Application Type	Biologics License Application
STN#	125549
CBER Received Date	June 16, 2014
PDUFA Goal Date	February 14, 2015
Division / Office	DVRPA/OVRR
Priority Review	Yes
Reviewer Name	Lucia Lee, M.D.
Review Completion Date / Stamped Date	October 29, 2014
Supervisory Concurrence	Jeff Roberts, M.D., Chief, CRB1
Applicant	Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Established Name	Meningococcal B Vaccine
Trade Name	Trumenba
Pharmacologic Class	Vaccine
Formulation (0.5mL dose)	60µg MnB rLP2086 subfamily A protein and 60µg MnB rLP2086 subfamily B protein (120µg total protein) Other ingredients: 0.25 mg aluminum (as AlPO4, -b(4)---), 10 mM histidine buffer, -b(4)----- NaCl, polysorbate 80 (--b(4)----------); pH 6.0.
Dosage Form, Route of Administration	Liquid suspension, intramuscular
Dosing Regimen	3-dose primary series (0-,2- and 6-month schedule)
Indication and Population	Active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B in individuals 10 years through 25 years of age.
Orphan Designation	No

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GLOSSARY

BLA	biologics license application
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cLIA	competitive Luminex immunoassay
fHBP	factor H binding protein
GMT	geometric mean titer
HPV	human papillomavirus
hSBA	serum bactericidal activity with human complement
IgA	immunoglobulin A
LLOQ	lower limit of quantitation
LOD	lower limit of detection
MCV4	tetravalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MenB	meningococcal serogroup B
b(4)	--b(4)----------
NDCMC	Newly Diagnosed Chronic Medical Conditions
OMV	outer membrane vesicle
PeRC	Pediatric Review Committee
PISRT	Project Independent Safety Review Team
PorA	porin A
PREA	Pediatric Research Equity Act
SAE	serious adverse event
Tdap	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. EXECUTIVE SUMMARY

Trumenba is a bivalent meningococcal group B vaccine that contains two factor H binding protein (fHBP) antigens. fHBP is a conserved, outer membrane lipoprotein and a virulence factor that contributes to the ability of *Neisseria meningitidis* to avoid host defenses. The safety and immunogenicity data contained in the biologics license application support an indication for active immunization to prevent invasive disease caused by *N meningitidis* serogroup B in individuals 10 through 25 years of age, when administered according to a 0, 2 and 6-month schedule. The clinical data support accelerated approval of Trumenba in accordance with statutory regulations [21 CFR 601.41]. The demonstration of effectiveness was based on the ability of Trumenba to induce bactericidal antibodies (surrogate marker) to fHBP, as measured by serum bactericidal activity with human complement (hSBA) assays using meningococcal group B test strains that were representative of strains expressing fHBP variants that are prevalent in the US.

The diversity of serogroup B meningococci that cause invasive disease can be due to the genetic diversity and variable expression of surface proteins, including fHBP. The susceptibility of the meningococcal B (MenB) test strains to bactericidal killing by antibodies in the sera of Trumenba vaccinees was dependent on both the antigenic similarity of the bacterial and vaccine fHBPs, as well as the amount of fHBP expressed on the surface of the bacterial strains.

Immunogenicity of Trumenba
Trumenba was immunogenic based on evaluations of the following endpoints using four primary MenB test strains: 1) the proportion of participants with a $\geq$4-fold increase in hSBA titers (post-dose #3 compared to pre-dose #1) to the four individual primary MenB strains, and 2) the proportion of participants with a hSBA titer $\geq$ lower limit of quantitation (LLOQ) of the assay to all four primary strains (composite response) after the 3rd vaccination. The primary MenB strains included two subfamily A strains (expressing fHBP variant A22 and A56, respectively) and two subfamily B strains (expressing fHBP variant B24 and B44, respectively). In the US, invasive MenB disease is mainly caused by strains that express A22 and B24.

In three adolescent phase 2 studies (inclusive of individuals 11 to $\leq$18 years of age), which were conducted in the US and Europe, subjects received Trumenba with or without an adolescent vaccine recommended by the specific region for routine use. In one of the studies, Trumenba was administered according to different schedules, including a 0-, 2- and 6-month schedule. The primary objectives pertained to the evaluation of concomitantly administered vaccines or the immune responses to Trumenba administered according to different schedules. Analyses of 4-fold hSBA response to each primary strain and composite hSBA response to all primary strains, although descriptive, were most relevant to US licensure; these endpoints were evaluated in a substantial number of participants (i.e., an evaluable immunogenicity population of approximately 2300 subjects in the three phase 2 studies received Trumenba according to the final formulation and proposed schedule). The 4-fold and composite response endpoints described above were analogous to the primary endpoints agreed upon by CBER for the confirmatory phase 3 studies, in which Trumenba effectiveness also will be evaluated further using 10 additional MenB strains.

In the US phase 2 study, adolescents received Trumenba + Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV4, Gardasil) [Group1], Trumenba + Saline [Group 2], or Saline + HPV4 [Group 3]. The proportions of Group 1 Trumenba participants with a $\geq$4-fold increase in hSBA titer for the four primary MenB strains (83.4%, 85.3%, 77.0% and 95.0% for strains expressing B24, A22, B44 and A56, respectively) and the proportion of Group 1 participants with a hSBA titer $\geq$ LLOQ to all four MenB strains (composite response; 81.0%) were acceptable after the third vaccination. No substantial differences in hSBA responses were observed by gender or age. The hSBA responses

among adolescents in the two phase 2 studies in Europe were consistent with hSBA responses among US adolescents.

For subjects 19 to ≤25 years of age, hSBA responses using the four primary MenB strains were assessed in a smaller sample size of subjects, compared with adolescents. Immunogenicity in this dataset was consistent with anticipated results. Taken as a whole, the immunogenicity data across all age groups was adequate to support use in subjects 19 to <25 years of age. Immune responses to Trumenba in individuals 10 to <11 years of age are expected to be similar to immune responses in adolescents; thus, the applicant's proposal to extrapolate to this age group is acceptable.

Safety of Trumenba
The safety of Trumenba was evaluated in 7 studies. A total of 4335 subjects received at least one dose of Trumenba. At the time of enrollment, 58.1%, 40.0% and 2.0% of subjects were age 11 to ≤14 years, 15 to ≤18 years and >18 years of age, respectively. Of the 4335 subjects, 4282 were 11 to ≤25 years of age. Overall, 56% of subjects were male, and 90.6% were Caucasian, 6.3% were African American, 0.9% were Asian and 2.2% of participants were characterized as 'other'.

- 4 randomized, controlled studies comprised the core safety database of subjects who received Trumenba at 0, 2 and 6 months: 2566 subjects received at least 1 dose of Trumenba and 1012 subjects were included in control groups; 1994 and 513 subjects, respectively, were enrolled at US sites.
- In 3 non-randomized, non-controlled studies, a total of 1769 participants received Trumenba, which was administered according to a 2-dose or a 3-dose schedule.

Trumenba was more reactogenic than the comparator (saline) for local adverse reactions and generally more reactogenic than the comparator (saline, Tdap-containing vaccine or HPV4, depending on the study) for systemic adverse reactions; among adolescents in a US study, common solicited adverse reactions following Trumenba were pain at the injection site (≥ 85%), fatigue (≥40%), headache (≥35%), generalized muscle pain (≥30%) and chills (≥15%). Among the 4 controlled studies, similar percentages of participants in the Trumenba and control groups reported SAEs (2.0% vs, 1.6%) through 6 months after the last vaccination. The SAE rates among subjects who received at least one dose of Trumenba in the 7 studies and the 4 controlled studies were similar. One subject died in a motor vehicle accident, which was not related to vaccination. The safety profile of Trumenba in adults was similar to adolescents.

Thirteen of 4576 subjects who received Trumenba (any dosage or schedule) reported an autoimmune condition and 1 of 4576 Trumenba subjects reported a neuroinflammatory condition, compared to none of these conditions reported among 1028 subjects categorized as controls for comparison. Based on CBER-generated analyses and clinical review of individual cases, there was no conclusive evidence of excess risk of autoimmune or neuroinflammatory conditions among the overall population of rLP2086 vaccinees. Eleven of 14 subjects had evidence of pre-existing disease prior to vaccination or a non-vaccine cause of disease. The occurrence of autoimmune and neuroinflammatory cases in the study population was not significantly greater than the background rates for corresponding conditions in the general population of adolescents and young adults. Taken together, the autoimmune and neuroinflammatory conditions reported in Trumenba subjects did not suggest a pattern of a common pathophysiological mechanism.

Concomitant vaccination
No immunological interference with meningococcal hSBA responses was observed when Trumenba was administered concomitantly with HPV4 (Gardasil; HPV types 6, 11, 16 and 18), compared to hSBA responses when Trumenba was administered alone. When HPV4 was co-administered with Trumenba or alone, the statistical criteria, based on geometric mean titer (GMT) ratios, for three of the four HPV types were met. For HPV-18, the lower bound of the 95% CI for the GMT ratio was 0.62

(statistical criteria for no interference >0.67). In both study groups, the HPV seroconversion rate was ≥99% for each respective HPV type. The systemic reactogenicity of Trumenba (given without other vaccines) was greater than that of HPV4 (given without other vaccines) and similar to frequencies of reactions reported by subjects who received HPV4 and Trumenba concomitantly.

Pediatric Research Equity Act
In accordance with the Pediatric Research Equity Act (PREA), the requirement for studies in children ages 0 to <12 months was waived because safety data from a clinical study in infants vaccinated with a reduced dosage formulation showed an increased incidence of fever after a single dose. Submission of final study reports for studies in children ages 1 to <10 years were deferred because Trumenba is ready for use in individuals 10 to ≤25 years of age and the studies in children age 1 to <10 years have not been completed. The requirement for studies in children 10 to <17 years of age was fulfilled by studies included in the BLA.

Post-marketing Actions
- Post-Marketing Requirements
  - In accordance with the accelerated approval regulations, confirmatory studies in the post-marketing period are being conducted to evaluate Trumenba further, to verify and describe the clinical benefit, by demonstrating the effectiveness of Trumenba against meningococcal B strains that represent an extended range of antigenically diverse fHBP variants.
  - Studies in children 1 to <10 years of age are being conducted to fulfill PREA requirements.

- Post-marketing Commitments
  - The applicant committed to providing study reports from (1) an ongoing study to further describe the safety of Trumenba in individuals 10 to 26 years of age; (2) a completed study to assess the safety and immunogenicity when Trumenba is given concomitantly with Tdap and meningococcal tetravalent (serogroups A, C, W and Y) conjugate vaccines.
  - The applicant plans to conduct a study to examine pregnancy and birth outcomes following vaccination with Trumenba prior to or during pregnancy.

2. BACKGROUND

2.1 Clinical Background
Invasive Meningococcal Disease
Neisseria meningitidis is a significant cause of endemic and epidemic invasive meningococcal disease worldwide. Six serogroups (A, B, C, W, X and Y) are responsible for the majority of clinical disease, which is commonly meningitis and septicemia. A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, and seizure disorder) and approximately 10% of cases are fatal.

In 2012, based on Active Bacterial Core (ABC) surveillance data CDC estimated that the overall rate of serogroup B meningococcal (MenB) disease in the US (including Oregon, which has hyperendemic MenB disease) was 0.08 cases/per 100,000 population.[1] Meningococcal disease in the US is often sporadic, but outbreaks of meningococcal disease also occur.[2] Since 2009, five outbreaks of serogroup B disease have occurred in the US, including outbreaks of MenB disease at two universities in 2013.[3] During the outbreaks at the two universities, 13 students developed invasive meningococcal disease, including one student who required limb amputation and one death in an individual who developed disease following exposure to students at one of the universities.

2.2 Meningococcal Vaccines and Other Available Therapies

Capsular polysaccharide vaccines and polysaccharide-protein conjugate vaccines are currently licensed and available in the US to protect against meningococcal disease caused by serogroups A, C, Y and W. Development of similar vaccines against serogroup B meningococci has not been successful because the capsular polysaccharide of serogroup B is poorly immunogenic, even when conjugated to immunogenic carrier proteins. Serogroup B vaccine development instead has focused on non-capsular outer membrane structures as antigens.

Meningococcal B vaccines using the outer membrane vesicle (OMV) have been studied extensively and used in several countries as a public health measure to control specific outbreaks or epidemics of serogroup B disease. However, the duration of protection was age-dependent.[4] OMV vaccines mainly induce bactericidal antibodies to porin A (PorA) proteins, which are antigenically diverse among meningococci. Accumulated experience with OMV vaccines indicates that OMV induces protective antibodies against the homologous PorA serosubtype. Thus, MenB vaccines that contain only an OMV component are limited in their ability (due to narrow strain specificity) to prevent endemic meningococcal B disease, which is caused by a number of diverse strains. Implementation of OMV vaccines in the routine immunization schedule has been limited also by lack of effectiveness and short duration of effectiveness in young children.[4]

Development of meningococcal B vaccines to prevent endemic serogroup B disease has been challenging due to the need to select antigens that are both immunogenic and broadly protective against diverse pathogenic strains.

Antibiotic chemoprophylaxis is available. However, disease manifestations (e.g. bacteremia, sepsis) are prevented only if individuals at risk are identified in a timely manner.

2.3 Other Relevant Background Information

Bivalent rLP2086 Vaccine and Assay Development

For the remainder of the review, the investigational product name, bivalent rLP2086, is used to differentiate the final formulation (120µg; Trumenba) from formulations that contain different dosages.

Vaccine Composition

Bivalent rLP2086 vaccine consists of two recombinant lipidated variants of fHBP (variants A05 and B01, respectively). A protein from each of the fHBP subfamilies (A and B) was selected because cross-protection between the two subfamilies is limited.

Antigen Selection

Factor H-binding protein (fHBP), also known as LP2086, is a conserved, outer membrane lipoprotein that downregulates the complement pathway and is considered an essential virulence factor. fHBP is expressed on almost all meningococcal clinical disease isolates. fHBP peptide sequences have been categorized as two subfamilies (A and B) or as three variant families (1, 2, and 3), depending on the classification system. Variant 1 corresponds to subfamily B, and variants 2 and 3 correspond to subfamily A (see figure 1).

The applicant characterized fHBPs on 1263 meningococcal serogroup B clinical isolates, which were obtained from CDC ABC surveillance during 2000 to 2005 (n=432) and from national reference laboratories in Europe during 2000 to 2006:

- Surface expression of fHBP was measured on intact strains by flow cytometry. 96% of isolates had detectable levels of fHBP. There were 143 unique fHBP variants.

- Immunological cross-reactivity has been shown among strains within subfamily B (variant 1), and some immunological cross-reactivity exists among strains that express variants within subfamily A (variants 2 and 3); little cross-reactivity is seen between the two subfamilies. fHBP protein characterized as subfamily B and subfamily A were expressed in approximately 70% and 30% of isolates, respectively. Protein sequence identity within each subfamily was at least 84%, with identities of 60-75% between subfamilies.[5]

Primary Strain Selection
Both protein sequence diversity and variability in levels of fHBP antigen expression affect strain susceptibility to anti-fHBP bactericidal activity.

- The applicant characterized fHBPs on isolates obtained during 2006 to 2012 from ABC surveillance, which indicated that the distribution of variants in subfamilies A and B was similar compared to the collection of 1263 strains and the subset of 432 US strains from 2000-2005. The four primary MenB strains each expressed a variant from subfamily A or B, and two of the four test strains expressed variants found in the most prevalent MenB strains in the US (B24 and A22).

- Susceptibility of the isolates to bactericidal killing was hierarchical; that is, serum of vaccinated individuals that contained fHBP antibodies which were bactericidal against less susceptible strains was predictive of serum bactericidal killing of more susceptible strains. The primary strains expressed low or medium quantities of fHBP (depending on the strain).

2.4 Previous Human Experience
Trumenba is not licensed in any country.

2.5 Regulatory Background

2.5.1 Vaccines and Related Biological Products Advisory Committee Meeting

An approach to evaluate vaccines for the prevention of invasive group B meningococcal disease was discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held April 7, 2011. At the time of bivalent rLP2086 development, efficacy studies using clinical disease outcomes would have been difficult to conduct due to low incidence and sporadic occurrence of cases of disease in the US. Also, the number of distinct strains that would need to be tested to adequately represent US endemic disease would be infeasible using current hSBA assay methodologies.

The committee supported use of hSBA as a serological marker that could be used to evaluate effectiveness of protein-based meningococcal B vaccines. However, strain specificity and the diversity of vaccine antigen(s) limited generalizations of vaccine-induced protection to bacterial strains similar to the strain tested in the hSBA assay. The committee acknowledged that the genetic diversity and range of the level of expression of surface proteins, such as fHBP, posed an additional challenge to ascertaining effectiveness of meningococcal serogroup B vaccines against a diverse population of circulating meningococcal serogroup B strains.

2.5.2 Licensure Pathway

A biologics license application was can be submitted for consideration and review under the accelerated approval regulations [21 CFR 601.41] if certain criteria are met. Those criteria, along with analysis of their application to the rLP2086 program, are listed below.

(a) *The vaccine is intended to prevent a serious condition*

Invasive meningococcal disease is a serious condition.

(b) *The vaccine provides a meaningful advantage over available therapies.*
At present, no meningococcal B vaccines are licensed or available in the US. Available therapy for adolescents/young adults, for prevention of invasive meningococcal disease, includes antibiotic chemoprophylaxis. However, disease manifestations (e.g. meningitis, sepsis) are prevented only if individuals at risk are identified in a timely manner.

(c) *Data from adequate and well-controlled clinical trials established that the vaccine has an effect on surrogate endpoints that is reasonably likely to predict clinical benefit.*

The surrogate endpoints were as follows:

- The proportion of subjects with a $\geq$ four-fold increase in hSBA titer (post-vaccination 3 compared to pre-vaccination dose 1) for each primary strain, and
- The proportion of subjects achieving a composite hSBA response (defined as the proportion of subjects with hSBA titer $\geq$ a specified titer for all four primary strains) after the 3rd vaccination.

(d) The accelerated approval regulations establish an expectation that postmarketing studies required to confirm clinical benefit would usually be underway at the time of submission of a licensure application.
Confirmatory studies in individuals 10 to <18 years and individuals 18 to <26 years of age are underway. Collectively, evaluation of hSBA responses with the four primary strains and hSBA responses with a panel of ten secondary strains will provide clinical data to verify and describe the breadth of coverage for meningococcal B strains that are epidemiologically relevant in US adolescents and young adults (see section 9.2.1).

Development of bivalent rLP2086 vaccine was granted Fast Track and then Breakthrough Therapy Designations under IND 13812. Measurement of hSBA in an assay using the primary MenB strains and evaluation according to the endpoints described above was viewed, in the regulatory context of breakthrough therapy designation, as an established surrogate for a clinically meaningful endpoint.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Financial Disclosures

Covered clinical study (name and/or number): 7 clinical studies (see section 6)		
Was a list of clinical investigators provided:	Yes ☑	
Total number of investigators identified: 1036		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☑	
Is a description of the steps taken to minimize potential bias provided:	Yes ☑	
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	n/a	

4. PERTINENT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

There were no issues identified that would impact the clinical review of the studies submitted in the BLA.

4.2 Serological Assays

The CBER serological assay reviewer concluded that the following assays were adequate for their intended use in the studies submitted to the BLA.

- hSBA assays performed at -------b(4)----------) using strains PMB80 (fHBP variant A22) and PMB2948 (fHBP variant B24)
- hSBA assays performed at Pfizer Vaccine Research – --b(4)---------- using strains PMB2001 (fHBP variant A56) and PMB2707 (fHBP variant B44)

4.3 Nonclinical Toxicology

The CBER toxicology reviewer concluded that there were no significant safety issues.

4.5 Biostatistics

The CBER statistical reviewers concluded that the quality of the clinical trial data submitted to the BLA was sufficient to enable statistical evaluation. For study B1971011, a study with primary objectives to evaluate the immune responses following co-administration of bivalent rLP2086 and Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [HPV4; Gardasil], the co-primary objectives were formally not achieved because 5 of 6 comparisons of the null hypothesis were rejected. For the one null hypothesis that was not rejected, the lower limit of the 2-sided 95% CI for the HPV-18 GMT ratio was 0.62, which was below the pre-specified non-inferiority threshold of 0.67. From a clinical perspective, the statistical difference was not clinically significant. The HPV seroconversion rate was $\geq$99% for each respective HPV type among subjects who received HPV4 and bivalent rLP2086 concomitantly. Importantly, in the last 10 years, no breakthrough infections (precancerous cervical dysplasia) due to HPV-18 have been reported among HPV4-vaccinated individuals.

A CBER-generated statistical analysis indicated no conclusive evidence of excess risk of autoimmune or neuroinflammatory conditions among the overall population of bivalent rLP2086 vaccinees; a total of 14 cases (13 autoimmune conditions, 1 neuroinflammatory condition) were identified among 4576 bivalent rLP2086 participants, compared with no such conditions reported in participants who received $\geq$1dose of a control injection (e.g. saline).

4.6 Pharmacovigilance

The CBER reviewer concluded that the autoimmune or neuroinflammatory conditions reported among bivalent rLP2086 participants in the 7 studies were not a safety concern.

4.7 BioResearch Monitoring

The CBER BioResearch Monitoring (BIMO) reviewer concluded from FDA inspections at three clinical study sites (#1007, 1023, and 1069) did not reveal significant problems that impacted the safety data submitted in the BLA.

5. CLINICAL DATA SOURCES

All information in the following modules (m) and sections (s) were reviewed:
Amendment 0: m2 (s2.7.1 Summary of biopharmaceutical studies and associated analytical methods).
Amendment 1: m5 (s5.3.5 Studies B1971004, B1971005, B1971010, B1971003 and B1091012).
Amendment 3: m1 (s1.11 Responses to CBER information requests [IR] dated 19-May-2014: immunogenicity data).
Amendment 4: m1 (s1.3 Administrative information, s1.9 Request for pediatric waivers and deferrals, s1.14 Label, s1.16 Risk management plan); m2 (s2.2 Introduction, s2.5 Clinical overview, s2.7 Clinical summaries); m5 (s5.3.5 Studies B1971011 and B1971042, and Integrated summaries of safety and efficacy).
Amendment 6: m1 (s1.11 Partial responses to CBER IR dated Jun-2014 (17^{th}, 20^{th}): autoimmune cases).
Amendment 7: m1 (s1.9 Pediatric study plan).
Amendment 9: m1 (s1.11 Partial responses to CBER IR dated 17-Jul-2014: data monitoring committee).
Amendment 10: m5 (s5.3.5 Partial responses to CBER IR dated 17-Jul-2014: autoimmune cases)
Amendment 11: m1 (s1.11 Response to CBER clinical IR dated 07-Aug-2014: clinical summary of safety analyses).
Amendment 12: m1 (s1.11 Response to CBER IR dated 01-Aug-2014: pharmacovigilance plan); m5 (study B1971052 protocol)
Amendment 13: m1 (s1.11 Response to CBER IR dated 17-Jun-2014: autoimmune cases).
Amendment 15: m1 (s1.3 Administrative information, s1.11 Response to CBER IR dated 07-Aug-2014: financial disclosures)
Amendment 17: m1 (s1.11 Response to CBER IR dated 8-Aug-2014: datasets, analysis populations)
Amendment 20: m1 (s1.11 Responses to CBER IR dated 29-Aug-2014: hSBA GMTs (clinical comment #7))
Amendment 23: m1 (s1.11 Response to CBER IR dated 18-Sept-2014: hSBA responder rates)
Amendment 26: m1 (s1.14 Responses to CBER IR dated 6-Oct-2014: Package insert labeling comments)
Amendment 27: m1 (s1.11 Responses to CBER IR dated 16-Oct-2014: Clinical postmarketing studies)

The applicant's written responses contained in the amendments described above were satisfactory.

