	0.72 (0.67, 0.77)
One Month Postdose 3	% with ≥ 3 fold increase (s/n)	458	97.82 (448/458) (96.02, 98.95)	239	98.33 (235/239) (95.77, 99.54)
	GMT	522	278.19 (246.99, 313.32)	274	274.46 (232.83, 323.52)
Antigen: Rota SNA G1					
Pre-Vaccination 1	GMT	790	32.55 (30.10, 35.20)	391	34.18 (30.41, 38.42)
One Month Postdose 3	GMT	528	128.58 (115.60, 143.01)	277	111.85 (96.59, 129.53)
Antigen: Rota SNA G2					
Pre-Vaccination 1	GMT	790	12.51 (11.77, 13.30)	392	12.29 (11.27, 13.40)
One Month Postdose 3	GMT	528	27.89 (25.28, 30.78)	278	30.05 (26.32, 34.31)
Antigen: Rota SNA G3					
Pre-Vaccination 1	GMT	778	8.65 (7.77, 9.63)	390	9.65 (8.22, 11.33)
One Month Postdose 3	GMT	520	40.08 (35.88, 44.78)	274	36.46 (31.78, 41.83)
Antigen: Rota SNA G4					
Pre-Vaccination 1	GMT	790	16.08 (15.17, 17.04)	392	16.64 (15.22, 18.19)
One Month Postdose 3	GMT	528	125.04 (115.31, 135.59)	278	107.78 (95.64, 121.48)
Antigen: Rota SNA P1					
Pre-Vaccination 1	GMT	790	37.10 (34.11, 40.34)	392	37.56 (33.36, 42.28)
One Month Postdose 3	GMT	528	109.77 (99.62, 120.96)	278	110.85 (96.74, 127.01)

[1] The 95% CI for response rate was based on the exact binomial method by Clopper and Pearson. The 95% CI for GMT was based on the t-distribution of the natural log-transformed antibody titer.

PR5I Group received PR5I + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos; DAPTACEL™ + PedvaxHIB™ + Prevnar 13™ at 15 mos.

Control Group received PENTACEL™ + Prevnar 13™ + RotaTeq™ at 2, 4, 6 mos, RECOMBIVAX HB™ at 2, 6 mos; DAPTACEL™ + ActHIB™ + Prevnar 13™ at 15 mos.

CI = Confidence interval, GMT = Geometric mean titer, n = Number of subjects included in the analysis, PP-RW = Per-protocol-Revised Windows (defined as vaccination window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51 following Dose 3 or the toddler dose), s = Number of responders, SNA = Serum neutralization assay.