6. CLINICAL STUDIES

Table 1. Overview of Clinical Studies

Study/ Country	Study Description	Age (years)	Schedule (months [m]) Group	Number of 120µg bivalent rLP2086 subjects n (%)	Number of Control Group subjects
Main Immunogenicity Studies (using 4 primary MenB strains)					
B1971011 US	Phase 2: safety and immunogenicity, concomitant vaccine	11 to ≤17	0,2,6 Schedule, 120 µg rLP2086		
			Group 1: rLP2086+HPV4	992	
			Group 2: rLP2086+saline	990	

	evaluation: HPV4		Group 3: saline+HPV4		501
B1971010 Europe	Phase 2: safety and immunogenicity, concomitant vaccine evaluation: dTaP-IPV	11 to ≤18	0,2,6m Schedule, 120 µg rLP2086		
			Group 1: rLP2086+dTaP-IPV	374	
			Group 2: dTaP-IPV+saline [0m], saline [2,6m]		378
B1971012 Europe	Phase 2: safety and immunogenicity of 2- and 3-dose schedules	11 to ≤18	Various schedules, 120 µg rLP2086[a]		
			0,1,6 Schedule (Group 1)	426	
			0,2,6 Schedule (Group 2)	414	0
			0,6 Schedule (Group 3)	451	
			0,2 Schedule (Group 4)	277	
			0,4 Schedule (Group 5)	128	
Supportive Adolescent Study; Adult Studies					
B1971005 Europe Australia	Phase 2: safety and immunogenicity, dose-ranging	11 to ≤18	0,2,6m Schedule, 120 µg rLP2086		
			60 µg rLP2086 (n=22)		
			120 µg rLP2086	198	
			200 µg rLP2086 (n=195)		
			Saline		12
B1971003 Australia	Phase 1/2: safety, assay development	18 to <40	0,1,6m Schedule		
			120 µg rLP2086	60	0
B1971004 US	Phase 1: safety and immunogenicity, dose-ranging	18 to <40	0,2,6m Schedule		
			60 µg rLP2086 (n=12)		
			120 µg rLP2086	12	
			200 µg rLP2086 n=12)		
			Tdap		12
B1971042 US	Phase 2: safety and immunogenicity in laboratory workers	18 to ≤65	0,2,6m Schedule		
			120 µg rLP2086	13	0

HPV4= Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [Gardasil].
dTap-IPV= Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) [Repevax].
Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Vaccine [Adacel].
[a] As vaccinated.

6.1 Study B1971011

NCT# 01461993

Title: A Phase 2, Randomized, Placebo-Controlled, Observer-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Gardasil (HPV4) and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 to <18 Years

6.1.1 Objectives

Primary Objectives

1. To demonstrate that immune responses to 4-valent human papillomavirus vaccine (HPV4) when co-administered with bivalent rLP2086 (Group 1) are non-inferior to corresponding immune responses when HPV4 is administered alone (Group 3), for each HPV type. Time point: 1 month after the 3rd bivalent rLP2086 vaccination.

   Criteria for non-inferiority
   Lower limit of the 2-sided 95% CI for the GMT ratio (Group 1 $_{rLP2086+HPV4}$ / Group 3 $_{HPV4}$) is greater than 0.67 for HPV types 6, 11, 16 and 18.

2. To demonstrate that the immune responses to bivalent rLP2086 when co-administered with HPV4 (Group 1) are non-inferior to corresponding immune responses when bivalent rLP2086 is administered alone (Group 2), as measured by hSBA assays performed with 2 MenB primary strains. Time point: 1 month after the 3rd bivalent rLP2086 vaccination.

   Criteria for non-inferiority

   Lower limit of the 2-sided 95% CI for the hSBA GMT ratio (Group 1 $_{\text{bivalent rLP2086+HPV4}}$ / Group 2 $_{\text{bivalent rLP2086}}$) is greater than 0.67, using MenB primary strain PMB80 [A22]. The same criterion was applied for the hSBA GMT ratio (Group 1 $_{\text{bivalent rLP2086+HPV4}}$ / Group 2 $_{\text{bivalent rLP2086}}$) using MenB primary strain PMB2948 [B24].

Secondary Objectives

- To describe the immune responses to bivalent rLP2086 as measured by hSBA assays performed with 4 MenB primary strains (Group 2). Strains: PMB80 [A22], PMB2948 [B24], PMB2001 [A56] and PMB2707 [B44] Time points: one month after the 3rd and 2nd bivalent rLP2086 vaccinations [Visits 5 and 3].

- To demonstrate that the HPV seroconversion rates when HPV4 is co-administered with bivalent rLP2086 (Group 1) is non-inferior to corresponding HPV seroconversion rates when HPV4 is given alone (Group 3). See section 6.1.8.2 for the definitions of seroconversion. Time point: 1 month after the 3rd HPV4 vaccination.

  Criterion for non-inferiority
  Lower limit of the 2-sided 95%CI for the difference in seroconversion rate is greater than -0.10 for each of the 4 HPV types. The cut-off levels are ≥20 mMU/mL for HPV-6, ≥16 mMU/mL for HPV-11, ≥20 mMU/mL for HPV-16, and ≥24 mMU/mL for HPV-18.

Exploratory Objectives
To describe the MenB immune response (4-fold response and composite response) as measured by hSBA assays using 4 MenB primary strains. Time points: one month after the 3rd and 2nd bivalent rLP2086 vaccinations [Visits 5 and 3].

Safety Objective
To describe the safety profile of bivalent rLP2086 vaccine.

6.1.2 Design

Randomized, controlled, observer-blinded trial. N=2500 (Group 1 n=1000, Group 2 n=1000, Group 3 n=500)

Table 2. Study B1971011. Study Design

Study Group	Vaccine schedule		
	Month 0	**Month 2**	**Month 6**
1	HPV4 + bivalent rLP2086	HPV4 + bivalent rLP2086	HPV4 + bivalent rLP2086
2	bivalent rLP2086 + saline	bivalent rLP2086 + saline	bivalent rLP2086 + saline
3	HPV4 + saline	HPV4 + saline	HPV4 + saline

HPV4= Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [Gardasil].

6.1.3 Population

The study was conducted at 64 sites in the US.

Inclusion Criteria

- Male or female subjects between ages ≥11 to <18 years at the time of enrollment.
- Healthy male or female subjects as determined by medical history and physical examination.
- Females: negative urine pregnancy test.
- Able to comply with study procedures for the duration of the trial.
- Informed consent/assent obtained.

Exclusion Criteria

- A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as subjects with congenital or acquired defects in B cell function, those receiving chronic systemic (oral, intravenous or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy.
- Chronic use of systemic antibiotics.
- Previous vaccination with any serogroup B meningococcal or HPV vaccine.
- Contraindication of vaccination with Gardasil or any HPV vaccine.
- Any neuroinflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
- History of culture-proven disease caused by N *meningitidis* or *N gonorrhea*.
- Previous anaphylactic reaction to any vaccine or vaccine-related component.
- Significant neurological disorder or history of seizure (excluding febrile seizure).
- Receipt of any blood products, including immunoglobulin within 6 months before study vaccination.
- Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.
- Pregnant or breastfeeding.
- Receipt of any allergen immunotherapy with a non-licensed product, or receipt of allergen immunotherapy with a licensed product and are not on stable maintenance doses.
- Participation in other studies in the 30-day period before study start and/or during the conduct of the study. Participation in purely observational studies is acceptable.
- Received any investigational drugs or devices within 28 days before administration of the first study vaccination.

Temporary exclusion criteria

- Febrile illness (oral T≥38.0°C) or other acute illness within 48 hours before study vaccine administration.
- Receipt of any non-live vaccine within 2 weeks prior to study vaccination #1 or live vaccine within 4 weeks prior to study vaccination #1.
- Subject has received <5 days of systemic antibiotics.

6.1.4 Randomization/Blinding

The study subjects, investigators and the applicant were blinded to the treatment allocation (i.e. observer-blinded). Persons dispensing and administrating study vaccine were not blinded to the treatment assignment (appearance of both vaccines and saline differed). Study personnel collecting safety information were separate from personnel dispensing/administering study vaccine. HPV4 was offered to Group 2 after the safety follow-up evaluation six months post-vaccination 3. A statistical team that was not part of the applicant's organization or involved in the conduct of the study (independent statistical center [ISC]) provided a blinded listing of samples for testing of MenB strains to laboratory personnel.

6.1.5 Study Products

Study products

- Bivalent rLP2086 vaccine: Each 0.5 mL dose contained 60ug of rLP2086 protein from subfamily A and 60ug of rLP2086 subfamily B, polysorbate 80 (in ---b(4)----------, 0.25

mg of aluminum as AlPO4 (--b(4)-------) in 10mM histidine buffer pH 6.0. Packaged as a liquid in a pre-filled syringe. Lot #11-003091.

- HPV4 (Gardasil; Merck & Co): Each 0.5-mL dose contained approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein, 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant) and 50 mcg of polysorbate 80. Lot #10-087622 and 12-002982.
- Saline (0.9% sodium chloride). Lot #11-002694.

Permitted vaccines
Tetravalent meningococcal conjugate vaccine (MCV4) and Tdap vaccines were permitted any time after the blood sampling visit post study vaccination 3. Vaccines other than MCV4 and Tdap that were part of the recommended immunization schedules were permitted any time after the blood sampling visit post-study vaccination 2, but not within 2 weeks (for non-live vaccines) and not within 4 weeks (for live vaccines) of study vaccination.

Concomitant medications
Topical and inhaled corticosteroids and topical antibiotics were permitted during the study. The name and date of administration of any non-study vaccine (or allergen immunotherapy) given from the date of the informed consent to the blood draw at Visit 5 was recorded on the case report form (CRF).

6.1.6 Assessments

Prior receipt of Hib vaccine conjugated to meningococcal OMP (PRP-OMP), MCV4 or Tdap was recorded on the CRF. Females: urine pregnancy test on the day of each vaccination.

Safety Evaluation

- Solicited reactions, antipyretic use: Information was recorded daily for 7 days in an e-diary.
- Localized pain, erythema and swelling at bivalent rLP2086 and saline injection sites, but not the HPV4 site, were recorded. Systemic AEs: fever (T≥38.0°C), headache, fatigue, nausea, vomiting, chills, diarrhea, fever, muscle pain, joint pain.
- Grading scale: Injection site redness/swelling: none: 0 to 2.0 cm, mild: 2.5 to 5.0 cm; moderate: 5.5 to 10.0 cm; severe: >10.0 cm. Injection site pain: mild: does not interfere with daily activity, moderate: interferes with daily activity, severe: prevents daily activity. Headache/fatigue/chills/ myalgia /joint pain: mild: does not interfere with daily activity, moderate: some interference with daily activity, severe: prevents daily activity. Diarrhea (number of stools/per 24 hours): mild: 2-4; moderate: 4-5; severe: >6. Vomiting (number of episodes/per 24 hours): mild: 1-2, moderate: 2, severe: requires IV hydration. Fever: T≥38.0°C; temperature (oral) was recorded in 0.5C increments: 38.0-38.4°C; 38.5-38.9°C; 39.0-40.0°C; >40.0°C.

  The parent/legal guardian or the subject was requested to contact the study staff for a medical assessment if severe swelling at the injection site on the left arm, a T≥39.0°C or a severe headache was noted in the 7 days after vaccination.

- Unsolicited AEs
  - Immediate AEs: any AE that occurred within 30 minutes after vaccination
  - Non-serious, unexpected AEs: assessed from day of informed consent [ICD] to 30 days after the 3rd vaccination, and recorded at the next scheduled visit.

  From day of first vaccination [Day 1] to 6 months after the 3rd vaccination: recorded at the next scheduled visit, and by telephone for the 6-month follow-up visit.
  - SAEs

- Medically attended AEs: defined as a non-serious AE that resulted in an evaluation at a medical facility.
- Newly diagnosed chronic medical conditions: defined as a disease or medical condition, not previously identified, which is expected to be persistent or otherwise long-lasting in its effects.
- Neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.

External Data Monitoring Committee (EDMC): responsible for ongoing monitoring of the immunogenicity and safety of subjects in the study. The recommendations made by the EDMC to alter the conduct of the study were forwarded to applicant's steering committee for final decision.

Immunogenicity (methods)
Blood samples were collected prior to vaccination #1, one month post-vaccinations #2 and #3. The interval between post-vaccination and blooding sampling visits was 28-42 days.

MenB vaccine antigens: hSBA assays using meningococcal strains PMB80 [A22] and PMB2948 [B24] were performed at Pfizer ----------b(4)----------; the lower limit of quantitation (LLOQ) was 1:16 and 1:8 for hSBA assays using A22 and B24, respectively. hSBA assays using meningococcal strains PMB2001 [A56] and PMB2707 [B44] were performed at –b(4)----------; the LLOQs was 1:8 for hSBA assays using A56 or B44. The limit of detection for all hSBA assays was 1:4.

HPV antigens: competitive Luminex immunoassay (cLIA) was performed at –b(4)----------. LLOQs: 11 mMU/mL, 8 mMU/mL, 11 mMU/mL and 10 mMU/mL for types 6, 11, 16 and 18, respectively.

6.1.7 Statistical Analysis Plan/Data analysis

Sample size calculations
Planned enrollment included 2500 participants (Group 1 n=1000, Group 2 n=1000, Group 3 n=500) to result in 1750 evaluable participants (700/700/350 for Groups 1, 2 and 3, respectively). The difference in natural log scale of each type-specific HPV titer (types 6, 11, 16 and 18) and hSBA response using a MenB strain (PMB80 [A22] and PMB2948 [B24]) was assumed to be 0.13 less in Group 1 (concomitant bivalent rLP2086 vaccine + HPV4) than corresponding antibody titers in Group 3 (HPV4 alone) or Group 2 (bivalent rLP2086 vaccine alone); data sources: HPV4 package insert, study B1971005. Other assumptions: immunogenicity outcomes for each of the co-primary objectives occurred independently; 30% dropout rate.

The individual study power to achieve the primary objectives for HPV types 6,11,16 and 18 was 99.8%, 99.3%, 93.2% and 96.8%, respectively, The study power to achieve the rLP2086 primary objectives was 95.2% and 98.2% for A22 and B24, respectively. The overall study power is 83.6%. The overall type I error for this study was 2.5% (1-sided test of non-inferiority).

Primary hypotheses
The study would be declared success if null hypotheses were rejected for each of the six co-primary objectives.
H_0: For each of the four HPV types, the lower limit of the 95% CI for the difference in the mean of the log-transformed titers (Group 1 $_{rLP2086+HPV4}$ - Group 3 $_{HPV4}$) is $\leq$1.5.
H_A: For each of the four HPV types, the lower limit of the 95% CI for the difference in the mean of the log-transformed titers (Group 1 $_{rLP2086+HPV4}$ - Group 3 $_{HPV4}$) is >1.5.
H_0: For hSBA responses to each MenB strain, the lower limit of the 95% CI for the difference in the mean of the log-transformed titers (Group 1 $_{rLP2086+HPV4}$ - Group 2 $_{rLP2086}$) is $\leq$1.5.

H_A: For hSBA responses to each MenB strain, the lower limit of the 95% CI for the difference in the mean of the log-transformed titers (Group 1 $_{rLP2086+HPV4}$ - Group 2 $_{rLP2086}$) is >1.5.

Populations Analyzed
Evaluable populations
The immunogenicity analyses for the co-primary objectives were based on the following populations:

- (Post-dose 3) *evaluable immunogenicity population*: eligible for the study, randomized to Group 1, 2, or 3; received scheduled investigational products combination as randomized for Visit 1, Visit 2, and Visit 4; blood drawn prior to the first dose of vaccine and post-vaccination 3 (Visit 5) within 28-42 days after vaccination 3 (Visit 4), valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment.
- *Baseline HPV-seronegative evaluable immunogenicity subset*: a subset of the evaluable immunogenicity population who was randomized to Groups 1 or 3 and was seronegative for the respective HPV type at baseline.
- Post-dose 2 evaluable population: eligible for the study, fulfilled inclusion/exclusion criteria for visits 1-3, randomized to Group 1 or 2, received scheduled investigational products combination as randomized for Visits 1 and 2, had blood drawn prior to the first dose of vaccine and post-vaccination 2 (Visit 3) within 28-42 days after vaccination 2 (Visit 2), valid and determinate assay results for the proposed analysis, received no prohibited vaccines or treatment during Visits 1 through Visit 3.

Modified intent-to-treat (mITT) immunogenicity population: all randomized subjects who have at least 1 valid and determinate assay result.

Safety populations: defined for each vaccination

- Vaccination #1 Safety Population: all subjects who received any investigational product at Visit 1 and for whom safety information from visit 1 to prior to visit 2 is available.
- Vaccination #2 Safety Population: all subjects who received any investigational product at Visit 2 and for whom safety information from visit 2 to prior to visit 4 is available.
- Vaccination #3 Safety Population: all subjects who received any investigational product at Visit 4 and for whom safety information from visit 4 to visit 5 is available.
- Follow-up Safety Population: all subjects who received at least 1 dose of investigational product (bivalent rLP2086 or HPV4 vaccine) and for whom safety information is available from after visit 5 to visit 6. Subjects who receive the wrong investigational product and are followed for 6-month safety will not be included in this population.

Analyses were performed according to the study product received.

Immunogenicity Analyses
Primary endpoints and NI criteria

- HPV4: lower limit of the 2-sided 95% CI for the GMT ratio (Group 1 $_{rLP2086+HPV4}$ / Group 3 $_{HPV4}$) is > 0.67 for vaccine type 6, 11, 16 and 18. Time point: one month after the 3rd HPV4 vaccination.
- rLP2086: lower limit of the 2-sided 95% CI for the GMT ratio (Group 1 $_{rLP2086+HPV4}$ / Group 2 $_{rLP2086}$) is > 0.67 for hSBA responses to bivalent rLP2086 vaccine using two MenB primary strains (PMB80 [A22] and PMB2948 [B24]). Time point: one month after the 3rd bivalent rLP2086 vaccination.

Secondary endpoints
*HPV4 (*four types): Group 1 vs. Group 3

- GMTs one month after the 3rd HPV4 vaccination
- % of subjects who are seropositive at baseline (i.e. type-specific HPV titer $\geq$ the cLIA cutoff level prior to HPV4 vaccination #1)
- Seroconversion rate: defined as the % of subjects with seropositive type-specific HPV titer one month after the 3rd HPV4 vaccination and were seronegative at baseline (i.e. type-specific HPV titer < the

cLIA cutoff level prior to HPV4 vaccination #1). Cut-off levels: ≥20 mMU/mL, ≥16 mMU/mL, ≥20 mMU/mL and ≥24 mMU/mL for HPV types 6, 11, 16 and 18, respectively.

Meningococcal B (four primary strains): Group 1 vs. Group 2
Strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24] and PMB2707 [B44]). *Time points:* prior to bivalent rLP2086 vaccination #1, one month after the 2nd and 3rd bivalent rLP286 vaccinations.

Exploratory endpoints (descriptive)
Four MenB primary strains (as described above):

- % of subjects with ≥ 4-fold increase in hSBA titer (each post-rLP2086 vaccination time point compared to baseline) for each strain, defined as follows
  - For subjects with a baseline hSBA titer below the limit of detection (LOD) or an hSBA titer of <1:4, a 4-fold response is defined as a hSBA titer ≥1:16.
  - For subjects with a baseline hSBA titer of ≥ LOD (i.e., hSBA titer ≥1:4) and < LLOQ, a 4-fold response is defined as a hSBA titer ≥ four times the LLOQ.
  - For subjects with a baseline hSBA titer ≥ LLOQ, a 4-fold response is defined as a hSBA titer ≥ four times the baseline titer.

- % of subjects achieving a composite hSBA response, defined as hSBA titer ≥LLOQ for all 4 primary strains, for each post-vaccination time point.

Values below the LLOQ or denoted as below LLOQ were set to ½ LLOQ for analysis purposes. A sensitivity analysis was performed to examine the possible introduction of bias, due to defining hSBA titers that were <LLOQ as ½ LLOQ, on GMT. GMTs were presented using baseline hSBA, study group, site, race, gender age as a covariate. Sensitivity analyses were conducted if the percentage of subjects with missing data exceeds 10%.

Safety Analyses

- Incidence of local reactions and systemic events within 7 days after each vaccination, categorized by adverse event, severity and vaccine group, with 95% CIs
- Use of antipyretic medication after each injection
- Occurrence of unsolicited AEs, classified by MeDRA preferred terms
- Description of SAEs, newly diagnosed major illnesses or conditions; neuroinflammatory and autoimmune conditions

Group 1 vs. 2 and Group 1 vs. 3

- % of subjects reporting solicited local reactions within 7 days after each vaccination
- % of subjects reporting solicited systemic AEs within 7 days after each vaccination
- % of subjects reporting antipyretic use within 7 days after each vaccination
- % of subjects who develop at least one adverse event occurring during the following time periods:
  - 30 days after each vaccination
  - 30 days after any vaccination
  - During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 5]]
- % of subjects reporting at least one immediate adverse event after each vaccination.
- % of subjects with at least one SAE during the following time periods:
  - 30 days after each vaccination
  - 30 days after any vaccination
  - During the vaccination phase
  - During the follow-up phase (from 1 month after the last study vaccination [Visit 5] through 6 months after the third study vaccination [Visit 6])

  - Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 6]).
- % of subjects reporting at last one newly diagnosed major illnesses throughout the study period

6.1.8 Amendments to the Protocol/SAP

Protocol (Highlights of main changes)
Amendment 1, dated 7-Mar-2011
- Study design was changed from open label (with regard to subjects, site personnel, investigator, applicant) to observer-blinded
- Included a co-primary objective to demonstrate NI (within 1.5-fold difference in GMT) of HPV antibody responses after the 3rd HPV4 vaccination (Group 1 vs. Group 2)
- Primary objective: MenB strain from subfamily A was changed from variant [A05] to PMB2001 [A56]
- Specified LLOQs for cLIA assay, and preliminary LLOQs for MenB primary strains

Amendment 2, dated 29-Aug-2011
- Specified the remaining MenB strains to be used for the primary analyses
- Specified how GMTs would be calculated
- Specified criteria for analysis populations
- Included additional sensitivity analyses

Amendment 3, dated 01-Nov-2011
- Study blind: all subjects were notified of HPV vaccination status after the safety evaluation six months after vaccination visit 3 (Visit 6), at which time HPV4 vaccine would be offered to Group 2 subjects. Administration non-study HPV4 vaccination was contraindicated until after Visit 6.
- Clarified that non-study vaccines (other than MCV4 and Tdap) could be administered any time during the study

Amendment 4, dated 18-Sept-2012
- Primary and secondary objectives: changed number of MenB strains tested from 2 to 4. An independent statistical center (ISC) provided a subject list without treatment allocation for testing sera using four MenB primary strains
- Added exploratory objectives to describe hSBA 4-fold response and a composite endpoint. Time points: post-rLP2086 vaccinations 2 and 3
- Added safety analyses categorized by 7 time intervals. Added a 4th safety analysis population (time period from 1 month post-vaccination 3 to 6 months post-vaccination 3)
- Added analyses for newly diagnosed major illness and neuroinflammatory and autoimmune conditions (no change in methods or time points for collecting information)

Statistical analysis plan
Version (v) 2.0 (dated 08-Apr-2011), v3.0 (31-Aug-2011), v4.0 (dated 28-Nov-2011) and v5.0 (dated 16-Oct-2012) incorporated the changes listed in protocol amendments 1, 2 3 and 4, respectively.

SAP v5.1 (dated 6-Sept-2013) and v5.2 (dated 2-Dec-2013)
- Updated LLOQs for hSBA assays and for cLIA (HPV type 6)
- Included an additional analysis to assess 4-fold response for strain PMB80 [A22]

SAP appendix v1.0, dated 06-May-2013: clarified rules for handling safety data (missing or incomplete data, AE start and resolve dates) and determining the time point for study completion.

6.1.9 Results

The study was conducted from September 28, 2011 to July 6, 2013 (last subject last visit).

Subject Disposition
Of 2499 (Group 1 n=999, Group 2 n=998, Group 3 n=502) randomized participants, the safety population for the first vaccination included 2483 (99.4%) participants (Group 1 n=992, Group 2 n=990, Group 3 n=501); 15 subjects (Group 1 n=4, Group 2 n=5, Group 3 n=1) withdrew from the study prior to receiving any vaccinations. One subject was randomized to Group 1, but received non-study vaccines prior to first vaccination and no study vaccines at vaccination visits 1-3. A total of 312 (12.5%) subjects did not complete the vaccination phase (defined as the time period from Visit 1 through one month after the third vaccination visit), which included participants no longer willing to participate in the study, were lost to follow-up, no longer met eligibility criteria, or had a protocol violation(s); 23 subjects withdrew due to an AE (Group 1 n= 9, Group 2 n= 11, Group 3 n= 3). (see section 6.1.9.2 for details). A total of 2127 (85.1%) participants (Group 1 n= 848, Group 2 n= 841, Group 3 n= 438) completed the 3 vaccination visits and the follow-up visit six months after the third vaccination visit; an additional 75 participants (Group 1 n= 27, Group 2 n= 38, Group 3 n=10) completed the 6 month follow-up visit but did not receive all products (e.g. withdrew due to an AE but continued the safety evaluations).

Immunogenicity populations
The modified intent-to-treat population (mITT) consisted of 2484 participants (Group 1 n=993, Group 2 n=990, Group 3 n=501).

The post-dose 3 evaluable immunogenicity population included 2049 participants (Group 1 n=814 (81.5%), Group 2, n= 812 (81.4%); Group 3, n= 423 (84.3%)). The baseline (pre-vaccination #1) HPV seronegative evaluable immunogenicity population included 1228 (Group 1 n=993, Group 3 n=501) participants. The post-dose 2 evaluable population consisted of 1706 participants (Group 1 n=857, Group 2 n=849).

A total of 450 (Group 1 n=185, Group 2 n=186, Group 3 n=79) participants were excluded from the post-dose 3 evaluable immunogenicity population, mainly due to the following reasons: a blood sample was not drawn prior to the first vaccination, the post-vaccination 3 blood sample was not drawn within 28-42 days of vaccination, did not receive all study products as randomized at all vaccination visits, or no valid and determinate assay results for the given time point. Participants were excluded from the post-dose 2 evaluable population for similar reasons.

Site deviations
Site #1007: 160 participants (Group 1 n=64, Group 2, n=63, Group 3 n=33) were randomized this site. The study coordinator was unblinded to the treatment allocation prior to the 6-month safety follow-up evaluation.

Site #1051: 15 participants (Group 1 n=6, Group 2, n=6, Group 3 n=3) were randomized at this site. The site management organization (SMO) contract was discontinued. Also, the study investigator was non-compliant with study procedures. The applicant verified safety data from the electronic diary (solicited AEs) and electronic medical records (unsolicited AEs). Subjects for whom eligibility criteria could not be verified or a post-dose 3 blood sample was not obtained were excluded from the evaluable immunogenicity population.

Sensitivity analyses were performed, which indicated that safety outcomes were unaffected by inclusion of subjects from both sites in the safety population. The personnel performing the laboratory testing was blinded to the group allocation throughout the study.

Demographics and Other Baseline Characteristics

In total, 66.5% of subjects were male (Group 1: 66.0%, Group 2: 67.0%, Group 3: 66.3%) and 33.5% were female. 65.9% of participants were 11 to ≤14 years age and 34.1% were 15 to <18 years of age; the age distribution was similar among the three study groups. The population overall was 81.6% Caucasian, 13% African American, 1.2% Asian, and 4.3% participants that were classified as 'other'. The applicant attributes enrollment of a higher proportion of males aged 11 to ≤14 years in the study was due to updated recommendations by the Advisory Committee on Immunization Practices (ACIP) in late 2009 for the prevention of HPV disease to include routine HPV vaccination in males at age 11 or 12 years.

6.1.9.1 Immunogenicity Outcomes

Primary objectives

HPV Geometric Mean Titers (GMTs) after the 3rd HPV4 vaccination (Group 1 vs. Group 3)

For HPV types 6, 11 and 16, the lower limit of the 2-sided 95% CI for the GMT ratio (Group 1 $_{rLP2086+HPV4}$ / Group 3 $_{HPV4}$) was >0.67, which met the criterion for non-inferiority (1.5-fold differences) for each type. For HPV-18, the lower limit of the 2-sided 95% CI for the GMT ratio was 0.62. Please see Table 5for additional information.

Meningococcal hSBA GMTs after the 3rd bivalent rLP2086 vaccination (Group 1 vs. Group 2; two MenB strains: PMB80 [A22] and PMB2948 [B24])

The lower limit of the 2-sided 95% CI for the hSBA GMT ratio (Group 1 $_{rLP2086+HPV4}$ / Group 2 $_{rLP2086}$), assessed using MenB strains PMB80 [A22] and PMB2948 [B24] in the hSBA assay, was >0.67, which met the criterion for non-inferiority (1.5-fold differences) for each strain. Please see Table 4 for additional information.

Other Objectives

Meningococcal hSBA responses using 4 primary MenB strains

In the context of the accelerated approval pathway, analyses of the following endpoints using four primary MenB strains were most relevant to US licensure: the proportion of participants with a ≥4-fold response to each of the four MenB strains and the proportion of participants with a hSBA response ≥ LLOQ to all of the primary strains (composite response). The endpoints were analogous to the primary endpoints in the phase 3 studies being conducted with bivalent rLP2086. The MenB strains expressing fHBP variants A56, B24, B44 and A22, respectively, refer to strains PMB2001, PMB2948, PMB2707 and PMB80. The hSBA GMTs and proportion of participants with a ≥4-fold increase in hSBA titer (post-vaccination compared to pre-vaccination1) presented for A22 were based on calculations using an LLOQ of 1:16. The LLOQs for the remaining strains were 1:8.

4-fold hSBA responses (each strain) and composite response (all strains) after the 3rd bivalent rLP2086 vaccination (each strain)

Table 3. Study B1971011. Percentage of Individuals 11 to <18 Years of Age with a ≥4-Fold Rise in hSBA Titer and a Composite Response – Evaluable Immunogenicity Population

fHBP variant[a] / Time point[d]	rLP2086 + HPV4		rLP2086 + Saline	
	N=736-792		N=726-788	
	%[b]	(95% CI)	%[b]	(95% CI)
≥4-fold increase in hSBA titer				
A22				
Post-Vaccination 2	73.1	(69.9, 76.2)	74.2	(71.0, 77.3)
Post-Vaccination 3	85.3	(82.6, 87.7)	86.4	(83.8, 88.7)
A56				
Post-vaccination 2	92.5	(90.4, 94.3)	92.6	(90.4, 94.4)
Post-vaccination 3	95.0	(93.2, 96.5)	95.3	(93.6, 96.8)
B24				
Post-vaccination 2	61.3	(57.7, 64.8)	63.4	(59.9, 66.9)
Post-vaccination 3	83.4	(80.5, 85.9)	84.8	(82.0, 87.2)
B44				
Post-vaccination 2	45.7	(42.1, 49.3)	47.4	(43.8, 51.0)
Post-vaccination 3	77.0	(73.9, 79.9)	80.7	(77.8, 83.4)
Composite response (hSBA titer ≥LLOQ for all 4 primary strains)	**rLP2086 + HPV4**		**rLP2086 + Saline**	
	N=710-751		N=711-763	
	%[c]	(95% CI)	%[c]	(95% CI)
Before vaccination 1	0.3	(0.0, 1.0)	0.7	(0.2, 1.6)
Post-vaccination 2	49.9	(46.1, 53.6)	51.9	(48.2, 55.6)
Post-vaccination 3	81.0	(78.0, 83.7)	83.9	(81.1, 86.4)

hSBA= serum bactericidal assay using human complement; LLOQ= lower limit of quantitation; CI= confidence interval.

[a] The strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively.

[b] ≥4-fold increase in hSBA titer: %=n/N = number of subjects with a hSBA fold rise ≥4 from baseline (pre-vaccination #1) for the given strain/ number of subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline.
A ≥4-fold increase in hSBA titer is defined as follows: (1) For subjects with a baseline hSBA titer <1:4, a response was defined as an hSBA titer ≥1:16. (2) For subjects with a baseline hSBA titer ≥1:4, a 4-fold response was defined as an hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer, whichever was higher.

[c] Composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains): %=n/N= number of subjects with observed hSBA titer ≥ LLOQ for all 4 primary strains at the given time point/ number of subjects with valid and determinate hSBA results on all 4 strains at the given time point.

[d] Serum samples were obtained approximately one month after the second and one month after the 3rd bivalent rLP2086 vaccinations.
LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.
Source: Adapted from study B1971011 report.pdf, Table 23, page 100.

Proportion of subjects with hSBA titer ≥LLOQ (each strain; pre-vaccination #1, post-vaccination #3)

> *Reviewer Comment:* A hSBA titer ≥1:8 is a conservative threshold of protection, provided that the hSBA assay can accurately quantify titers at this level. The LLOQ for hSBA assays using strains expressing A56, B24 or B44 was 1:8. The LLOQ for the hSBA assay using the strain expressing A22 was 1:16.

Group 2 (bivalent rLP2086+saline): Prior to the 1st bivalent rLP2086 vaccination, the proportions of subjects in Group 2 with a hSBA titer ≥ 1:8 was 9.3%, 6.9% and 2.5%, respectively, for strains expressing A56, B24 and B44. The corresponding proportions in Group 2 after the 3rd vaccination were 99.4%, 92.9% and 85.7%. For A22, the proportions of subjects in Group 2 with a hSBA titer ≥ 1:16 prior to vaccination #1 and post-vaccination 3 were 16.4% and 96.3%, respectively.

Group 1 (HPV4+bivalent rLP2086): Prior to the 1st bivalent rLP2086 vaccination, the proportions of subjects in Group 1 with a hSBA titer ≥ 1:8 was 9.2%, 5.1% and 1.4%, respectively, for strains expressing A56, B24 and B44. The corresponding proportions in Group 1 after the 3rd vaccination were 98.9%, 90.5%, and 82.7%. For A22, the proportions of subjects in Group 2 with a hSBA titer ≥ 1:16 prior to vaccination #1 and post-vaccination 3 were 13.7% and 94.0%, respectively.

hSBA GMTs

The GMTs at baseline were below the hSBA LLOQs for both groups.

Table 4. Study B1971011. Meningococcal hSBA GMTs – Evaluable Immunogenicity Population

fHBP variant[a] / **Time point[d]**	**Bivalent rLP2086 + HPV4**		**Bivalent rLP2086 + Saline**	
	N=757-806[b]		**N=740-805[b]**	
	GMT[c]	**(95% CI)**	**GMT[c]**	**(95% CI)**
A22				
Pre-vaccination 1	9.6	(9.3, 10.0)	9.9	(9.6, 10.3)
Post-vaccination 3	53	(50, 57)	58	(54, 61)
A56				
Pre-vaccination 1	5.0	(4.8, 5.3)	5.0	(4.8, 5.3)
Post-vaccination 3	117	(110, 125)	128	(121, 136)
B24				
Pre-vaccination 1	4.3	(4.2, 4.5)	4.5	(4.4, 4.7)
Post-vaccination 3	26	(24, 28)	28	(26, 30)
B44				
Pre-vaccination 1	4.1	(4.0, 4.2)	4.2	(4.1, 4.3)
Post-vaccination 3	27	(25, 30)	32	(29, 35)

HPV4 = human papillomavirus vaccine [Gardasil]

[a] The strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively.

[b] N = number of subjects with valid and determinate hSBA titers for the given strain.

[c] Geometric mean titers (GMTs) were calculated using all subjects with valid and determinate hSBA titers at the given time point.

[d] Serum samples were obtained approximately one month after the 3rd bivalent rLP2086 vaccination.

Source: Adapted from study B1971011 report.pdf, Table 22, page 97.

hSBA responses after the 2nd bivalent rLP2086 vaccination

4-fold response (each strain)

For Group 2 (bivalent rLP2086+saline), the proportion of subjects with a ≥4 increase in hSBA titer (from baseline to 1 month after vaccination 2) was 74.0% for A22, 92.7% for A56, 63.5% for B24, and 48.8% for B44. The corresponding proportions in Group 1 subjects were 73.3%, 92.8%, 61.8%, and 46.0%.

Composite hSBA response (all strains)

The proportion of participants in Group 2 and Group 1 who achieved a composite response (post-vaccination 2 hSBA titer ≥ LLOQ for all 4 MenB strains combined) was 52.6% and 50.1%, respectively.

Proportion of subjects with hSBA titer ≥LLOQ (each strain)

After the 2nd bivalent rLP2086 vaccination, the proportion of Group 2 subjects with a hSBA titer ≥1:8 was 98.5% for A56, 74.2% for B24, and 57.1% for B44. The corresponding proportions in Group 1 subjects were 97.5%, 70.6% and 54.5%. For A22, the proportion of Group 2 and Group 1 participants with a hSBA titer >1:16 was 85.8% and 83.0%, respectively.

Antibody responses to HPV antigens

HPV GMTs

Table 5. Study B1971011. HPV GMTs – Evaluable Immunogenicity Population

Antigen Time Point[b]	Bivalent rLP2086 + HPV4 N=813-814[a]		Saline + HPV4 N=423[a]	
	GMT	**(95% CI)**	**GMT**	**(95% CI)**
HPV-6				
Pre-vaccination 1	5.8	(5.7, 5.9)	6.0	(5.7, 6.3)
Post-vaccination 3	452	(418, 489)	550	(490, 618)
HPV-11				
Pre-vaccination 1	4.2	(4.1, 4.3)	4.3	(4.1, 4.5)
Post-vaccination 3	893	(840, 950)	1084	(997, 1179)
HPV-16				
Pre-vaccination 1	5.8	(5.6, 6.0)	6.1	(5.7, 6.5)
Post-vaccination 3	3695	(3426, 3986)	4763	(4286, 5294)
HPV-18				
Pre-vaccination 1	5.2	(5.1, 5.3)	5.3	(5.1, 5.5)
Post-vaccination 3	744	(688, 805)	1047	(939, 1168)

HPV4 = human papillomavirus vaccine [Gardasil]

LLOQ = 11 mMU/ml for HPV-6, 8 mMU/ml for HPV-11; 11 mMU/ml for HPV-16; and 10 mMU/ml for HPV-18. Concentrations below the LLOQ were set to 0.5*LLOQ for analysis.

[a] N = number of subjects with valid and determinate titer for the given antigen.

[b] Serum samples were obtained approximately one month after the 3rd HPV4 vaccination.

Source: Adapted from study B1971011 report.pdf, Table 24, page 107.

HPV seroconversion (Group 1 vs. Group 3)

One month after the third HPV4 vaccination, ≥99% of subjects in both study groups seroconverted to all HPV types. Seroconversion was defined as the proportion of subjects with antibody concentrations at or above a pre-defined antibody concentration after the 3rd vaccination (seropositive) and who were below the corresponding antibody concentration prior to the first vaccination. The HPV antibody concentrations

measured by cLIA were ≥20 mMU/mL, ≥16 mMU/mL, ≥20 mMU/mL and ≥24 mMU/mL for HPV types 6, 11, 16 and 18.

For each of the HPV types, the proportion of subjects in Group 1 and 3 who were seronegative was <2.5%.

Sensitivity analyses

Study site

The outcomes for HPV (Group 1 and 2) and MenB (Groups 1 and 3) including or excluding site #1007 from the evaluable immunogenicity population were similar.

Differences in hSBA responses by gender (lower responses in male participants to subfamily B strains) and age (lower responses in individuals 15 to <18 years of age to subfamily A strains) were noted, but the differences were not substantial.

6.1.9.2 Safety Outcomes

Immediate AEs

30 minute observation period

The proportions of subjects in Group 1, 2 and 3 who reported at least 1 immediate AE within 30 minutes after Vaccination 1 were 2.1%, 1.6%, and 1.0%, respectively; after Vaccination 2 were 2.7%, 2.2%, and 1.9%, respectively; and after Vaccination 3 were 1.5%, 0.9%, and 1.3%, respectively.

A total of 49 (4.9%) subjects reported 77 immediate AEs in Group 1, 41 (4.1%) subjects reported 60 immediate AEs in Group 2, and 19 (3.8%) subjects reported 27 immediate AEs in Group 3. Injection site pain and headache were most common and were mainly reported as mild.

- *Bivalent rLP2086 injection site*: 29 participants in the concomitant vaccine group (Group 1) reported pain bivalent rLP2086 injection site (vaccination 1 n=11, vaccination 2 n=11, vaccination 3 n=7), compared with 31 participants in Group 2, who received bivalent rLP2086 vaccine + saline (vaccination 1 n=11, vaccination 2 n=14, vaccination 3 n=6).
- *HPV4 injection site*: 23 Group 1 participants reported pain at the HPV4 injection site (vaccination 1 n=5, vaccination 2 n=14, vaccination 3 n=4), compared with 7 participants in Group 3, who received HPV4+saline (vaccination 1 n=1, vaccination 2 n=5, vaccination 3 n=1).
- Headache was reported by 9 (0.9%) subjects in Group 1, 4 (0.4%) subjects in Group 2, and 2 (0.4%) subjects in Group 3.
- Syncope occurring within 1 day after an injection was observed in 6 subjects (Group 2 n=4, Group 1 n=2).

Solicited local reactions

Within 7 days after each vaccination visit

Among participants who received bivalent rLP2086 vaccine concomitantly with HPV4 (Group 1) or bivalent rLP2086 vaccine (Group 2), the frequencies of local reactions reported at the rLP2086 injection site after any vaccination were similar (97.6% and 96.9%, respectively) and were higher than the frequencies of local reactions reported at the saline injection site (56.7%) by participants who received saline+HPV4 (Group 3). Local reactions after bivalent rLP2086 vaccination (Groups 1 and 2) were most frequent after the first dose. Pain at the bivalent rLP2086 site was the most frequent local reaction (range: 83.8% to 93.6%) and the most frequent severe local reaction (range: 5.2% to 8.5%).

Table 6. Study B1971011. Percentage of Individuals 11 to 18 Years of Age With Local Adverse Reactions Within 7 Days After Each and After Any Vaccination

Local Reaction	Bivalent rLP2086 injection site			Bivalent rLP2086 injection site			Saline Injection site		
	Group 1[a]			Group 2[a]			Group 3[a]		
	Dose 1 N=985 (%)[b]	Dose 2 N=919 (%)[b]	Dose 3 N=842 (%)[b]	Dose 1 N=985 (%)[b]	Dose 2 N=907 (%)[b]	Dose 3 N=846 (%)[b]	Dose 1 N=496 (%)[b]	Dose 2 N=468 (%)[b]	Dose 3 N=438 (%)[b]
Pain at injection site[c]									
Any[d]	93.6	85.6	83.8	92.0	86.7	85.1	36.9	29.1	23.3
Mild	42.3	49.9	44.2	42.6	49.9	44.0	33.1	24.6	20.8
Moderate	42.7	30.5	33.8	41.5	32.7	35.5	3.6	4.5	2.3
Severe	8.5	5.2	5.8	7.8	4.0	5.7	0.2	0.0	0.2
Redness[e]									
Any[d]	20.2	16.5	15.3	20.5	13.2	16.3	1.2	1.7	1.1
Mild	9.0	6.6	7.1	9.0	6.6	7.6	1.0	1.7	0.9
Moderate	8.9	8.5	6.8	9.3	5.4	7.3	0.2	0.0	0.2
Severe	2.2	1.4	1.4	2.1	1.2	1.4	0.0	0.0	0.0
Swelling[e]									
Any[d]	21.5	18.5	19.7	21.6	18.0	20.6	2.8	2.8	1.8
Mild	12.6	11.3	11.2	12.5	10.3	12.2	1.8	2.1	1.4
Moderate	8.1	6.7	8.3	8.9	7.5	8.2	1.0	0.6	0.5
Severe	0.8	0.4	0.2	0.2	0.2	0.2	0.0	0.0	0.0

[a] At each vaccination visit (0,2, and 6 months), study group 1 received bivalent rLP2086 + HPV4 concomitantly, study group 2 received bivalent rLP2086 + saline and study group 3 received saline+HPV4. Local adverse reactions were assessed at the bivalent rLP2086 injection site (Groups 1 and 2) or the saline injection site (Group 3.

[b] %: n/N= number of subjects reporting severity of mild, moderate, or severe based on the severity scales/ Number of subjects with known values after the vaccination.

[c] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.

[d] Any: defined as the cumulative frequency of subjects who reported a reaction as "mild", "moderate" or "severe" within 7 days of vaccination.

[e] Mild = 2.5 to 5.0 cm, moderate = 5.5 to 10.0 cm, and severe is >10.0 cm.

Source: Adapted from study B1971011 report.pdf, Table 26, pages 119-121.

The median duration of pain at the rLP2086 injection site (Groups 1 and 3) was 3 days (range 1 to 20 days) and 2 days for the remaining solicited reactions (range 1 to 18 days). For all solicited reactions at the saline injection site (Group 3), the median duration was 1 day (range 1 to 21 days).

Nine subjects (Group 1 n=5, Group 2 n=2, Group 3 n=3) reported 12 injection site reactions with a duration >14 days (pain n=6, swelling n=3, redness n=3). Moderate or severe injection site reactions that lasted >14 days were reported by five participants (Group 1 n=3, Group 2 n=2).

Solicited systemic reactions

7 days after each vaccination visit
The overall frequencies of systemic AEs in the concomitant vaccine group (Group 1) were similar to frequencies of corresponding AEs in participants receiving bivalent rLP2086+saline (Group 2) and higher than frequencies of systemic AEs in participants receiving HPV4+saline (Group 3) (91.6%, 91.1% and 80.9%, respectively).

After vaccination visit 1, more Group 1 than Group 3 participants experienced headache (56.9% vs 43.1%, respectively), fatigue (64.4% vs 50.6%) and chills (30.3% vs 16.7%). Fever ($T \geq 38.0°C$) occurred 8.3% of Group 1 and in 0.8% of Group 3 participants, of which 0.6% (Group 1) and 0.2% (Group 3) of fevers were between T39.0°C-40.0°C. Headache that interfered with daily activities were reported by 17.8% of Group 1 participants and 9.3% of Group 3 participants, and fatigue that interfered with daily activities developed in 20.6% and 13.1% of participants, respectively. The proportion of Group 1 and Group 3 participants who used antipyretic medication was 26.3% and 13.3%, respectively. In both groups, the frequencies of systemic adverse events were lower with subsequent vaccinations.

Table 7. Study B1971011. Percentage of Individuals 11 to 18 Years of Age Reporting Solicited Systemic Adverse After Each Vaccination and After Any Vaccination – Safety Population

Systemic Reaction	Bivalent rLP2086 + HPV4			Bivalent rLP2086 + Saline			Saline + HPV4		
	Group 1			Group 2			Group 3		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
	N=985	N=919	N=842	N=985	N=907	N=846	N=496	N=468	N=438
	%[a]	%[a]	%[a]	%[a]	%[a]	%[a]	%[a]	%[a]	%[a]
Fever									
≥38.0°C	8.3	2.1	2.1	6.4	1.3	1.1	0.8	0.9	0.7
38.0° to ≤38.4°C	4.9	1.2	1.1	3.7	1.1	0.8	0.4	0.4	0.2
38.5° to ≤38.9°C	2.5	0.4	0.6	1.5	0.1	0.1	0.0	0.2	0.0
39.0° to ≤40.0°C	0.6	0.3	0.4	1.0	0.1	0.1	0.2	0.2	0.2
Vomiting[b]									
Any[c]	7.8	2.8	2.4	7.4	2.4	2.5	3.4	3.0	1.6
Mild	5.8	2.1	2.1	5.3	1.4	1.8	3.2	2.4	0.9
Moderate	1.9	0.7	0.2	1.7	0.9	0.5	0.2	0.6	0.7
Severe	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Diarrhea[d]									
Any[c]	14.5	10.9	9.3	15.2	9.3	8.9	15.5	11.1	9.4
Mild	12.6	9.1	7.7	13.3	7.5	7.3	12.5	9.8	7.8
Moderate	1.7	1.6	1.1	1.7	1.8	1.2	2.6	1.3	1.6
Severe	0.2	0.1	0.5	0.2	0.0	0.4	0.4	0.0	0.0
Headache[e]									
Any[c]	56.9	44.8	41.0	54.8	40.8	34.8	43.1	36.5	27.4
Mild	37.7	32.9	30.0	36.1	28.3	24.0	33.3	25.4	21.0
Moderate	17.8	11.1	10.5	16.5	10.7	10.2	9.3	10.5	6.2
Severe	1.4	0.9	0.5	2.1	1.8	0.6	0.6	0.6	0.2
Fatigue[e]									
Any[c]	64.4	48.9	44.1	62.4	44.8	42.9	50.6	34.4	31.5
Mild	39.5	33.4	28.4	39.1	30.8	30.9	37.1	25.6	24.2
Moderate	20.6	12.8	14.3	19.7	12.3	10.9	13.1	7.9	7.1
Severe	4.3	2.6	1.4	3.7	1.7	1.2	0.4	0.9	0.2
Chills[e]									
Any[c]	30.3	19.2	17.5	29.0	17.4	15.6	16.7	12.0	8.2
Mild	21.5	13.8	13.1	22.0	13.6	12.5	13.9	9.6	7.1
Moderate	7.4	4.1	3.7	5.6	2.9	3.0	2.6	2.1	1.1
Severe	1.3	1.2	0.7	1.4	1.0	0.1	0.2	0.2	0.0
Muscle pain (generalized)[e]									

Any[c]	41.1	36.6	35.3	42.4	30.5	30.9	28.6	24.6	20.8
Mild	24.7	25.0	22.2	25.7	19.8	21.3	23.4	19.4	16.2
Moderate	13.3	10.2	11.2	13.9	9.3	8.5	4.6	4.9	3.9
Severe	3.1	1.3	1.9	2.8	1.4	1.1	0.6	0.2	0.7
Joint pain[e]									
Any[c]	21.6	15.5	19.2	21.6	15.4	17	13.7	12.2	11
Mild	15.7	11.1	13.4	14.7	11.8	13.7	10.9	9.8	8.7
Moderate	5.0	3.8	4.9	5.9	3.0	3.1	2.8	2.4	1.6
Severe	0.9	0.5	1.0	1.0	0.7	0.2	0.0	0.0	0.7
Use of antipyretic medication	26.3	16.1	16.5	27	17.5	17	13.3	13.9	6.6

[a] %: n/N = number of subjects reporting specific characteristic as present after the vaccination/ Number of subjects with known values after the vaccination.
[b] Mild: 1-2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires IV hydration.
[c] Any: defined as the cumulative frequency of subjects who reported a reaction as "mild", "moderate" or "severe" within 7 days of vaccination.
[d] Mild: 2-3 loose stools in 24 hours; moderate: 4-5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
[e] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
Source: Adapted from study B1971011 report.pdf, Table 28, page 128-133.

For most of the solicited systemic reactions, the median duration was 1-2 days for each study group. Twenty-nine subjects (Group 1 n=11, Group 2 n=10, Group 3 n=8) reported 42 systemic events with duration >14 days (fatigue n=19, headache n=13, joint pain n=4, muscle pain n=3, chills n=2, fever n=1, which were mainly categorized as mild.

Unsolicited adverse events

Within 30 days after each vaccination visit

The proportions of subjects (Groups 1, 2 and 3, respectively) who reported at least 1 unsolicited AE within 30 days after vaccination were as follows: Vaccination 1 (13.3%, 14.8%, and 12.8%, respectively), Vaccination 2 (15.6%, 12.2%, and 18.5%, respectively), and Vaccination 3 (12.2%, 11.6%, and 13.1%, respectively). In all study groups, the adverse events most frequently reported were events included in the MeDRA system organ class (SOC) of 'infections and infestations', of which upper respiratory tract infection, pharyngitis and nasopharyngitis were common.

During the vaccination phase (from the first vaccination visit through 1 month after the last study vaccination), none of the AEs reported by $\geq$1% of subjects in Group 1 (bivalent rLP2086+HPV4) or Group 3 (saline+HPV4) occurred more frequently among subjects in the concomitant vaccine group. Of the AEs reported by $\geq$1% of subjects in Group 1 (bivalent rLP2086+HPV4) or Group 2 (bivalent rLP2086 vaccine+saline), only headache occurred more frequently in the concomitant vaccine group (4.9% vs. 3.8%, respectively). A total of 48 (4.8%) subjects in Group 1 and 18 (3.6%) subjects in Group 3 reported AEs that were categorized as severe (i.e. interferes significantly with the subject's usual function), including injection site pain (Group 1 n=4 [bivalent rLP2086 vaccine injection site], Group 3 n=1 [HPV4 injection site]), chills (Group 1 n=4, Group 3 n=0) and headache (Group 1 n=5, Group 1 n=1). A total of 45 (4.5%) subjects in Group 2 reported severe AEs, which were similar in distribution to severe AEs reported by Group 1.

Serious adverse events

Day 1 through 6 months after the last vaccination visit

During the time period starting on the day of vaccination through 6 months after the last vaccination visit

- Group 1: 12 of 992 subjects (1.2%) reported 13 SAEs, which included injury (n=4), psychiatric disorders (n=4), cardiac disorders (n=1 [supraventricular tachycardia], benign follicular hyperplasia (n=1) and appendicitis (n=2) and migraine headache (n=1).
- Group 2: 16 of 990 subjects (1.6%) reported 17 SAEs, which included injury (n=6), psychiatric disorders (n=5), asthma exacerbation (n=1), facial cellulitis due to tooth abscess (n=1), nodular fasciitis (n=1), appendicitis (n=1), chronic abdominal pain (n=1) and slipped femoral epiphysis (n=1).
- Group 3: 4 of 501 subjects (0.8%) reported 4 SAEs, which included migraine (n=1), biliary dyskinesia (n=1), psychiatric disorder (n=1) and hemorrhoid (n=1).

None of the SAEs led to premature study discontinuation.

Deaths
There were no deaths during the study period.

Premature study discontinuations

Participants who withdrew from the study due to an AE included 9 of 992 Group 1 subjects (0.9%) who reported 15 events, 11 of 990 Group 2 subjects (1.1%) who reported 17 events and 3 of 501 Group 3 subjects (0.6%) reported 8 events.

- Withdrawal due to solicited AE: 9 of 9 subjects in Group 1 (concomitant vaccine group) and 8 of 11 subjects in Group 2 (bivalent rLP2086+saline) withdrew due to a solicited AE, mostly after the 1st vaccination, compared to 2 of 3 subjects in Group 3 (HPV4+saline).
- In Group 2, 4 of 8 subjects reported $\geq$2 solicited AEs that were categorized as moderate or severe with duration of symptoms that ranged from one to six days; the AEs occurred after the first vaccination visit for the four subjects. One Group 3 participant reported five AEs (moderate chills/fatigue/fever/myalgia, mild arthralgia, and severe headache) with duration of symptoms that lasted three to five days; symptoms developed after the second vaccination visit.

One subject who was diagnosed with immunoglobulin A (IgA) nephropathy withdrew from the study due to fulfillment of the exclusion criteria for autoimmune condition.

Of participants in Groups 1 and 2 who voluntarily withdrew from the study, approximately 35% of Group 1 participants and 25% of Group 2 participants withdrew after the first vaccination for reasons that frequently included preferences to discontinue further vaccinations.

Newly diagnosed medical illnesses

Day 1 through 6 months after the last vaccination visit
In total, 23 subjects were diagnosed with newly diagnosed major illnesses during the time period starting from the day of vaccination to 6 months after the last vaccination. In Group 1 (bivalent rLP2086 + HPV4) there were eight subjects with asthma-related events, 1 subject with migraine headaches, and one subject with myopia. In Group 2 (bivalent rLP2086 + saline), there was one subject with allergy to dog hair, one subject with herpes simplex virus 1 infection, 1 subject with hypocholesterolemia, one subject with hypertension, one subject with partial seizure disorder, and one subject with IgA nephropathy. Three of the 23 subjects were newly diagnosed with major illnesses between 1 month and 6 months after vaccination visit 3: asthma in two Group 1 subjects and hypertension in one Group 2 subject.

Autoimmune and neuroinflammatory conditions

Day 1 through 6 months after the last vaccination visit
Two participants were diagnosed with autoimmune conditions (Sydenham's chorea, IgA nephropathy) and one participant developed Bell's palsy. Please see section 8 (integrated summary of safety) for case narratives.

Sensitivity analyses

Gender

Among subjects who received bivalent rLP2086 non-concomitantly (Group 2), the frequencies of solicited reactions were approximately 10-15% lower in male participants for swelling at the rLP2086 injection site (e.g., after the first vaccination: 19.0% vs. 26.9%), headache (e.g., after the first vaccination: 50.8% vs. 63.2%) and fatigue (after the second vaccination: 40.3% vs. 58.8%).

Among participants who received HPV4 non-concomitantly (Group 3), the frequencies of pain at the HPV4 injection site, headache and fatigue were 15%-20% lower in male participants than female participants.

Within group comparisons (Group 2, Group 3) of unsolicited AEs and SAEs rates were similar by gender.

Age

Among participants who received bivalent rLP2086 non-concomitantly (Group 2), there were no notable differences in analyses of local reactions stratified by age. The frequencies of systemic reactions after the first vaccination was lower among Group 2 subjects 15 to <18 years of age vs. subjects 11 to <14 years of age for fever (T ≥38.0°C; 3.0 vs. 8.2), chills (23.1% vs. 32.1%) and antipyretic use (20.8% vs. 30.2%).

Among participants who received HPV4 non-concomitantly (Group 3), the frequencies of pain at the HPV4 injection site and myalgia were approximately 10%-15% lower among subjects 15 to <18 years of age vs. subjects 11 to <14 years of age.

Within group comparisons (Group 2, Group 3) of unsolicited AEs and SAEs rates were similar by age.

6.1.10 Summary and Conclusions

Study B1971011 was one of the main studies to support (a) immunogenicity of bivalent rLP2086 among adolescents when administered according to a 3-dose series at 0, 2 and 6-month schedule (Group 2), as measured by hSBA responses using four primary MenB strains expressing fHBP variants A22, B24, A56 and B44; (b) safety of bivalent rLP2086, and (c) concomitant administration of HPV4 and bivalent rLP2086. In total, 66.5% of subjects were male and 33.5% were female. The age distribution participants 11 to <14 years age and 15 to <18 years of age was 65.9% and 34.1%, respectively.

Immunogenicity of bivalent rLP2086

In the context of the accelerated approval pathway, analyses of the following endpoints using four primary MenB strains were most relevant to US licensure: the proportion of participants with a ≥4-fold response to each of the four MenB strains and the proportion of participants with a hSBA response ≥LLOQ to all of the primary strains (composite response). The analyses for the endpoints described above were descriptive; however, hSBA responses were evaluated in a substantial number of participants (Group 1 n=999, Group 2 n=998). The 4-fold and composite endpoints described above are analogous to the primary endpoints in the phase 3 studies being conducted with bivalent rLP2086.

- The immunogenicity data supported use of bivalent rLP2086 as a 3-dose series. The proportion of bivalent rLP2086 subjects with a ≥4 increase in hSBA titer was substantially higher after 3 doses than after 2 doses, especially for subfamily B strains (variant B24: 83.4% vs. 61.8%; variant B44: 77.0% vs. 46.0%). The proportion of participants with post-vaccination hSBA titer ≥ LLOQ to all 4 primary MenB strains (composite response) was 81.0% and 50.1% after the 3rd and 2nd vaccination, respectively. There were no substantial differences in hSBA responses by gender or age.

Concomitant vaccine administration

- No immunological interference was observed for hSBA responses (using strains expressing fHBP variant A22 and B24) when bivalent rLP2086 was administered concomitantly (Group 1) or non-concomitantly (Group 3) with HPV4. The HPV GMTs following co-administration of HPV4 and bivalent rLP2086 (Group 1) were lower than when HPV4 was not co-administered with bivalent rLP2086 (Group 2). For HPV-18, the lower bound of the 95% CI for the GMT ratio was 0.62, which corresponded to greater than a 1.5 difference in GMTs. However, for both groups 1 and 2, the HPV seroconversion rate was ≥99% for each respective HPV type. Importantly, in the last 10 years, no breakthrough infections (precancerous cervical dysplasia) due to HPV-18 have been reported among HPV4-vaccinated individuals.

Safety of bivalent rLP2086
Bivalent rLP2086 is reactogenic, even when compared with HPV4. Safety analyses stratified by gender and age suggested some differences, but they were consistent with similar trends demonstrated for HPV4, which is a licensed product.

For all study groups, the rate of SAEs reported through the 6 month visit after the last vaccination was <2%. Two bivalent rLP2086 participants were diagnosed with autoimmune conditions (Sydenham's chorea, IgA nephropathy) and one participant bivalent rLP2086 developed Bell's palsy; please see section 8 (Integrated Summary of Safety).

6.2 Study B1971012

NCT# 01299480

Title: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability, and Immunogenicity of Bivalent rLP2086 Vaccine When Administered in Either 2- or 3-Dose Regimens in Healthy Subjects Aged ≥11 to <19 Years

6.2.1 Objectives and Endpoints

Primary Objectives
The co-primary objectives were to assess immune responses among subjects who received bivalent rLP2086 according to a 0-, 1- and 6-month schedule (Group 1) and among subjects who received bivalent rLP2086 according to a 0-, 2- and 6-month schedule (Group 2), as measured by hSBA assay performed with four MenB primary strains after the 3rd rLP2086 vaccination.

Primary endpoints
% of subjects with hSBA titer ≥LLOQ

> *Reviewer Comment:* This study was designed to evaluate possible endpoints and to provide immunogenicity data to support sample size and power calculations for phase 3 studies. For purposes of this review, the hypotheses tested for Groups 1 and 2 were not relevant since the endpoints for phase 3 studies were not based on the proportion of subjects with a hSBA titer ≥LLOQ.

Secondary Objectives
1. To assess the immune response among subjects who received bivalent rLP2086 according to a 0- and 6-month schedule (Group3), as measured by hSBA assay performed with four MenB primary strains. Time point: one month after the 2nd bivalent rLP2086 vaccination.
   Endpoints (for each of the four primary strains): % of Group 3 subjects with a hSBA titer ≥LLOQ

2. To describe the immune response as measured by hSBA assay performed with four MenB primary strains throughout the study (all study groups; see Table 8). Time points: Visit 0, Visit 3, Visit 4 and

Visit 6. The primary MenB strains are the same as the test strains as described in Study B1971011, section 6.1.1.

Endpoints
For each of the MenB strains and blood sampling time point
- GMTs
- % of subjects with hSBA titer ≥LLOQ
- % of subjects with hSBA titer ≥1:8, 1:16, 1:32, 1:64 and 1:128

Exploratory Objectives
To describe the MenB immune response (4-fold response and composite response) as measured by hSBA assays using four MenB primary strains. Time points: blood draw visit after each bivalent rLP2086 vaccinations (Visits 3, 4 and 6; see Table 8).

Safety Objective
To describe the safety profile of bivalent rLP2086 vaccine.

6.3.2 Design

Subjects were randomized to 5 study groups (3:3:3:2:1 ratio) to receive bivalent rLP2086 as follows:

Table 8. Study B1971012. Study Design

Visit #	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Visit Description	**Injection 1 Blood Draw**	**Injection 2**	**Injection 3 Blood Draw**	**Blood Draw**	**Injection 4**	**Blood Draw**	**Telephone call**
Approximate Month	**Month 0**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 7**	**6 months after last study vaccination**
Visit window prior to study pause (per-schedule)	Day 1	28 to 42 days After Visit 1	56 to 70 days After Visit 1*	28 to 42 days After Visit 3	105 to 126 days After Visit 3	28 to 42 days After Visit 5	
Visit window after study pause	Day 1	28 to 132 days After Visit 1	56 to 160 days After Visit 1*	28 to 42 days After Visit 3	105 to 156 days After Visit 3	28 to 42 days After Visit 5	168 to 196 days After Visit 5
Group 1	Bivalent rLP2086	Bivalent rLP2086	Saline		Bivalent rLP2086		
Group 2	Bivalent rLP2086	Saline	Bivalent rLP2086		Bivalent rLP2086		
Group 3	Bivalent rLP2086	Saline	Saline		Bivalent rLP2086		
Group 4	Bivalent rLP2086	Saline	Bivalent rLP2086		Saline		
Group 5	Saline	Saline	Bivalent rLP2086		Bivalent rLP2086		

*Visit 3 must be at least 21 days after vaccination at Visit 2.
Source: Adapted from B1971012 report.pdf, Schedule of Activities, page 7.

Planned enrollment included a total of 1716 subjects.

6.2.3 Population

The study was conducted at 61 sites (Czech Republic n=18, Denmark n=1, Finland n=12, Germany n=8, Poland n=11, Spain n=8, Sweden n=3).

Inclusion criteria
- Male or female subject aged ≥11 and <19 years at the time of enrollment
- Informed consent/assent obtained
- Negative urine pregnancy test for female subjects
- Available for the entire study period and can be reached by telephone
- Able to comply with study procedures

Pertinent exclusion criteria
- Previous vaccination with any meningococcal serogroup B vaccine.
- Anaphylactic reaction to any vaccine or vaccine-related component
- Contraindication to vaccination with diphtheria, tetanus, pertussis, or poliomyelitis virus- containing vaccine.
- Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.
- Known or suspected disease of the immune system or those receiving immunosuppressive therapy.
- History of culture-proven disease caused by *N meningitidis*
- Significant neurological disorder or history of seizure (excluding simple febrile seizure).
- Receipt of any blood products, including immunoglobulin within 6 months before the first study vaccination.
- Current chronic use of systemic antibiotics.
- Pregnant or breastfeeding.
- Participation in other studies during study participation (purely observational studies are acceptable).
- Received any investigational drugs, vaccines or devices within 28 days before administration of the first study vaccination.
- Any neuroinflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.

6.2.4 Randomization/Blinding

This study was a single-blinded (i.e. subjects were blinded to their allocated vaccine group). All study groups received a total of 4 injections. A single injection (bivalent rLP2086 or saline) was administered at Visit 1, Visit 2, Visit 3 and Visit 5. Saline was administered to maintain the blind at a given injection visit (i.e. same number of injections/per visit for each study group) and to serve as a comparator for solicited adverse reactions. Enrollment was stratified by age group (≥11 to <14 and ≥14 to <19 years of age, respectively). The method for randomization (interactive response system) was the same as for study B1971010.

6.2.5 Study Products

Study vaccines provided by the sponsor
- Bivalent rLP2086 vaccine: same composition and formulation as for study B1971011. Lot# 10-087986.
- Saline (0.9% sodium chloride). Lot# 10-087728.

Permitted vaccines
- Non study vaccines that are part of recommended immunization schedules are allowed anytime following the post-vaccination 2 visit (Visit 3) but not within 2 weeks of study vaccine

administration. Nonstudy vaccines that were used in the event of a disease outbreak or pandemic were allowed at any time during the study.

6.2.6 Assessments

Safety Evaluation
Solicited local and systemic adverse reactions were assessed after each injection visit. Subjects were observed for 20 minutes (or longer depending on the study site) for immediate adverse reactions. For all study groups, the vaccination phase was defined as the time period from the first study injection (Visit 1) through 1 month after the last study injection (Visit 6, which is one month after the last bivalent rLP2086 vaccination in Groups 1-3 and 5, and 5 months after the last bivalent rLP2086 vaccination in Group 4). The safety data collection methods and EDMC role/responsibilities were the same as for study B1971011.

Immunogenicity (methods)
For each of the MenB strains, the designated laboratory that performed the hSBA assays was the same as for study B1971011. The LLOQs for PMB2948(B24), PMB2001(A56), and PMB2707(B44) are 1:8. LLOQ for PMB80(A22) is 1:16.

6.2.7 Statistical Analysis Plan/Data Analysis

For purposes of this review, the hypotheses tested for Groups 1-3 were not relevant. Please see section 6.2.1

Populations analyzed
Modified intent to treat (mITT) population
Included all randomized subjects who had as least 1 valid and determinate assay results for the proposed analysis.

Evaluable immunogenicity population
Comprised of all eligible subjects randomized to Groups 1, 2, 3, 4 or 5; who received bivalent rLP2086 at all injection visits as randomized; had blood drawn within the required time frame prior to the first dose of vaccine and 1 month after the last vaccination (i.e. Groups 1-3 and 5: post-vaccination 3 blood drawn within 28-42 days after vaccination 3 (Visit 5); had valid and determinate assay results for the proposed analysis; received no prohibited vaccines or medications. This population included participants who received bivalent rLP2086 during the extended vaccination time period, as defined in protocol amendment 4. The vaccination windows were as follows: Visit 2 (injection 2): 28 to 132 days after Visit 1; Visit 3 (injection 3): 56 to 160 days after Visit 1; Visit 5 (injection 4): 105 to 156 days after Visit 3.

Per-Schedule evaluable immunogenicity population
The applicant temporarily paused enrollment and further vaccinations during an investigation of a SAE reported for a 15 year old participant with vertigo, and resumed 2 to 3 months later. Visits for injections 2, 3, and 5 were extended, with resultant extended study duration (see Table 8).

The criteria for inclusion in the per-schedule evaluable population were similar to the evaluable population, except that participants received bivalent rLP2086 as randomized and according to the vaccination windows defined in protocol amendment 1 (i.e. prior to study pause): Visit 2 (injection 2): 24 to 42 days after Visit 1; Visit 3 (injection 3): 56 to 70 days after Visit 1; Visit 5 (injection 4): 105 to 126 days after Visit 3.

Out-of-schedule immunogenicity population
Comprised of all of the subjects that were included the mITT population and excluded from the per-schedule population.

Safety populations
Included all subjects who received at least 1 dose of study product (i.e. bivalent rLP2086 or saline) and for whom safety data were available. Separate safety populations were defined for each injection (e.g. subjects who received injection 1 and had safety data available for the same visit).

Safety population as administered
This analysis population was further defined to account the subjects who may have missed an injection due to the study pause.

1. For subjects who were randomized to receive 3-dose of bivalent rLP2086 vaccine,
   - If the missed dose was saline, the 'as administered' study group was the same as the 'as randomized' study group. Solicited AE data for the given time point were counted as missing.
   - If the missed dose was vaccine, the 'as administered' study group was assigned to Group 3 (0.6-month schedule). The solicited AE data for visits in which vaccine was administered were analyzed according to the time points for visits corresponding to Group 3 (i.e. injection 1 and 4, respectively).

2. For subjects who were randomized to receive 2-dose of rLP2086 vaccine,
   - If the missed dose saline, the 'as administered' study group was the same as the 'as randomized' study group. The solicited AE data were analyzed according to the injection schedule for the given study group (e.g. time points for Group 4 were visits corresponding to injections 1 and 3). For subjects in Group 3 and Group 5, the solicited AE data for the last dose of saline was counted as missing. For subjects in Group 4, the solicited AE data for the saline dose was counted as missing.
   - If the missed dose was bivalent rLP2086
     - For subjects in Group 3 and Group 5, the solicited AE data for the bivalent rLP2086 that was administered were analyzed according to the time point which corresponded to the first bivalent rLP2086 dose (i.e. visit for injection 1 for Group 3, visit for injection 3 for Group 5)
     - For subjects in Group 4, the 'as administered' group was assigned to Group 3. The solicited AE data for visits in which vaccine was administered were analyzed according to the time point which corresponded to the first bivalent rLP2086 dose (injection 1); solicited AE data for visits in which saline was administered were analyzed as injection 2 and injection 3.
3. If there was no missed dose, but the incorrect study product was administered, the subject was included in the study group 'as administered'.

Immunogenicity Analyses
Secondary analyses (descriptive)
The remaining secondary endpoints were summarized by study group (as randomized) for each of the 4 MenB primary strain and blood sampling time point, and presented with 95% CIs. For GMT calculations, titers below the LLOQ were assigned a titer equal to ½ the LLOQ.

Exploratory analyses (descriptive)
Endpoints
- % of subjects with ≥4-fold increase in hSBA titer (after each bivalent rLP2086 vaccination compared to baseline) for each strain, defined as follows
  - For subjects with a baseline hSBA titer below the LOD or a hSBA titer of <1:4, a 4-fold response is defined as an hSBA titer ≥1:16.
  - For subjects with a baseline hSBA titer of ≥ LOD (i.e., hSBA titer ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer ≥ four times the LLOQ.

- For subjects with a baseline hSBA titer ≥ LLOQ, a 4-fold response is defined as an hSBA titer ≥ four times the baseline titer.

- % of subjects achieving a composite hSBA response, defined as hSBA titer ≥LLOQ for all 4 primary strains, for each post-vaccination time point.

A titer of 1:8 was used as the LLOQ for each of the 4 MenB primary strains.

Post-hoc Analyses
Analyses of the primary, secondary and exploratory endpoints were performed with 1:16 as the LLOQ for the hSBA assay using strain PMB80 [variant A22].

Safety Analyses
The safety endpoints and analyses were similar to study B1971011, except for: (a) Assessment of solicited AEs (7 days) and unsolicited AEs (30 days) was done at each injection visit (b) The observation period for immediate reactions was 20 minutes (or longer depending on the study site); (c) Visit 6 corresponded to the visit 1 month after the last study injection and Visit 7 corresponded to the visit (telephone call) 6 months after the last injection.

6.2.8 Amendments to the Protocol/SAP

Protocol: pertinent changes
Amendment 1, dated 19-Oct-2010: the timing of vaccinations was changed from 0, 2, 6 and 12 months to at 0, 1, 2 and 6 months; revised the primary objective as two co-primary objectives; updated inclusion/ exclusion criteria.

Amendment 2, dated 25-Jul-2011: vaccinations were temporarily paused on 01-Jul-2011 during an investigation of a SAE reported for a 15 year old participant with vertigo, and resumed 2 to 3 months later. Visits for injections 2, 3, and 5 were extended, with resultant extended study duration.

Amendment 3, dated 23-Apr-2012: updated to be consistent with updated FDA regulations for safety reporting for IND studies.

Amendment 4, dated 24-Sept-2012: added exploratory objectives to describe hSBA 4-fold response and composite response; updated safety endpoints to be consistent with Phase 3 program.

SAP: pertinent changes
Version 2.0, dated 28-Oct-2010: incorporated changes listed in protocol amendment 1.
Version 3.0, dated 10-Sept-2012: added exploratory objectives; included plan for handling missing data; included sensitivity analyses to assess any effects of delayed vaccinations on immune responses.

SAP Appendix v1.0, date 06-May-2013: included clarification of rules for handling safety data (missing or incomplete data, AE start and resolve dates) and determining the time point for study completion.

6.2.9 Results

The study was conducted from March 3, 2011 to September 18, 2012 (last subject last visit). Study centers: Czech Republic (n=331 subjects), Denmark (n=303 subjects), Finland (n=369 subjects), Germany (n=164 subjects), Poland (n=239 subjects), Spain (n=176 subjects), Sweden n=133 subjects).

Subject Disposition

In this study, all subjects received a single injection at time points 0, 1, 2 and 6 months after enrollment (injection visits 1-4). Subjects received bivalent rLP2086 at the following visits: Group 1: injection visits 1, 2 and 4. Group 2: injection visits 1, 3 and 4. Group 3: injection visits 1 and 4. Group 4: injection visits 1 and 3. Group 5: injection visits 3 and 4. At the remaining visits, subjects received a saline injection.

Of 1714 enrolled subjects, 1713 subjects were randomized (Group 1 n= 427, Group 2 n=430, Group 3 n=427, Group 4 n= 427, Group 5 n=143). Two participants (Group 3 n=1, Group 4 n=1) were randomized but received no injections. Participants who were partially vaccinated were included in study groups according to the number of doses and schedule as administered, as follows:
Group 1 (0,1,6m): dose 1 (injection 1) n=427, dose 2 (injection 2) n=408, dose 3 (injection 4) n=385
Group 2 (0,2,6m): dose 1 (injection 1) n=430 , dose 2 (injection 3) n=392, dose 3 (injection 4) n=396
Group 3 (0,6m): dose 1 (injection 1) n=426, dose 2 (injection 4) n=387
Group 4 (0,2m): dose 1 (injection 1) n=285, dose 2 (injection 3) n=259
Group 5 (2,6m): dose 3 (injection 3) n=128, dose 2 (injection 4) n=128

A total of 161 (9.4%) subjects received at least one injection and prematurely discontinued the study [as randomized: Group 1 n=42, Group 2 n=35, Group 3 n=40, Group 4 n=24, Group 5 n=20]; voluntary withdrawal was the most common reason. Nineteen subjects [as randomized: Group 1 n=6, Group 2 n=4, Group 3 n=5, Group 4 n=4, Group 5 n=0] withdrew due to an AE (please see the premature study discontinuation section for further details).

1550 randomized subjects (90.5%) received at least one injection, had not prematurely discontinued the study and provided safety information at the scheduled follow-up telephone call six months after the last injection visit. In addition, 95 subjects who had withdrawn from the study provided safety information at the follow-up telephone call described above.

Immunogenicity populations
1713 subjects were randomized (ITT population; Group 1 n= 427, Group 2 n=430, Group 3 n=427, Group 4 n= 427, Group 5 n=143). The applicant temporarily paused administration of study product during a DMC review of a SAE (please see section 6.2.9.2 for further information).

- 86-90% of subjects among groups 1-5 received injections 1 and 2 according to the visit and interval specified in the protocol version (amendment 1) prior to study pause; 60-63% of subjects received bivalent rLP2086 according to the visit and interval specified for injection 3 (i.e. 56-70 days after injection 1) and injection 4 (i.e. 105-126 days after injection 3).

  The administration interval was extended (protocol amendment 2) an additional 90 days for injection 2, an additional 90 days for injection 3 (i.e. 71-160 days after Injection 1), and an additional 30 days for injection 4 (i.e. 127 to 156 days after injection 3); 16-24% additional subjects/per group received bivalent rLP2086 vaccine at injection visits 3 and 4 during the extended timeframe.

- Of subjects in study groups that completed the bivalent rLP2086 series at injection visit 4 (Groups 1-3 and 5), 81%-87% of subjects had a blood sample collected during the interval 28-42 days post-injection. Group 4 subjects completed the bivalent rLP2086 series at injection visit 3; 83% of Group 4 subjects had a blood sample collected during the interval 28-42 days post-injection.

1450 of 1713 randomized subjects (84.6%) comprised the evaluable immunogenicity population (Group 1 n= 365, Group 2 n=360, Group 3 n=371, Group 4 n= 241, Group 5 n=113), and included subjects who received injections during the extended time frame described above. Subjects (n=263 [Group 1: 14.5%. Group 2: 16.3%, Group 3: 13.1%, Group 4: 15.7%, Group 21.0%]) were excluded from the evaluable immunogenicity population mainly because bivalent rLP2086 was not administered (as randomized) at all

of the designated injection visits (Group 1: 10.3%%. Group 2: 11.2%, Group 3: 9.4%, Group 4: 9.4%, Group 5: 15.4%), a pre or post-vaccination blood sample was not obtained within the interval specified in the protocol amendment 4 (i.e. 28-42 days after Visit 5 for Groups 1, 2, 3, and 5) or SAP version 3.0 (28-56 days after Visit 3 for Group 4) (Group 1: 14.1%. Group 2: 13.3%, Group 3: 12.9%, Group 4: 15.4%, Group 5: 21.0%) or a valid and determinate hSBA result was not available at the pre or post-vaccination time point (Group 1: 9.8%. Group 2: 8.1%, Group 3: 9.8%, Group 4: 15.4%, Group 5: 13.3%).

The per-schedule evaluable immunogenicity population was comprised of 822 subjects (48.0%) (Group 1: 45.2%, Group 2: 38.4%, Group 3: 48.9%, Group 4: 60.5%, Group 5: 57.3%) who received all injections as randomized and within the interval specified in protocol amendment 1.

The out-of-schedule population was comprised of 889 subjects (51.9%) who were included in the mITT population (1711 subjects) but not the per-schedule evaluable immunogenicity population.

Demographic and other baseline characteristics
The overall safety population (all study groups) consisted of 50.8% male participants and 49.2% female participants; the median age was 14 years (36.6% of participants were 11 to <14 years age and 63.4% were age 14 to <19 years). The population overall were 99.0% Caucasian, 0.1% African American, 0.3% Asia, and 0.6% of participants were classified as 'other'. The demographic and other baseline characteristics of the per-schedule evaluable immunogenicity population and the population who received study products as administered were similar to the randomized population.

6.2.9.1 Immunogenicity Outcomes

Primary Objectives
Please see section 6.2.1.

Other Objectives (Secondary, exploratory, post-hoc analyses)
<u>3-dose schedule</u>
0, 2 and 6 months

Table 9. Study B1971012. hSBA Responses After the Third Vaccination with Bivalent rLP2086 – Study Group 2, Per-Schedule Evaluable Immunogenicity Population

Immunogenicity Parameter (95% CI)	fHBP variant [a]				Composite response [hSBA ≥ LLOQ for all 4 primary strains (95% CI) [d]
	A22	A56	B24	B44	
	N=162-165[b]	N=160-165[b]	N=161-163[b]	N=159-161[b]	N=159[b]
% of subjects with ≥4 fold increase in hSBA titer (95% CI)[c]	87.7% (81.6, 92.3)	93.8% (88.8, 97.0)	78.3% (71.1, 84.4)	78.6% (71.4, 84.7)	
% of subjects with hSBA titer ≥LLOQ (95% CI)	97.6% (93.3, 99.5)	98.2% (94.2, 99.7)	90.8% (84.4, 95.2)	83.9% (76.3, 89.8)	
GMT (95% CI)	62 (55, 71)	153 (131, 178)	27 (29, 32)	32 (26, 39)	
					81.8% (74.9, 87.4)

hSBA= serum bactericidal assay using human complement; LLOQ= lower limit of quantitation; CI= confidence interval.

[a] The strains expressing variant A22, A56, B24, and B44 correspond to strains PMB80, PMB2001, PMB2948, and PMB2707, respectively. LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

[b] N= number of subjects with valid and determinate hSBA titers for the given strain(s) at the given time point(s).

[c] ≥4-fold increase in hSBA titer: %= n/N=number (n) of subjects with a hSBA fold rise ≥4 from baseline (pre-vaccination 1) for the given strain/ N. A ≥4-fold increase in hSBA titer is defined as follows: (1) For subjects with a baseline hSBA titer <1:4, a response was defined as an hSBA titer ≥1:16. (2) For subjects with a baseline hSBA titer ≥1:4, a 4-fold response was defined as an hSBA titer ≥4 times the LLOQ or ≥4 times the baseline titer, whichever was higher.

[d] Composite hSBA response (hSBA ≥ LLOQ for all 4 primary strains): %= n/N=number (n) of subjects with observed hSBA titer ≥ LLOQ for all 4 primary strains at the given time point/ N.

Source: Adapted from study B1971012 report.pdf [Table 14.83, pages 570-571 and Table 14.70, page 544] and study B1971012 report addendum.pdf, Table 6.29, page 127-127.

After the 2nd bivalent rLP2086 vaccination (Per-schedule evaluable population): The proportion of Group 2 subjects who achieved a ≥4-fold increase in hSBA titer (post-vaccination 2 compared to pre-vaccination 1) was 93.0%, 56.7%, 57.0% and 73.6%, respectively, for strains expressing A56, B24, B44 and A22. The post-vaccination 2 hSBA GMTs (listed in the same order) were 95, 15, 16 and 37. The proportion of Group 2 participants with hSBA titer ≥1:8 after the 2nd bivalent rLP2086 vaccination (individual strains) was 98.1%, 75.5%, and 62.5% of subjects achieved a hSBA titer ≥1:8 to A56, B24, and B44, respectively; 89.5% of subjects achieved a hSBA titer ≥1:16 for the strain expressing A22. The proportion of Group 2 participants with hSBA titer ≥1:8 after the 2nd bivalent rLP2086 vaccination (individual strains) was 98.1%, 75.5%, and 62.5% of subjects achieved a hSBA titer ≥1:8 to A56, B24, and B44, respectively; 89.5% of subjects achieved a hSBA titer ≥1:16 for the strain expressing A22. The proportion of subjects who had a hSBA titer ≥LLOQ to all 4 strains after the 2nd bivalent rLP2086 dose was 56.6%.

The evaluable population included subjects in the per-schedule evaluable population and subjects who received bivalent rLP2086 vaccine at injection visits 3 and 4 during the extended timeframes. Of 430 randomized participants in Group 2, bivalent rLP2086 was administered to 106 (24.7%) and 90 (20.9%) subjects at visits 3 and 4, respectively. The immunogenicity results based on the evaluable, the per-schedule evaluable and the out-of-schedule subset populations were similar.

2-dose schedules

0, 2-month schedule

Please see the preceding section (Group 2).

0, 6-month (Group 3) and 0, 4-month (Group 5) schedules

Per-schedule evaluable population:

≥4-fold increase in hSBA titer (post-dose 2 compared to pre-dose 1)

After the 2nd bivalent rLP2086 dose, >90.0% of subjects in both groups achieved a ≥4-fold increase in hSBA titer for the strain expressing A56. For the remaining strains, 64.5%, 66.0% and 82.3% in Group 3 and 55.0%, 60.5% and 75.0%% subjects in Group 5 achieved a ≥4-fold increase in hSBA titer, respectively, against strains expressing B24, B44 and A22.

Proportion of participants with hSBA titer ≥1:8 (≥1:16 for A22) for individual strains

- *Prior to bivalent rLP2086 vaccination*
  The proportion of subjects in Group 3 with a hSBA titer ≥1:8 to strains expressing A56, B24 and B44, respectively, was 18.7%, 12.9% and 4.3% respectively; 22.1% of subjects had a pre-vaccination hSBA titer ≥1:16 to the strain expressing A22. The proportion of subjects in Group 5 with a hSBA titer ≥1:8 to strains expressing A56, B24 and B44, respectively, was 19.5%, 14.8% and 6.1% respectively; 26.9% of subjects had a pre-vaccination hSBA titer ≥1:16 to the strain expressing A22.

- *After the 2nd bivalent rLP2086 vaccination*
  In both study groups, >98% of subjects achieved a hSBA titer ≥1:8 for the strain expressing A56. Also, >90.0% of subjects in both groups achieved a hSBA titer ≥1:16 for the strain expressing A22. For strains expressing subfamily B variants, 71.3% and 71.6% of subjects in Group 5 achieved a hSBA titer ≥1:8 to B24, and B44, respectively. Among subjects in Group 3, 80.0% and 75.8% of subjects achieved a hSBA titer ≥1:8 to B24, and B44, respectively.

Composite response (all strains)
The proportion of subjects in Group 3 and Group 5 who had a titer ≥LLOQ to all 4 strains after the 2nd bivalent rLP2086 dose was 73% and 59.0%, respectively.

hSBA GMT
For each of the strains, the hSBA GMT prior to the 1st dose and after the 2nd dose among Group 5 participants were similar to the corresponding hSBA GMT (at each time point) among Group 3 participants.

Subgroup analyses
Age: 36.4% of subjects were 11 to <14 years of age and 63.5% of subjects were ages 14 to <19 years of age. In both age groups, the proportions of subjects with a hSBA titer ≥ 1:8 (≥1:16 for A22) and the hSBA GMTs for each of the primary strains were similar.

Analyses by Geographic region
The distribution of subjects by geographic region was as follows: Czech Republic (n=331 subjects), Denmark (n=303 subjects), Finland (n=369 subjects), Germany (n=164 subjects), Poland (n=239 subjects), Spain (n=176 subjects), Sweden n=133 subjects).

> *Reviewer Comment:* The number of subjects in Group 5 was too small to make meaningful comparisons of results based on the evaluable, per-schedule evaluable, and out-of-schedule populations.

6.2.9.2 Safety Outcomes

Study enrollment and vaccination was temporarily paused during an evaluation of a 15 year old female from the Czech Republic (Group 2) who developed vertigo with consequent ataxia, chills and headache one (1) hour after the 2nd bivalent rLP2086 dose, and was hospitalized the same day for further evaluation. She had no prior medical history of vertigo. Physical examination was unremarkable and vital signs and clinical laboratory results (CBC/D, chemistry panel, C-reactive protein) were within normal limits. Her headache and chills resolved by the next day and vertigo resolved by the second hospital day. Medical treatments included ibuprofen and loratidine. She returned home after a 3-day hospital stay. She reported no further episodes at the follow-up study visit one month later. The subject withdrew from the study prior to the 3rd rLP2086 vaccination visit (4th injection visit). The study investigator and this reviewer considered the event related to vaccination.

Solicited local and systemic reactions
Local and systemic reactions were consistent with corresponding reactions in study B1971011.

Unsolicited AEs
Within 30 days after each injection visit
Among study groups who received a 3-dose bivalent rLP2086 series (Groups 1 and 2), the proportion of participants who reported an AE within 30 days of vaccination was 8% for the first dose, 7-8% for the

second dose and 8-9% for the third dose. Among study groups who received a 2-dose bivalent rLP2086 series (Groups 3-5), which was administered at intervals ranging from 2 to 6 months apart, 6%-8% of subjects reported an AE within 30 days of the first dose and 3-11% reported an AE within 30 days of the second dose. Among Groups 1-5, AEs reported in the SOC of Infections and Infestations ranged from 23.6% to 24.9%; nasopharyngitis, pharyngitis, gastroenteritis, upper respiratory tract infection were most common individual AEs in this SOC. Overall, AEs reported in the SOC of General Disorders and Administration Site Conditions ranged from 2.2% to 5.6%; fever, pain at the rLP2086 injection site, and fatigue were most common.

Seven subjects developed urticaria (Group 1 n=2, Group 2 n=3, Group 4 n=1, Group 5 n=1). Three reported symptoms after antibiotic treatment, solar erythema, and food allergy, respectively. The remaining four subjects reported urticaria 26-148 days after bivalent rLP2086 vaccination. One subject (Group 4) reported mild angioedema 60 days after the 2nd bivalent rLP2086 vaccination. Symptoms responded to treatment, and resolved after 8 days.

Immediate AEs
The following subjects reported an AE during the observation period (at least 20 minutes) following bivalent rLP2086 vaccination: Group 1: three subjects each reported one AE (headache , dizziness, neck muscle tightness). Group 2: one subject reported dizziness. Group 3: seven subjects reported 8 events (dizziness [n=4], nausea [n=1], headache [n=2], malaise [n=1]). Group 4 (n=0). Group 5: 4 subjects each reported one AE (dizziness, syncope, fever, malaise).

SAEs
Day 1 through 6 months after the last injection visit
In total, 44 subjects (Group 1 n=12, Group 2 n=14, Group 3 n=8, Group 4 n=7, Group 5 n=3) reported 51 SAEs (Group 1: 13 events, Group 2: 17 events, Group 3: 10 events, Group 4: 8 events, Group 5: 3 events). The percentage of subjects reporting at least 1 SAE within 30 days of each vaccination was <1.0% for each of the study groups. The percentage of subjects reporting at least 1 SAE from the day of the first injection to 6 months after the last study injection ranged from 1.6% [Group 3] to 3.4% [Group 2].

Nine subjects reported SAEs after a saline injection (constipation, dermatitis, gastroenteritis, stomatitis, pharyngitis, UTI, decreased appetite, appendicitis, hypersensitivity reaction), 18 subjects reported a SAE due to an injury or poisoning (e.g. limb fracture, alcohol intoxication), and 6 subjects reported an acute infection 40 to >100 days after vaccination (abdominal pain, gastroenteritis, gastritis, appendicitis, hyperbilirubinemia) or an event associated with another etiology (e.g. ovarian cyst, DVT, chronic appendicitis, urethritis, cough, migraine headache). One subject developed an urticarial rash 148 days after the 3rd bivalent rLP2086 vaccination. Please see the unsolicited AE section for additional details. Four subjects reported an acute infection within 30 days of vaccination (appendicitis, infectious mononucleosis, and sinusitis). One subject reported a spontaneous abortion 85 days after the 2nd bivalent rLP2086 vaccination. Two subjects reported newly diagnosed medical conditions (Crohn's disease, Type 2 diabetes mellitus).

Two subjects in Group 2 reported 5 SAEs that were considered by the investigator as related to vaccine reactogenicity

- One subject was hospitalized for further evaluation of vertigo, chills, and headache that developed 1 hour after the 2nd bivalent rLP2086 vaccination.
- The other subject was hospitalized for fever (T38.6°C) and moderate vomiting that developed the day after the 1st bivalent rLP2086 vaccination. On the same day, she developed mild headache (lasted 1 day), moderate fatigue (lasted 9 days; maximum severity reported as severe [Days 2-4]), severe chills (lasted 2 days), and moderate myalgia (lasted 1 day). She reported moderate swelling (lasted 14

days) and mild pain (lasted 2 days) at the rLP2086 injection site on the previous day. Her symptoms resolved after IV hydration and antipyretic treatment.

Deaths
No deaths were reported during the study period.

Premature study discontinuations
Overall, 19 of 1712 subjects (1.1%) withdrew from the study and an AE was reported as the reason for premature discontinuation (Group 1 n=6, Group 2 n=4, Group 3 n=5, Group 4 n=4, Group 5 n=0).

- Seven events were reported as SAEs:
  A Group 2 participant who developed vertigo chills and headache. One participant with a prior medical history of migraine headache had a recurrence 20 days after the 2nd bivalent rLP2086 dose. Four participants reported SAEs that temporally followed a saline injection (contact dermatitis, Crohn's disease, decreased appetite, type 2 diabetes mellitus). One participant experienced a deep vein thrombosis 9 days after her 2nd dose of bivalent rLP2086; she was vaccinated on the day of her return from a trip (stood 12 hours on the bus).
- Seven participants reported AEs associated with reactogenicity: injection site pain (moderate n=1, severe n=1), headache (severe n=1, mild n=1), fatigue (severe n=1). The AEs were considered by this reviewer to be related to bivalent rLP2086 vaccination.
- Four participants in Group 2 each reported one AE: headache, rheumatoid arthritis, vertigo and backache. One participant in Group 3 was diagnosed with hypothyroidism.

An 11 year old female (Group 2) from the Czech Republic developed T38.6°C and severe vomiting, moderate fatigue, severe chills, moderate myalgia and mild headache, and which all began one (1) day after the first bivalent rLP2086 vaccination. She was hospitalized the same day for further evaluation. The participant had neither preceding illness nor family members with recent history of similar symptoms. On physical examination, she was noted to have right-sided abdominal pain and T41.1°C. No jaundice or neck stiffness was present. Clinical laboratory evaluations indicated a white blood cell count of 12 x 10^9/L (normal range: 4.5-13.5 x 10^9/L) with 84% neutrophils, and mildly elevated LFTs. The subject was treated with IV saline solution 0.9% and antipyretic medications. Except for fatigue, her symptoms resolved by the second hospital day. Clinical evaluations for infectious etiologies were unremarkable. Her diagnosis on hospital discharge was vomiting and pyrexia. She went home after a 3-day hospital stay, with no notable findings at a follow-up visit one week after hospital discharge. The study investigator considered the event possibly related to vaccination. The subject voluntarily withdrew from the study.

Newly Diagnosed Major Illnesses
Day 1 through 6 months after the last injection visit
Eight subjects were diagnosed with major illnesses during the study, as follows: Crohn's disease (Group 1 n=1), scoliosis (Group 2 n=1), rheumatoid arthritis (Group 2 n=1), Type 2 diabetes mellitus (Group 3 n=1), migraine (Group 3 n=1), Basedow-Graves disease (Group 3 n=1), and hypothyroidism (Group 4 n=2). Please see the integrated summary of safety (section 8) for further details.

Neuroinflammatory and Autoimmune Conditions
Day 1 through 6 months after the last injection visit
Five subjects were diagnosed with an autoimmune condition: Crohn's disease (Group 1 n=1), rheumatoid arthritis (Group 2 n=1), Basedow-Grave's disease (Group 3 n=1), and hypothyroidism (Group 4 n=2). Please see the integrated summary of safety (section 8) for further details.

6.2.10 Summary and Conclusions

Study B1971012 was one of the main studies to support the immunogenicity of bivalent rLP2086 among adolescents when administered according to a 3-dose series at 0, 2 and 6-month schedule (Group 2), as measured by hSBA responses using four primary MenB strains expressing fHBP variants A22, B24, A56 and B44. Unsolicited AEs, including SAEs, autoimmune and neuroinflammatory condition, from subjects in this study provided supportive safety data for US licensure.

Safety
Study enrollment and vaccination was paused temporarily during the evaluation of a 15 year old female vertigo, chills, and headache 1 hour after receiving the 2nd bivalent rLP2086 vaccination. Her headache and chills resolved by the next day and vertigo resolved after 2 days. Medical treatments included ibuprofen and loratidine. She reported no further episodes at the follow-up study visit one month later. The study resumed thereafter.

The frequencies of unsolicited AEs reported within 30 days after bivalent rLP2086 vaccination was similar among subjects who received a 3-dose schedule (Group 1 and 2) and ranged from 7% to 9%. Among subjects who received a 2-dose schedule (Groups 3-5), the frequencies of unsolicited AEs within 30 days after 2nd bivalent rLP2086 vaccination was variable (3% to 11%), which might have been attributed to smaller numbers of subjects in Groups 4 and 5 relative to the other study groups. Please see the integrated summary of safety (section 8) for discussions about autoimmune conditions.

The percentage of subjects who reported at least 1 SAE from the day of the first study injection to 6 months after the last injection ranged from 1.6% [Group 3] to 3.4% [Group 2]. Overall (Groups 1-5), 1.1% of subjects withdrew from the study because of an AE.

Three subjects in Group 2 reported SAEs that were considered by this reviewer to be related to bivalent rLP2086 administration. The SAE for one subject (adolescent female) was described above, another subject reported fever (T38.6°C) and vomiting the day after the 1st bivalent rLP2086 vaccination. The third subject reported vomiting, fatigue, chills, myalgia and headache the day after the 1st bivalent rLP2086 vaccination.

Immunogenicity
The overall evaluation of immunogenicity included the following endpoints: the proportion of participants with a ≥4-fold response to each of the four MenB strains, the proportion of participants with a hSBA response ≥ LLOQ to all of the primary strains (composite response) and to each individual strain, and hSBA GMTs. Secondary objectives included immunogenicity evaluations of several 2-dose schedules (0 and 2 months; 0 and 4 months; 0 and 6 months).

3-dose schedule: Bivalent rLP2086 administered as a 3-dose series at 0, 2 and 6 months was immunogenic for each of the primary strains. In general, hSBA responses to subfamily A variants were higher than responses to subfamily B variants. The post-Dose 3 GMT values ranged from 62 to 153 for subfamily A strains and from 27 to 30 for subfamily B strains. The proportion of subjects with pre-existing hSBA titers ≥LLOQ was approximately 20% for subfamily A strains and ranged from 5% to 15% for subfamily B strains. However, hSBA GMTs prior to the 1st vaccination were below the LLOQ for each of the strains, which suggesting that the proportion of adolescents with pre-existing antibodies to any of the primary strains was low. Sensitivity analyses of the evaluable analysis populations indicated that delayed administration of bivalent rLP2086 due to the study pause did not substantially affect the immunogenicity outcomes.

3-dose (0, 2, 6 months) vs. 2-dose (0, 2 months): The magnitude of hSBA responses was higher after 3 doses of bivalent rLP2086 doses than after 2 doses, especially for subfamily B strains. After the 3rd bivalent rLP2086 dose, the proportion of subjects with a ≥4-fold response (B24: 78.3%, B44:78.6%) for strains expressing subfamily B variants were approximately 20% higher compared to corresponding responses after the 2nd dose (B24: 56.7%, B44:57%); the 95% CIs for the proportions of subjects with a ≥4-fold response after 3 doses and 2 doses were non-overlapping. For the subfamily A strains, the proportion of Group 2 subjects with a ≥4-fold response to A22 was higher after 3 doses (87.7%) than after 2 doses (73.6%), and >90% to A56 after either dose. The proportion of participants with a composite response (hSBA response ≥ LLOQ to all of the primary strains) was 54.7% after 2 doses and 81.8% after 3 doses. Analyses of the proportions of subjects with a hSBA titer ≥ 1:8 (≥ 1:16 for A22) and hSBA GMTs supported similar conclusions.

Dosing interval: For strains expressing B24, B44 and A22, a 2-dose schedule with a longer interval between doses was associated with increased proportions of participants with a ≥4-fold increase in hSBA titer to each individual strain, and increased proportions of subjects with a hSBA ≥1:8 for subfamily B variants. After the 2nd vaccination, the proportion of subjects who received bivalent rLP2086 at 0 and 6 months (Group 3) and at 0 and 4 months (Group 5) had a titer ≥LLOQ to all 4 strains was 73% and 59.0%, respectively.

The age distribution of subjects in the study was 36.4% and 63.5% for subjects 11 to <14 years of age and 14 to <19 years of age, respectively. The proportion of subjects ≥ 1:8 (1:16 for A22) and hSBA GMTs to each of the strains for both age groups were similar.

6.3 Study B1971010

NCT# 01323270

Title: A Phase 2, Randomized, Placebo-Controlled, Single-Blind Trial to Assess the Safety, Tolerability and Immunogenicity of Repevax and Bivalent rLP2085 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥11 To <19 Years.

A separate concomitant vaccine study, B1971015, was conducted to evaluate the safety and immunogenicity of bivalent rLP2086 co-administered with routine adolescent vaccines recommended by the ACIP. Only the study design elements pertaining to safety and immunogenicity evaluations of bivalent rLP2086 are presented in this review.

6.3.1 Objectives and Endpoints

The primary objectives pertained to immunogenicity evaluations of antigens contained in dTap-IPV.

MenB Secondary Objectives

- To describe the hSBA response using 4 primary MenB test strains, which are the same strains as described in study B1971011, section 6.1.1. Time points: 1 month after the 2nd and 3rd bivalent rLP2086 vaccination (subsets of participants).
  Endpoints
  For each of the 4 primary strains
  - % of subjects with hSBA titer ≥LLOQ
  - GMTs
  - % of subjects with hSBA titer ≥1:8, 1:16, 1:32, 1:64 and 1:128

- To describe the hSBA response and composite hSBA response using 4 primary MenB test strains. Time points: 1 month after the 2nd and the 3rd bivalent rLP2086 vaccinations.

Endpoints
For each of the 4 primary strains A22, A56, B24, B44 (subsets of participants)

- % of subjects achieving at least a 4-fold increase in hSBA titer from baseline to the post-vaccination 2 and post-vaccination 3 blood draw visits
  - o For subjects with a baseline hSBA titer below the limit of detection (LOD) or an hSBA titer of < (1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
  - o For subjects with a baseline hSBA titer of ≥ LOD (i.e., hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer ≥ four times the LLOQ.
  - o For subjects with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥ four times the baseline titer.

For subjects who have all 4 strains tested:

- % of subjects with a composite response at each applicable blood sampling time point. The composite response is defined as hSBA titers ≥LLOQ for all 4 primary MenB test strains.

For all of the MenB objectives, a hSBA titer of 1:16 was used as the LLOQ for A22, and a hSBA titer of 1:8 was used as the LLOQ for A56, B24 and B44.

Sera from a 50% of subjects (50% subjects from Group 1 and 50% subjects from Group 2) were tested with hSBA assays using strains expressing variants A22 and B24, and sera from the other 50% of subjects were tested with hSBA assays using strains expressing variants A56 and B44.

Safety Objective
To describe the safety of bivalent rLP2086 vaccine.

6.3.2 Design

Randomized, placebo-controlled, single-blind. N=750 (n=375/per group)

Table 10. Study B1971010. Study Design

	Visit #	**Visit 1**	**Visit 3**	**Visit 5**
	Approximate Month	**0**	**2**	**6**
Group 1		bivalent rLP2086 + dTap-IPV	bivalent rLP2086	bivalent rLP2086
Group 2		saline + dTap-IPV	saline	saline

dTap-IPV (Sanofi-Pasteur MSD): Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) [Repevax]
Source: B1971010 report.pdf, page 7.

6.2.3 Population

The inclusion and exclusion criteria for this study were similar to eligibility criteria for study B1971012, except for the vaccination history. In study B1971010, individuals 11 to <19 years of age who had received the full series of DTP/DTaP vaccines and OPV/IPV vaccines (per country specific recommendations applicable at the time of receipt) were eligible for study enrollment, and individuals who were vaccinated with any Tdap or poliomyelitis vaccine with 5 years of the first study vaccination were not eligible for enrollment.

6.3.4 Randomization/Blinding

This study was a single-blinded (i.e. subjects were blinded to their allocated vaccine group). Subjects were randomized in a 1:1 ratio (Group 1: Group 2) via an interactive voice response or internet-based response system.

6.3.5 Study Products

Study vaccines provided by the sponsor

- Bivalent rLP2086 vaccine: same as for Study B1971011. Lot#10-087724.
- Repevax (Sanofi-Pasteur MSD; dTap-IPV): each 0.5 mL dose contains 2 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 2.5ug pertussis toxoid (PT), 5ug filamentous hemagglutinin (FHA), 3ug pertactin (PRN), 5ug fimbriae (FIM) Types 2 and 3, inactivated poliovirus (Type 1: 40 D antigen units, Type 2: 8 D antigen units, Type 3: 32 D antigen units), 0.33 mg aluminum as AlPO4, and trace amounts of neomycin and bovine serum albumin. Lot#10-087786, 11-007210, 11-006046.
- Saline (0.9% sodium chloride). Lot# 10-087728.

Permitted vaccines

- Non study vaccines that are part of recommended immunization schedules are allowed anytime following the post-vaccination 2 visit (Visit 3) but not within 2 weeks of study vaccine administration. Nonstudy vaccines that were used in the event of a disease outbreak or pandemic were allowed at any time during the study.

6.3.6 Assessments

Safety evaluation

Solicited local and systemic adverse reactions were assessed after each vaccination visit. The safety parameters, data collection methods and EDMC role/responsibilities were the same as for study B1971012. The observation period for immediate adverse reactions was at least 20 minutes (or longer depending on the site).

Immunogenicity Methods

Subset of participants

MenB: time points: pre-vaccination 1, post-vaccination 1, 2 and 3

- hSBA assays using strains PMB80(A22) and PMB2948(B24) were performed at Pfizer,--b(4)----------). Sera from 50% of subjects from Group 1 and 50% of subjects from Group 2 will be tested using these strains.
- hSBA assays using strains PMB2001(A56) and PMB2707(B44): performed at -----b(4)----------. Sera from the other 50% of subjects from Group 1 and Group 2 will be tested using these strains.

The LLOQs for PMB2948(B24), PMB2001(A56), and PMB2707(B44) were 1:8. The LLOQ for PMB80(A22) was 1:16. When subject enrollment was completed, the applicant provided one subject listing to the sample management personnel for hSBA testing using A22 and B24, and another subject listing for hSBA testing using A56 and B44. The laboratory personnel performing assay were blinded to the study group allocation.

6.3.7 Statistical Analysis Plan/Data Analysis

Populations Analyzed

Evaluable MenB immunogenicity population

An evaluable population following the 3rd vaccination visit was defined as all eligible subjects randomized to Groups 1 or 2; who received the study products at all vaccinations at Visit 1, Visit 3, and Visit 5 as randomized; had blood drawn for prior to the first dose of vaccine and 1 month after vaccination 3 within the required time frame (i.e. post-vaccination 3 blood drawn (Visit 6) within 28-42 days after Vaccination 3 (Visit 5); had valid and determinate assay results for the proposed analysis. Evaluable MenB populations were not defined for the 1st or 2nd vaccination visits.

Modified intent-to-treat (mITT) *population*
Included all randomized subjects who received at least 1 vaccination of an investigational product and had at least 1 valid and determinate assay result. All subjects were analyzed according the investigation products that they were assigned.

Safety population
Included all subjects who received at least 1 dose of study product and for whom safety data are available.

Immunogenicity Analyses
For GMT calculations, ½ LLOQ was used for subjects with hSBA titers <LLOQ.

Handling of missing data
For the hSBA assay results: The proportion of subjects with missing data at each blood sampling visit for each strain, the reasons for missing data (insufficient volume (i.e. QNS), indeterminate, Not Done, blood sample not collected (e.g. dropout); the denominator was the ITT population (all randomized). Also, the proportion of subjects with indeterminate data was summarized at each blood sampling visit for each strain; the denominator included all subjects tested at each visit in the assay and excluded all subjects with missing data.

Sensitivity Analyses
A mixed-effect model with repeated measurement was used to assess the effect of race, center and gender, in which both baseline and the post-vaccination titers (in logarithmic scale) were modeled as dependent variables for each primary strain. This model used maximum likelihood estimation method, thus; the mixed-effect model also served as a sensitivity analyses on missing data for the GMT.
See CBER statistical review for additional details.

Safety Analyses
The safety endpoints and analyses were similar to study B1971011, except for: (a) The observation period for immediate reactions was 20 minutes (or longer depending on the study site); (b) Visit 6 corresponded to the visit 1 month after the last study vaccination and Visit 7 corresponded to the visit (telephone call) 6 months after the last vaccination.

The end of the vaccination phase was the date of the last visit attended prior to Visit 7. The end of the study was the date of the lasted attended visit during the vaccination phase (e.g. if the subject prematurely discontinued the study) or the date of telephone call for the 6-month safety follow-up, whichever was later.

Subgroup analyses
Immunogenicity and safety analyses were summarized by race, gender and country.

6.3.8 Amendments to the Protocol/SAP

Protocol: pertinent changes
Amendment 1, dated 19-Oct-2010: updated inclusion/ exclusion criteria.

Amendment 2, dated 15-Jul-2011: vaccinations were temporarily paused on 01-Jul-2011 during an investigation of a SAE reported for a 15 year old participant with vertigo in another ongoing study (study B1971012), and resumed 2 to 3 months later. Vaccination windows were extended for Visit 3 (interval changed from 56-70 days to 56-160 days) and Visit 5.

Amendment 4, dated 13-Dec-2012: updated to correspond with changes made in SAP version 2.0.

SAP: pertinent changes
Version 2.0, dated 14-Nov-2012: deleted secondary objectives for IgG antibody evaluation; added secondary and exploratory objectives to assess hSBA responses; updated safety endpoints to be consistent with endpoints included in phase 3 studies.

SAP appendix 1.0, dated 06-May-2013: clarified rules for handling safety data (missing or incomplete data, AE start and resolve dates) and determining the time point for study completion.

6.3.9 Results

The study was conducted from March 18, 2011 to February 19, 2013 (last subject last visit). Study centers: Finland (12 sites; n=378 subjects), Germany (10 sites, n=151 subjects), Poland (12 sites, n=220 subjects)

Subject Disposition
Of 753 enrolled subjects, 749 subjects were randomized (Group 1 n= 373, Group 2 n=376). At site #1014, four subjects received study vaccines (bivalent rLP2086+dTap-IPV n=2, saline+dTap-IPV n=2) at visit 1 but were not randomized.

Of the 749 randomized subjects, study vaccines [bivalent rLP2086, dTap-IPV or saline] were administered to 748 subjects (Group 1 n=372, Group 2 n=376) at Visit 1, 701 (93.6%) subjects (Group 1 n=342, Group 2 n=359) at Visit 3; and 682 (91.1%) subjects (Group 1 n=331, Group 2 n=351) at Visit 5. A total of 42 (11.3%) subjects in Group 1 and 29 subjects (7.7%) in Group 2 withdrew from the study, mainly due to voluntary withdrawal (5.1% in Group 1, 2.7% in Group 2), protocol violation (2.4% in Group 1, 1.9% in Group 2), lost to follow-up (1.1% in Group 1, 1.3% in Group 2), or an adverse event (Group 1 n=9 [2.4%; including subject who died in a motor vehicle accident], Group 2 n=0 [0%]. Please see the premature study discontinuation section for additional information.

677 randomized subjects (Group 1 n= 330 [88.5%], Group 2 n= 347 [92.3%]) received at least one study vaccine, had not prematurely discontinued the study and provided safety information at the scheduled follow-up telephone call six months after the last vaccination visit. In addition, 47 subjects (Group 1 n=28, Group 2 n= 19) who had withdrawn from the study provided safety information at the follow-up telephone call described above.

Immunogenicity populations
The mITT population included 748 subjects (Group 1 n= 372, Group 2 n=376). One subject in Group 1 was randomized but not vaccinated at Visit 1.

During a safety review of a SAE in study B1971012, the applicant paused enrollment and vaccinations in all studies that were ongoing, including this study.

- More than 99.5% all subjects received vaccines at Visit 1 according to the interval specified in the protocol version (amendment 1) prior to clinical pause; 60-65% of subjects received vaccinations according to the interval specified for the 2nd vaccination visit (i.e. 42-70 days after Visit 1) and 58-62% of subjects received vaccinations according to the interval specified the 3rd vaccination visit (i.e. 105-126 days after Visit 3).

The administration interval was extended (protocol amendment 2) an additional 90 days for the 2nd vaccination visit (i.e. 71-160 days Visit 1) and an additional 30 days for the 3rd vaccination visit (i.e. 127 to 156 days after Visit 3); an additional 230 subjects (~30% additional subjects/per group), received study vaccines during the extended timeframe for the 2nd vaccination visit, and an additional 216 subjects ~30% additional subjects/per group) received study vaccines during the extended timeframe for the 3rd vaccination.

- Of subjects in study groups that completed the bivalent rLP2086 series at injection visit 4 (Groups 1-3 and 5), 84-87% of subjects had a blood sample collected during the interval 28-42 days post-injection.

The evaluable MenB immunogenicity population was comprised of 637 participants (Group 1 n= 307 [82.3%], Group 2 n=330 [87.8%]), and included subjects who received injections during the extended time frame described above. 112 subjects (Group 1 n= 66, Group 2 n=46) were excluded from the evaluable MenB immunogenicity population mainly because a pre-vaccination #1 or post-vaccination #3 blood sample was not obtained within the interval specified in the protocol amendment 4 (n=104; [Group 1: 16.4%. Group 2: 11.4%]), subjects did not receive all vaccines as randomized at all vaccination visits according to protocol amendment 4 (n=67; [Group 1: 11.3%. Group 2: 6.6%]), did not have valid and determinate hSBA result the pre-vaccination 1 or post-vaccination 3 time point (n=73; [Group 1: 12.1%. Group 2: 7.4%]).

Demographic and other baseline characteristics

Overall, the safety population (vaccine as administered) was comprised of 51.1% male and 48.9% female; the median age at the time of the first vaccination was 13 years (57.8% of participants were 11 to <14 years age and 42.2% were age 14 to <19 years). The population overall were 98.9% Caucasian, 0.1% African American, 0.8% Asian, and 0.1% of participants were classified as 'other'. The demographic and other baseline characteristics of the evaluable immunogenicity population were similar to the randomized population. The demographic and other baseline characteristics of the evaluable MenB immunogenicity population were similar to the randomized population.

6.3.9.1 Immunogenicity Outcomes

Primary Objectives: pertained to immunogenicity evaluations of antigens contained in dTap-IPV.

Meningococcal B outcomes

In the following section, the hSBA GMTs and proportion of participants with a ≥4-fold increase in hSBA titer (post-vaccination compared to pre-dose 1) for the strain expressing fHBP variant A22 were based on calculations using an LLOQ of 1:16. The MenB strains PMB2001, PMB2948, PMB2707 and PMB80 represented strains expressing fHBP variant A56, B24, B44 and A22, respectively. The strains are sometimes denoted only by the respective variant. A composite response (i.e. proportions of participants with a hSBA response ≥ LLOQ to all of the primary strains) was not evaluated because sera from subset populations were frequently tested for only two of the 4 strains.

Secondary Objectives

Proportion of subjects with hSBA titer ≥1:8 (≥1:16 for strain PMB80[A22]) to individual strains

Strains expressing rLP2086 variants A22 and B24 (50% of participants)

- Strain PMB2948 [B24]: The proportion of Group 1 (bivalent rLP2086 + dTap-IPV) participants with a hSBA titer ≥1:8 was 12.7% (n=20 of 157) prior to vaccination visit 1 and 96.8% after vaccination visit 3. Among Group 2 (saline+dTap-IPV), the proportion of participants with a hSBA titer ≥1:8 prior to vaccination visit 1 was 12.9% (n=22 of 170) and remained unchanged after vaccination visit 3.

- Strain PMB80 [A22]: The proportion of Group 1 participants with a hSBA titer ≥1:16 was 14.4% (n=22 of 153) prior to vaccination visit 1 and 95.6% after vaccination visit 3. Among Group 2, the

proportion of participants with a hSBA titer ≥1:16 prior to vaccination visit 1 was 23.0% (n=38 of 165) and 19.9% after vaccination visit 3.

Strains expressing rLP2086 variants A56 and B44 (50% of participants)

- Strain PMB2001 [A56]: The proportion of Group 1 participants with a hSBA titer ≥1:8 was 18.2% (n=25 of 137) prior to vaccination visit 1 and 100% after vaccination visit 3. Among Group 2, the proportion of participants with a hSBA titer ≥1:8 prior to vaccination visit 1 was 21.8% (n=31 of 142) and 26.3% after vaccination visit 3.

- Strain PMB2707 [B44]: The proportion of Group 1 participants with a hSBA titer ≥1:8 was 6.2% (n=9 of 146) prior to vaccination visit 1 and 81.5% after vaccination 3. Among Group 2, the proportion of participants with a hSBA titer ≥1:8 prior to vaccination visit 1 was 6.3% (n=10 of 158) and 8.2% after vaccination visit 3.

The numbers of subjects in each of the subsets described above, categorized by region, included approximately 25 to 40 subjects/per study group from Germany, 45 to 60 subjects/per study group from Poland and 65 to 90 subjects/per study group from Finland. The number of subjects per region was too small to make definitive conclusions about geographical differences.

hSBA GMTs

Prior to vaccination visit 1, the hSBA GMTs for each of the strains (same subsets as described above) were below the assay LLOQs, for both study groups. After the 3rd vaccination, the hSBA GMTs were 28, 63, 152, and 37 for B24, A22, A56, and B44, respectively. Among Group 2 participants, the hSBA GMTs was essentially unchanged after the 3rd vaccination for each of the strains.

Exploratory Objectives

4-fold hSBA responses

The proportion of Group 1 participants (same subsets as described above) with a ≥4-fold increase in hSBA titer (post-vaccination 3 compared to pre-vaccination 1) was 80.8% for B24, 87.6% for A22, 92.6% for A56, and 77.6% for B44.

6.3.9.1 Safety Outcomes

Solicited local and systemic reactions

Characterization of reactogenicity was not relevant to US licensure, since both study groups received a non-US licensed vaccine (dTap-IPV) at variance with US medical practices.

Unsolicited AEs

Within 30 days after each vaccination visit

Altogether, the proportions of subjects (Group 1 and Group 2, respectively) who reported at least 1 unsolicited AE within 30 days after vaccination were as follows: Vaccination 1 (8.8% and 11.4%, respectively), Vaccination 2 (9.4% and 12.8%, respectively), and Vaccination 3 (9.7% and 8.5%, respectively). In all study groups, the adverse events most frequently reported were events included in the MeDRA system organ class (SOC) of 'infections and infestations' (25.1% and 29.1%, respectively), of which nasopharyngitis, pharyngitis, URI were common.

Of the AEs reported by ≥1% of subjects in Group 1 (bivalent rLP2086+ dTap-IPV) or Group 2 (saline +dTap-IPV) during the vaccination phase, sinusitis [2.1% vs. 1.6%], contusion [1.1% vs.0.8%] and headache [2.7% vs. 2.4%] occurred more frequently among Group 1 subjects. Eight (2.1%) subjects in Group 1 reported 9 non-serious, unexpected AEs categorized as severe (i.e. interferes significantly with

the subject's usual function). One Group 1 subject each reported sinusitis, chills, arthralgia, headache [2 subjects], gastroenteritis, insect bite, pain and swelling at the rLP2086 injection site). No subjects in Group 2 reported a non-serious, unexpected AE categorized as severe.

Immediate AEs
Two subjects (Group 1 n=1, Group 2 n=1) reported three AEs during the observation period (at least 20 minutes) following the 1st 120µg bivalent rLP2086 vaccination. The participant in Group 1 reported severe swelling at the rLP2086 site, which lasted 3 days, in association with other symptoms consistent with post-infectious arthritis; the subject withdrew from the study (fulfilled the exclusion criterion for autoimmune disease). The participant in Group 2 reported mild procedural dizziness and mild headache, which resolved the same day, and no subsequent episodes of dizziness after the 2nd and 3rd bivalent rLP2086 vaccinations.

SAEs
A total of 22 subjects (Group 1 n= 12, Group 1 n=10) reported 28 SAEs (Group 1: 15 events, Group 2: 13 events) during the study period. The percentage of subjects reporting at least 1 SAE within 30 days of each vaccination was <1.0% for both groups.

Fifteen subjects reported 19 SAEs during the vaccination phase (time of informed consent through one month after the last vaccination).

- In Group 1, 11 subjects (2.9%) reported a total of 12 SAEs. Six subjects each reported a SAE, as follows: vertigo [46 days after the 2nd bivalent rLP2086 vaccination], cellulitis, gastroenteritis, sinusitis, tonsillitis, and headache [11 days after the 3rd bivalent rLP2086 vaccination]. One subject was hospitalized for depression, and then re-admitted 8 months later for worsening symptoms. Four subjects experienced a SAE (hydrocephalus, motor vehicle accident, idiopathic thrombocytopenic purpura, post-infectious arthritis, respectively) that led to premature study discontinuation.
- In Group 2, four subjects (1.1%) reported a total of 7 SAEs (appendicitis, peritonsillar abscess, hip fracture, joint dislocation, syncope, drug abuse, and ruptured ovarian cyst).

Seven subjects reported 9 SAEs during the follow-up phase (one month after the last vaccination through six months after the last vaccination).

- In Group 1, one subject (0.3%) reported 3 SAEs (appendicitis, abdominal abscess, and perforated appendicitis).
- In Group 2, six subjects (1.6%) each reported a SAE (syndactyly, appendicitis, urinary tract infection, injury, depression, and dyspnea, respectively).

Deaths
One subject died in a motor vehicle accident (see below).

Premature study discontinuations
Ten subjects in Group 1 reported an AE which led to premature study discontinuation. A total of 19 AEs were reported by Group 1 subjects:

- Two events were SAEs. One subject died in a motor vehicle accident 38 days after the 1st bivalent rLP2086 vaccination visit. The other subject developed anosmia 48 days after the 1st vaccination and was hospitalized for further evaluation. He was diagnosed with a CNS glioma with associated hydrocephalus. This reviewer considered both SAEs to be unrelated to vaccination.
- One subject reported 11 AEs. Five events started on the day of the 1st vaccination visit (Day 1): moderate diarrhea (lasted 1 day), moderate arthralgia (lasted 1 day), mild fatigue (lasted 9 days), and moderate injection site pain and swelling (each lasted 10 days). The next day, he developed mild vomiting (lasted 1 day), fever 38.7°C (lasted 1 day), moderate headache (lasted 2 days), and mild

chills (lasted 1 day). On post-vaccination Day 5 and Day 6, the subject experienced mild fatigue (lasted 6 days) and mild chills (lasted 1 day). The subject was treated with antipyretic medication for a total of 3 days. This reviewer considered all of the AEs to be related to vaccination.

- Two subjects were each reported to have withdrawn due to a single AE (chills and malaise, respectively). Of note, each subject also experienced multiple other AEs. This reviewer considered all of the AEs to be related to vaccination.
  - A 17- year old male developed the following symptoms on the day of the 1st vaccination visit (Day 1): severe chills (lasted 1 day), fever (T38.2°C; lasted 1 day), mild headache, fatigue, and joint pain (each lasted 2 days), and moderate pain at the rLP2086 injection site (lasted 4 days). The next day, he developed mild myalgia (lasted 1 day) and moderate redness at the rLP2086 injection site (lasted 1 day). He received antipyretic medication for one day.
  - A 17-year old female developed the following reactions on the day of the 1st vaccination visit (Day 1): moderate pain at the rLP2086 injection site (lasted 1 day), moderate headache (lasted 6 days), mild fatigue (lasted 6 days), moderate chills (lasted 1 day). On post-vaccination Day 2, he experienced mild pain at the rLP2086 injection site (lasted 2 days), mild myalgia and mild joint pain on post-vaccination Day 6 (each lasted 1 day), and moderate malaise on post-vaccination Day 7 (lasted 1 day).
- A 13 year old female developed headache on the day of the 1st vaccination, which lasted 3 days. The maximum severity reported was severe (Day 2). This reviewer considered the AE to be related to vaccination.
- One subject reported recurrent sinusitis >8 months after the 1st vaccination.
- Autoimmune conditions were reported for two subjects (Hashimoto's thyroiditis, post-infectious arthritis) after the 1st vaccination visit. Please see section 8 (Integrated Summary of Safety) for further details.

No subjects in Group 2 withdrew from the study due to an AE.

Newly Diagnosed Major Illnesses

Day 1 through 6 months after the last vaccination visit

Three subjects in Group 1 (scoliosis, autoimmune thyroiditis, and migraine, respectively) and 1 subject in Group 2 (migraine) were diagnosed with major illnesses during the study. Scoliosis was diagnosed as an incidental finding, which was identified during a routine health visit 108 days after the 2nd vaccination visit. Both subjects with migraine headache had no prior history. The Group 1 participant developed headache was >80 days after the 2nd bivalent rLP2086 vaccination (Group 1) and >30 days after saline injection (Group 2), respectively. Please see section 8 (Integrated Summary of Safety) for further details.

Neuroinflammatory and Autoimmune Conditions

Day 1 through 6 months after the last vaccination visit

Autoimmune conditions were reported in four subjects in Group 1: Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, exacerbation of celiac disease (pre-existing condition), and post-infectious arthritis, respectively. Please see the integrated summary of safety (section 8) for further details.

6.3.10 Summary and Conclusions

Study B1971010 was one of the main studies to support the immunogenicity of bivalent rLP2086 among adolescents when administered according to a 3-dose series at 0, 2 and 6-month schedule (Group 2), as measured by hSBA responses using four primary MenB strains expressing fHBP variants A22, B24, A56 and B44. The safety data from subjects in this study contributed to the main safety database for US licensure.

Immunogenicity

Enrollment and vaccination in this study was paused temporarily during the evaluation of a SUSAR in another ongoing study (see study B1971012). Sensitivity analyses to assess the impact of an extended vaccination window (i.e. 3rd vaccination was extended by 3 months) on hSBA responses were not performed. However, in study B1971012, sensitivity analyses were performed and the impact of an extended vaccination time interval for the 3rd vaccination on hSBA responses was minimal for the study group receiving bivalent rLP2086 according to a 0-, 2- and 6-month schedule.

The proportion of participants in a subset of Group 1 with a ≥4-fold increase in hSBA titer (post-vaccination 3 compared to pre-vaccination 1) were 80.8% for B24 and 87.6% for A22. The proportions participants with a ≥4-fold increase in hSBA titer (post-vaccination #3 compared to pre-vaccination #1) using strains expressing A56 or B44 (measured in another subset of Group 1 participants) were 92.6% and 77.6%, respectively. A composite response (i.e. proportions of participants with a hSBA response ≥ LLOQ to all of the primary strains) was not evaluated in this study because sera from subset populations were frequently tested for only two of the 4 strains.

Safety
The frequencies of unsolicited AEs within 30 days of vaccination were among subjects who received bivalent rLP2086 and concomitant dTap-IPV [Group 1] and subjects who received dTap-IPV without bivalent rLP2086 [Group 2] were similar (9% to 10% vs. 9% to 13%, respectively). The nature and frequency of events reported were consistent with illnesses commonly observed in an adolescent population. The overall frequencies of SAEs reported throughout the study for Group 1 and Group 2 were similar (3.2% vs. 2.4%, respectively) were consistent with events observed in adolescents. Please see the integrated summary of safety (section 8) for discussions about autoimmune conditions.

6.4 Study B1971004

NCT# 00879814

Title: A Phase 1, randomized, open-label, parallel group, active- and placebo-controlled study to assess the safety and tolerability of 60µg, 120µg, and 200µg of meningococcal group B rLP2086 vaccine in healthy adult subjects

In this trial, the immunogenicity of bivalent rLP2086 was assessed by –b(4)----- and not by hSBA. Therefore, the study design sections pertinent to the safety evaluations are presented in this review.

Study design
This study was randomized, open-label, controlled trial with primary objectives to assess the safety and tolerability of three dosages (60µg, 120µg, 200µg) of bivalent rLP2086. A total of 48 adults (n=12 per group) aged 18 to 40 years received bivalent vaccine at 0, 2 and 6 months. Autoimmune and neuroinflammatory conditions were not an exclusion criterion. The study was conducted at 1 site in the US.

The same dosage of bivalent rLP2086 was administered for all visits (Group 1: 60µg, Group 2 120µg, Group 3: 200µg). The control group (Group 4) received Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Vaccine (Adacel; Tdap) at the first vaccination visit, then saline placebo at the subsequent two vaccination visits. Each 0.5 mL dose of Tdap contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg PT, 5 mcg FHA, 3 mcg PRN, 5 mcg FIM types 2 and 3], and 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant.

Safety evaluation
Solicited local and systemic reactions were recorded daily by electronic diary for 7 days. Information about general unsolicited AEs, SAEs, hospitalizations and NDCMCs were collected from the time of

informed consent to 30 days after vaccination #3. Immediate AEs were not assessed, and information about autoimmune and neuroinflammatory conditions was not specifically queried by study personnel.

Clinical laboratory evaluations included the following: coagulation panel (prothrombin time (PT), INR, partial thromboplastin time (PTT), fibrinogen, and D-dimer) complete blood count (CBC) and differential, liver function tests (alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), SGOT (AST), SGPT (ALT), lactic acid dehydrogenase (LDH), total bilirubin) total protein, albumin, and chemistry panel (blood urea nitrogen (BUN), creatine phosphokinase (CPK), creatinine, sodium, and potassium) and urinalysis. Time points: pre-vaccination 1, and 2-4 days after each vaccination. For results that were not within normal limits, a follow-up evaluation was performed 7-10 days after vaccination.

Protocol amendments
Study enrollment and vaccinations were temporarily paused on 11-Oct-2009 during an investigation of a SAE reported for a 13-year old male participant in another ongoing study (study B1971005). The DMC, which reviewed safety data from both trials, recommended sequential enrollment of the remaining subjects in this study by dosage cohort. The vaccination window for the 3rd vaccination was extended by approximately 4 to 7 months (106-238 days) after vaccination #2. As a result, bivalent rLP2086 vaccinations were administered at 0, 2, and 6-9 months.

Results
The study was conducted from April 2009 to March 2010.

Study population: Of the 48 enrolled, 28 were 18 to <26 years of age. Overall, 79.2% of subjects were Caucasian and 20.8% were African American. The study population overall was 60.4% male and 39.6% female. The median age for each study group (1-4) was 28.5, 28.0, 31.5, and 27.0 years of age, respectively. Seven subjects (n=3, 1, 1 and 2 for groups 1-4, respectively) voluntarily withdrew during the study.

At the time of study pause, 12 subjects had received the 3rd vaccination.

Safety
After vaccination visit 1, pain at the bivalent rLP2086 or Tdap injection site was the most commonly reported local reaction. After vaccination visits 2 and 3, subjects who received bivalent rLP2086 reported local reactions at the injection site, and no subjects reported reactions at the saline injection site. Four subjects (120µg n=2, 200µg n=2) reported a total of 6 severe local reactions.

For all groups, fatigue, headache, and muscle pain were most commonly reported. A total of 5 subjects reported fever within 7 days after vaccination: T38.0-38.4°C (200µg n=1, 120µg n=1), T38.5-38.9°C (200µg n=1, 120µg n=1), T39.0-40.0°C n=1 (120µg). One subject in the 60µg group and 4 subjects in the 200µg group reported a total of 6 severe events (headache, muscle, nausea and fatigue).

No SAEs were reported during this study.

Increases in fibrinogen levels were noted after each of the 3 doses, were dose-dependent, but transient (peaked at Day 3-4 and resolved by Day 14). There were no vascular events associated with these laboratory abnormalities.

Conclusions
The safety data supported the bivalent rLP2086 formulation (120µg) selected by the applicant for phase 2 studies in young adults (19 to ≤25 years of age). Transient increases in fibrinogen levels were observed mainly on post-vaccination days #3-4, which was consistent with results from pre-clinical toxicology studies with bivalent rLP2086, and has been observed with OMV vaccines.[6]

6.5 Study B1971003

NCT# 00780806

Title: An Open-Label Safety and Blood Collection Study In MnB RLP2086 Vaccinated Healthy Adult Volunteers for Immunological Assay Development

Study Design
This study was a Phase 1/2 open-label study with a primary objective to collect blood as a source for sera used in assay development and to assess the safety of bivalent rLP2086 administered at a dosage of 120µg. Sixty adults aged 18 to 40 years received a 3-dose bivalent rLP2086 series administered at 0, 1, 6-months. Assessment of hSBA responses and/or levels of antibody specific to rLP2086 antigens was included as an exploratory objective. The study was conducted at 4 sites in Australia.

Autoimmune and neuroinflammatory conditions were not an exclusion criterion.

Safety evaluation
The safety data collection methods and duration of monitoring for solicited reactions were the same as described in study B1971004. Information about general unsolicited AEs was collected from the time of informed consent to 7 days post-vaccination #2, from vaccination #3 to 7 days after vaccination #3, and for 7 days after each blood draw visit. Information about SAEs, hospitalizations, newly diagnosed chronic medical conditions (NDCMCs) was collected from the time of informed consent through 6 month after the last vaccination.

Results
The study was conducted from October 27, 2008 to May 11, 2010 (last blood draw).

Study population: Of the 60 enrolled subjects, 28 were ages 18 to <26 years, and 32 subjects were ages 26 to <40 years. The median age was 26.0 years of age. Overall, 93.3% of subjects were Caucasian, and 26.7% were male.

Safety
Adults 18 to <26 years of age

- Solicited local and system reactions
  - Pain at the injection site was the most commonly reported local reaction (88.5% to 96.4%, depending on the number of doses received); pain characterized as moderate (repeated use of non-narcotic pain reliever >24 hours or interferes with activity) was reported by approximately one third of subjects. No subjects reported severe (prevents daily activity) localized pain.
  - The most common systemic reactions were headache, fatigue and generalized muscle pain; the corresponding frequencies of reactions were approximately 60% to 70%, 45% to 60% and 30% to 40%, respectively, depending on the number of vaccinations received. Fever occurred in 4 subjects (T38.0-38.4°C, n=2; T38.5-38.9°C, n=2). One subject reported 4 severe systemic events (fatigue, headache, nausea, and vomiting) on day 5 after the 3rd dose. The nausea and vomiting lasted 1 day and the fatigue and headache lasted 4 days. This subject did not report any reactions after doses 1 or 2.

  The frequencies of solicited local and systemic reactions were in general were highest after the first vaccination.

- Unsolicited AEs were reported by 21 subjects (75%), which were most commonly reported as events included in the MedDRA SOC of Infections and infestations (upper respiratory tract infection was most common) and nervous system disorders (headache was most common). One subject each

reported a SAE (pregnancy, suicide attempt). Autoimmune conditions were reported in two participants (exacerbations of psoriasis and celiac disease, respectively), which were both pre-existing conditions. Please see section 8 (Integrated Summary of Safety) for additional information.

Immunogenicity
Immunogenicity of bivalent rLP2086, evaluated as part of the study objectives, was assessed using MenB strains other than the primary strains and the methodology used to calculate hSBA titers differed from the method used for planning the phase 3 studies.

As part of hSBA assay development, sera from this study was used to generate preliminary data with three of the four primary strains (PMB2948 [B24], PMB2707 [B44] and PMB2001 [A56]). The hSBA titers were calculated without interpolation, which was the method accepted by CBER for phase 3 studies, and are herein described. The proportion of subjects with a hSBA titer $\geq$1:8 prior to vaccination was 28.0% (n=7/25), 19.2% (n=5/26) and 20.0% (n=5/25), for B24, B44 and A56, respectively. After the 3rd bivalent rLP2086 vaccination, the corresponding proportions of subjects with a hSBA titer $\geq$1:8 were 81.0%, 94.7% and 100%.

Conclusions
The safety data in adults 18 to <26 years of age and preliminary hSBA data using strains PMB2948 [B24], PMB2707 [B44] and PMB2001 [A56]) supported the dosage (120µg) of bivalent rLP2086 selected by the applicant for phase 3 studies.

6.6 Study B1971005

NCT# 00808028

Title: A Randomized, Single-Blind, Placebo-Controlled, Phase 2 Trial of the Safety, Immunogenicity and Tolerability of Meningococcal Serogroup B (MnB) rLP3086 Vaccine at Doses 60, 120, and 200µg in Healthy Adolescents Aged 11 to 18 Years

Study Design [Stage 1]
This study was a randomized, single-blind, controlled trial in individuals aged 11 to $\leq$18 years to assess the safety and immunogenicity of bivalent rLP2086 according to a 0, 2, 6-month schedule. The study was conducted in Europe and Australia.

Stage 1 of this study was designed to assess the safety and immunogenicity of bivalent rLP2086 administered a several dosage levels (60µg, 120µg and 200µg).

- A small number of subjects (sentinel cohort) were randomized in a 2:1 ratio to receive bivalent rLP2086 (60µg, 120µg or 200µg in a sequential manner) or a saline placebo [22 subjects/per dosage group: 11 subjects/per comparator group). After all subjects in a given dosage group had received the first vaccination, safety data from all subjects in the dosage group was reviewed by a Project Independent Safety Review Team (PISRT). If no adverse safety outcomes had occurred (as determined by the PIRST), enrollment proceeded to the next higher dosage group.
- Expanded enrollment of subjects in the 120µg and 200µg dosage groups proceeded if no adverse safety outcomes occurred (as determined by the PIRST) after first vaccination in the 200ug dosage group of the sentinel cohort.
- Study enrollment and vaccination was temporarily paused during an investigation of a SAE reported in a 13-year old male participant in this trial. The participant developed severe headache and vomiting approximately 50 minutes after the 3rd bivalent rLP2086 vaccination (200µg). At the time of the study pause, a total of 75 subjects (bivalent rLP2086 and saline groups) had received their 3rd vaccination. Following review of the cumulative safety data, the PISRT recommended that the study

could resume with gradual enrollment of subjects in the 120µg and 200µg dosage cohorts. The protocol was amended to extend the time interval for the third vaccination by 3 months.

Safety evaluation
The safety evaluation included assessments for solicited local and systemic adverse reactions (7 days) and unsolicited AEs (through one month after the 3rd bivalent vaccination) and SAEs (through 6 months after the 3rd vaccination).

Immunogenicity evaluation
This study was conducted prior agreements between the applicant and CBER regarding the section of the primary strains and methods for calculating hSBA titers. The immunogenicity of bivalent rLP2086 was evaluated using MenB strains other than the primary strains or the methodology used to calculate hSBA titers differed from the method used for planning the phase 3 studies.

A total of 539 subjects were enrolled in the study (99 subjects during the sentinel enrollment phase, 440 subjects during the expanded enrollment phase); the overall distribution of subjects (both enrollment phases) was as follows: 60µg n=22, 120µg n=198, 200µg n=198, saline n=121. Distribution of subjects overall by geographic region was as follows: Australia n=133 subjects, Spain n=144 subjects, and Poland n=172 subjects.

Results
The study was conducted from February 9, 2009 to May 10, 2010 (last blood draw).

Safety
The reactogenicity of bivalent rLP2086 was dose-dependent. For all bivalent rLP2086 dosage groups, the proportion of subjects reporting solicited local and systemic adverse reactions was higher than in subjects who received a saline injection.

Nineteen subjects reported 24 SAEs:
60µg group: Of 22 subjects, 1 subject reported appendicitis and headache, 1 subject reported gastroenteritis.
120µg group: Of 198 subjects, 3 subjects reported 4 SAEs (concussion, jaw fracture, limb injury, ovarian cyst), 1 subject reported sinusitis and allergic rhinitis.
200µg group: Of 195 subjects, 8 subjects reported 10 SAEs (appendicitis, anaphylactic reaction, gastroenteritis, mononucleosis syndrome, pneumonia, abdominal injury, chest injury, depression, asthma, hypertension), 2 (1.0%) subjects reported 2 SAEs (hand fracture and cerebellar tumor).
Saline group: 3 subjects reported 3 SAEs (lymphadenitis, forearm fracture, cough).

Of note, a 13-year old male experienced sudden onset of severe headache and vomiting approximately 50 minutes after the 3rd bivalent vaccination (200µg), with associated nausea, chills, and generalized blotchy rash. In the emergency room, he was noted to be ill-appearing, alert and oriented, had no respiratory distress or meningeal signs. Clinical improvement was noted following ondansetron and intranasal fentanyl treatment. He was hospitalized for further observation, and was treated epinephrine and an oral antihistamine for a hypotensive episode. Except for a mild headache, his symptoms resolved the next day. The treating physician and study investigator viewed the event to be consistent with an anaphylactic reaction.

Conclusions
The safety data support the bivalent rLP2086 dosage selected for phase 3 studies.

6.7 Study B1971042

NCT# 01768117

Title: A Single-Arm, Open-Label Study to Describe the Safety, Tolerability and Immunogenicity of Bivalent rLP2086 Vaccine in Laboratory Workers ≥18 to <65 Years of Age

Study Design
This study was an open-label trial to assess the safety and immunogenicity of bivalent rLP2086 (120μg) when administered to laboratory personnel. Individuals 18 to ≤65 years of age who worked directly with pathogenic *N meningitidis* received a 3-dose series was administered according to a 0, 2, and 6-month schedule. The primary immunogenicity objective was to describe hSBA responses using 4 primary MenB strains (same strains as in study B1971011), measured one month after the 3rd vaccination.

History of microbiologically proven disease caused by *N meningitidis*, prior vaccination with any vaccine specifically targeted to fHBP or LP2086 antigens, any autoimmune or neuroinflammatory condition were exclusion criteria. The study was conducted at 2 sites in the US.

Safety evaluation (e.g. data collection methods, duration of safety monitoring) in this study was similar to study B1971011with regard to solicited local and systemic reactions and SAEs.

Immunogenicity evaluation

- The primary endpoints were the proportion of participants with a hSBA titer ≥LLOQ using primary MenB strains PMB80(A22), PMB2948(B24), PMB2001(A56), and PMB2707(B44). The LLOQs were 1:8 for B24, A56 and B44 was 1:16 for A22.
- Secondary endpoints included the proportion of subjects with a ≥4-fold response (each strain) and a composite response (all strains). The definitions of 4-fold and composite response were the same as in study B1971011.
- The laboratory performing the strain-specific hSBA assays were the same as for study B1971011.

There were no hypotheses tested.

Results
The study was conducted from February 11, 2013 to February 25, 2014 (last subject last visit).

Subject Disposition: 13 individuals were enrolled in the study. All 13 subjects received the 1st vaccination, 8 (61.5%) received the 2nd vaccination, and 7 (53.8%) received 3rd vaccination (53.8%). Six subjects withdrew during the study due to the following reasons: exclusion criterion for pre-existing autoimmune condition met (n=3), voluntary withdrawal of consent (n=2) and lost to follow-up (n=1).

The safety population consisted of 13 subjects for vaccination#1, 8 subjects for vaccination #2, 7 subjects for vaccination #3 and 10 subjects for the follow-up phase (one month through six months after the last vaccination).

Demographic characteristics: 4 of the 13 subjects were male (30.8%) and 69.2% were female. 76.9% of subjects were Caucasian and 23.1% were Asian. The median age at enrollment was 51 years of age (range: 37 to 62 years).

Safety
Pain at the injection site within 7 days of any vaccination was reported by all subjects. The median duration of injection site pain was 3 days (range 1 to 9 days). Fatigue and generalized muscle pain were common solicited systemic reactions. There were no SAEs reported.

Immunogenicity

Proportion of participants with hSBA titer ≥1:8 (≥1:16 for A22) for individual strains

Prior to the 1st vaccination, 2 of 6 subjects had a hSBA titer ≥1:8 for A56 and B24, respectively, and 2 of 6 subjects had a hSBA titer ≥1:16 for A22. No subjects had a hSBA titer ≥1:8 for B44. After the 3rd vaccination, 5 of 5 subjects had an hSBA titer ≥1:8 for A56, 6 of 6 subjects had an hSBA titer ≥1:8 for B24, 6 of 6 subjects had an hSBA titer ≥1:16 for A22, and 3 of 6 subjects had an hSBA titer ≥1:8 for B44.

Composite response (all strains)

None of subjects had a hSBA titer ≥LLOQ for all 4 primary MenB test strains at baseline (before Vaccination 1). After the 3rd vaccination, 3 of 5 subjects achieved a composite response (hSBA ≥LLOQ for all 4 primary strains).

≥4-fold increase in hSBA titer (post-dose 3 compared to pre-dose 1)

Five (5) of 5 subjects achieved an hSBA titer fold rise ≥4-fold response for A56, 4 of 6 subjects for B24, 5 of 6 subjects for A22, and 3 of 6 subjects for B44.

hSBA GMT (each strain)

Prior to vaccination visit 1, the hSBA GMTs for each of the strains were below the assay LLOQs. After the 3rd vaccination, the hSBA GMTs were 147 for A56, 32 for B24, 51 for A22 and 14 for B44.

Conclusions

In this study, the safety and immunogenicity of bivalent rLP2086 were assessed in laboratory personnel who work directly with pathogenic *N meningitidis*. More than 40% of subjects had no measurable pre-existing antibodies to any of the primary strains. Vaccine-induced antibody responses were observed using the 4 primary MenB strains, as measured by the proportions of subjects with a ≥4-fold increase in hSBA titer and by a composite response, and support the immunogenicity of bivalent rLP2086. The ability to make definite conclusions from this study is limited due to the small number of subjects.

7. INTEGRATED SUMMARY OF EFFICACY

7.1 Demographic and Baseline Characteristics

The pooled analyses were not informative, because (a) For 3 of the 7 studies, no hSBA data for all 4 primary MenB strains were available from these studies, as the final strain selection used to determine the immunogenicity of the vaccine occurred later in clinical development. Immunogenicity in studies B1971005, B1971003 and B1971004 was evaluated using MenB strains other than the primary strains or the methodology used to calculate hSBA titers differed from the method used for planning the phase 3 studies, or was measured only by –b(4)---------; (b) Study B1971042: immunogenicity data was available for 6 subjects.

7.2 Analyses

The studies B1971011, B1971012 and B1971010, antibody responses were measured in hSBA assays using the 4 primary strains. Study B1971011 was conducted in the US and studies B1971012 and B1971010 were conducted in Europe; hSBA responses among subjects who received bivalent rLP2086 at 0, 2, and 6 months in the three studies were similar. The immunogenicity data from each study are described in section 6 (Clinical Studies).

7.3 Product-Product Interactions

With regard to safety and immunogenicity data to support concomitant vaccination with routine adolescent vaccines in the US, please see section 6 (Clinical Studies) for review of study B1971011.

8. INTEGRATED SUMMARY OF SAFETY

8.1 Safety Database

Seven clinical studies were included in the BLA. B1971004, B1971005, B1971010 and B1971011 were designed as controlled studies; B1971003, B1971012 and B1971042 were non-controlled studies.

A total of 4576 subjects received at least one dose of bivalent rLP2086 (any dosage, any schedule), and 1028 participants were included in studies with a control group.

4335 subjects received the final formulation of bivalent rLP2086 (120µg):

- Of the 4282 subjects ages 11 to ≤25 years, 99.3% of subjects were ages 11 to ≤18 years (adolescent) and 0.7% were ages 19 to ≤25 years (adult) at the time of enrollment.
  - Subjects from 4 randomized, controlled studies comprised the core safety database of subjects who received bivalent rLP2086 (120µg) according to vaccination schedule (0, 2 and 6 months) intended for US licensure: 2557 subjects age 11 to ≤25 years received at least 1 dose of 120µg bivalent rLP2086 vaccine and 1004 subjects were included in control groups; 1994 and 513 subjects, respectively, were enrolled at US sites.

  - In 3 non-randomized, non-controlled studies, a total of 1725 participants who received 120µg bivalent rLP2086 vaccine, which was administered according to a 2-dose or a 3-dose schedule. Sixteen subjects in study B1971012 (Group 5) received only a single saline injection.

- 53 subjects received 120µg bivalent rLP2086 and were older than age 25 years (upper age limit: age 62 years) [studies B1971004, B1971003, B1971042]

241 subjects received 60µg or 200µg dosages of bivalent rLP2086 in dose selection studies [studies B1971004, B1971005].

Control groups received saline, HPV4, Tdap or Tdap-IPV, depending on the study.

8.2 Safety Assessments

For all studies, safety evaluations included solicited local and systemic adverse reactions after each vaccination visit (or injection visit) [7 days] was recorded daily in an electronic diary; general unsolicited AEs [through one month after the last vaccination], and SAEs [through one or six months after the last vaccination, depending on the study] were recorded on the case report form. In certain studies, immediate AEs [at least 20 minutes post-vaccination], newly diagnosed chronic medical conditions [through 6 months after the last vaccination], and autoimmune and neuroinflammatory conditions [through 6 months after the last vaccination] were assessed, which were all recorded on case report forms.

8.3 Demographic and Baseline Characteristics

Overall (7 studies; N=4576), 56.1% of participants were male; 90.8% of participants were White, 6.1% were Black, 0.9% were Asian, and 2.2% were categorized as other. 58.1% of subjects were age 11-14 years, 40.0% were age 15-18 years and 2.0% were old than age 18 years.

In studies with a control group (B1971004, B1971005 Stage 1, B1971010, and B1971011), a total of 2566 subjects received at least 1 dose of 120µg bivalent rLP2086 vaccine according to a 0, 2, 6-month schedule and 1012 subjects were included in control groups.

- In the 120µg bivalent rLP2086 group, 1656 (64.5%) of subjects were ages 11 to ≤14 years, 889 (35.0%) subjects were ages 15 to ≤18 years and 2 (0.1%) subjects were ages 19 to ≤25 years,

compared to 65.8%, 33.0% and 0.4% of subjects, respectively, in the control group. The mean age at first vaccination was 13.8 years (range: 11 to 40 years).
- Of participants in the 120µg bivalent rLP2086 group, 1600 (62.4%) were male and 966 (37.6%) were female. Of participants in the control groups, 590 (58.3%) were male and 422 (41.7%) were female.
- Overall (4 studies), 86.6% of subjects were Caucasian, 10.6% were Black, 1.1% were Asian and 3.3% were listed as 'other'. The distribution of subjects by race was similar in the 120µg bivalent rLP2086 and control groups.
- Overall (4 studies), participants in the 120µg bivalent rLP2086 group included 1194 (77.7%), 537 (20.9%) and 35 (1.4%) of subjects from study sites in the US, Europe and Australia, respectively; the control group included (listed in the same order) 513 (50.6%), 457 (45.2%) and 42 (4.2%) of subjects, respectively.

The number of subjects in each individual study was included in Table 1.

8.4 Safety Analyses

Subject Disposition

Of the 7 studies, of 4335 subjects who received the final formulation of bivalent rLP2086 (120µg)
- 4335 subjects received the first dose of bivalent rLP2086, 4052 received the second dose, and 3099 (71.5%) received the third dose.
- 3866 (89.2%) completed the vaccination phase (Day 1 through one month after the 3rd vaccination). The main reasons for withdrawal during the vaccination phase were: voluntary withdrawal (4.3%), lost-to-follow-up (1.7%) and protocol deviations (1.2%). 50 subjects (1.5%) discontinued study participation due to an AE.
- 3820 (88.1%) completed the study (received three bivalent rLP2086 doses and completed the 6 month follow-up visit). 190 (7.1%) of subjects prematurely discontinued the study, but completed the 6 month follow-up visit.

The subjects disposition in the 4 controlled studies and the 7 studies overall was similar, except that the percentage of subjects receiving the 3rd dose was 87.5%.

8.4.1 Immediate Adverse Events

120µg rLP2086 dosage level

Pooled analyses were not informative, since immediate AEs were not recorded in 3 of the 7 studies, >95% of the immediate AEs in studies that included a control group were from one study (B1971011), and all immediate AEs in the non-controlled studies were from in one study (B1971012). Please see section 6 (Clinical Studies) for a review of the individual study.

8.4.2 Solicited Local and Systemic Adverse Reactions

120µg rLP2086 dosage level; 0, 2, 6-month schedule

Of the studies for which comparative safety data were available, solicited local and systemic reactions were sufficiently characterized in US study B1971011 (1982 bivalent rLP2086 adolescents, 501 control group participants). Study B1971004 was the only adult study that included a control group. Please see section 6 (Clinical Studies) for a review of the individual studies.

8.4.3 Unsolicited Adverse Events

a. Four studies with a control group (120µg rLP2086 dosage level; 0, 2, 6-month schedule)
The study products administered to participants in the control group varied by study (saline alone, or saline + a non-meningococcal vaccine, or a non-meningococcal vaccine [e.g. Tdap vaccine]). The

vaccination phase was defined as the time interval from day of first vaccination through one month after the third vaccination.

The most frequently reported AEs during the vaccination phase were events included in the MedDRA SOC of Infections and infestations (bivalent rLP2086 23.0%, control group 28.0%). AEs (by SOC) reported by ≥1% subjects and for which the AE rate was higher in the bivalent rLP2086 group than in the control group were as follows: General disorders and administration site conditions (any: 7.7% vs 5.1%; injection site pain 3.8% vs 2.1%; pyrexia 1.2% vs 1.0%), Nervous system disorders (any: 5.7% vs 5.1%, headache 3.9% vs 3.8%), Injury, poisoning and procedural complications (ligament sprain 1.5% vs 1.2%), Infections and infestations (sinusitis 1.4% vs 1.1%), Respiratory, thoracic and mediastinal disorders (any: 6.3% vs 5.6%; oropharyngeal pain 1.6% vs 1.3%), Eye disorders (any: 1,3% vs 0.7%). Of the subjects who received bivalent rLP2086, 4.4% reported a severe AE, compared to 2.3% in the control group. Higher proportions of subjects in the bivalent rLP2086 group than in the control group reported AEs categorized as severe for headache (0.51% vs 0.10%), injection site pain (0.31% vs 0.10%), injection site erythema (0.8% vs 0%), chills (0.23% vs 0%) and myalgia (0.08% vs 0%).

Safety-related study discontinuations

Thirty four subjects in studies with a control group withdrew due to an AE, of which 30 (1.2%) subjects had received at least one dose of 120µg bivalent rLP2086 compared to 4 (0.4%) subjects in the control group. Of the 33 subjects who received 120µg bivalent rLP2086 and withdrew from the study due to an AE, 19 subjects had developed an AE associated with reactogenicity (e.g. local reactions at the rLP2086 or saline injection site, headache), compared to 1 of 4 subjects in the control group. The most commonly reported AEs resulting in study withdrawal in the 120µg bivalent rLP2086 groups were localized pain at the rLP2086 injection site (8 subjects [0.35%]) and headache (7 subjects [0.27%]). Among the control groups, 0 (0%) participants reported localized pain at the saline injection site and 1 (0.1%) subject reported headache.

Of 19 subjects who received 120µg bivalent rLP2086 and withdrew from the study due to an AE associated with reactogenicity, 13 bivalent rLP2086 subjects experienced reactogenicity categorized as severe and 3 bivalent rLP2086 subjects withdrew from the study due to the occurrence of ≥3 AEs (range: 3 to 11 AEs); 1 subject in the control group (who received saline+HPV4) experienced severe reactogenicity and had 6 AEs. Multiple AEs included occurrences of the same AE reported >1 time or multiple AEs of a different type that were reported once. The number and proportion of participants reporting a SAE, participants who withdrew from the study due to a SAE and a description of SAEs is described in the section 8.4.4.

Age

Similar proportions of subjects age 11 to ≤14 years in the 120µg bivalent rLP2086 group and the control group reported an AE during the vaccination phase (42.0% vs. 46.0%, respectively), as well as proportions of subjects age 15 to ≤18 years in the corresponding study groups (bivalent rLP2086 41.3% and control 44.3%). The proportions of subjects age 11 to ≤14 years and age 15 to ≤18 years who reported an AE within 30 days of a vaccination visit were similar for 120µg bivalent rLP2086 and control groups within the same age group and between age groups.

Study B1971004, a phase 1 study, was the only trial that included both a control group and participants older than 18 years of age (2 subjects in the 120µg bivalent rLP2086 group and 4 subjects in the control group were age 19 to ≤25 years). Ten of 11 (91.0%) study B1971004 subjects in the 120µg bivalent rLP2086 group and 11 of 12 (91.7%) subjects in the control group experienced an AE during the vaccination phase. The AEs reported in study B1971004 were primarily clinical laboratory abnormalities.

Gender

The number of male participants was approximately 1.5 times more than the number of female participants in the group that received at least one dose of 120µg bivalent rLP2086, (n=1600 vs 966) and in the control groups (n=590 vs 422). Similar proportions of male and female subjects reported an unsolicited AE within 30 days after any 120µg bivalent rLP2086 (29.3% vs. 29.6%, respectively) vaccination or control (male 32.0% and female 31.2%, respectively).

b. Three studies without a control group (120µg rLP2086 dosage level; any schedule)
Subjects in study B1971012 (n=1696) received 120µg bivalent rLP2086 according to 2- or 3-dose schedule. In studies B1971003 (n=60) and B1971042 (n=13), 120µg bivalent rLP2086 was administered as a 3-dose schedule. Pooled analyses of unsolicited AEs from non-controlled studies were not informative, since 95% of subjects were from a single study. The number of subjects age 18 to ≤25 years was too small to make meaningful comparisons. Please see section 6 (Clinical Studies) for a review of the individual studies.

8.4.4 Serious Adverse Events

a. Studies with a control group
Participants receiving 120µg rLP2086 dosage level; 0, 2, 6-month schedule
Vaccination phase:The percentage of subjects who received at least one 120µg bivalent rLP2086 dose or designated control product during the vaccination phase and reported a SAE was 1.2% [31 of 2566] and 0.9% [9 of 1012], respectively. In the 120µg bivalent rLP2086 and control groups, SAEs during the vaccination phase were most commonly observed in the SOCs of Infections and infestations and Injury, poisoning, and procedural complications.

Follow-up phase: There were no SAEs reported by 120µg bivalent rLP2086 or control group participants in during the follow-up phase, which is defined as the time interval from one month period following the last vaccination in study B1971004. For studies B1971005, B1971010 and B1971011, the follow-up phase was defined as the 6 month time period after the last vaccination. SAE rates of subjects who received at least one 120µg bivalent rLP2086 dose or designated control product during the follow-up phase ranged from 0.3% (study B1971010) to 0.6% (study B1971011) for the 120µg bivalent group and 0% (study B1971005) to 1.7% (study B1971005) for the control group. SAEs observed during the follow-up phase were consistently observed in the SOCs of Infections and infestations and Injury, poisoning, and procedural complications.

Overall, the percentage of subjects in the 120µg bivalent rLP2086 group and the control group who reported SAEs throughout the study (time interval from the day of the first vaccination through the follow-up phase) was 1.7% and 1.6%, respectively.

Participants receiving 60µg or 200µg dosages of bivalent rLP2086
Two of the four controlled studies (B1971004 and B1971005) included participants who received 60µg or 200µg dosages of bivalent rLP2086. No SAEs were reported among participants in study B1971004 during the vaccination phase or the follow-up period 1 month after vaccination #3. In study B1971005, 1 (4.5%) subject in the 60µg group, 8 (4.1%) subjects in the 200µg group, and 3 (2.5%) subjects in the control group reported an SAE during the vaccination phase; during the 6 month follow-up phase, 1 (4.5%) subject in the 60µg group, 2 (1.0%) subjects in the 200µg group and no subjects in the control group reported a SAE.

b. Studies without a control group

All subjects in the three non-controlled studies received 120µg bivalent rLP2086. For all studies, the vaccination phase (including subjects in study B1971012 who received a 2-dose schedule) was defined as the time interval from the day of the first vaccination visit through the day of vaccination visit 6 months after vaccination visit #1. The percentage of subjects in the 120µg bivalent rLP2086 group who received at least one dose and reported a SAE was 0.2% after vaccination visit #1, 0.5% after vaccination #2, and 0.2% after vaccination #3 (in subjects who received a 3-dose series). Overall, the percentage of subjects in the 120µg bivalent rLP2086 group who received at least one dose of a 2-dose schedule or 3-dose schedule was 0.4% and 1.1%, respectively. SAEs observed during the follow-up phase were consistently observed in the SOC of Infections and infestations.

During the follow-up phase, which for most studies was the time interval from the day of the first vaccination through 6 months after the last vaccination, the percentage of subjects in the 120µg bivalent rLP2086 group who received at least one dose and reported a SAE during the follow-up period was 0.9%. SAEs observed during the follow-up phase were commonly observed in the SOC of Injury, poisoning, and procedural complications.

Three subjects experienced SAEs that were considered by the study investigator and the applicant to be related to bivalent rLP2086

- Study B1971012: 15 year old female participant from the Czech Republic experienced severe vertigo, severe chills and severe headache 1 day after bivalent rLP2086 (120µg) vaccination visit #3. See study B1971012 (section 6) for further details.
- Study B1971012: 11 year old female participant from the Czech Republic developed fever (T41.1°C) and severe vomiting 2 days after bivalent rLP2086 (120µg) vaccination visit #1. See study B1971012 (section 6 Clinical Studies) for further details.
- Study B1971005: 13-year-old male participant from Australia experienced signs and symptoms of anaphylaxis 50 minutes after bivalent rLP2086 (200µg) vaccination #3. See study B1971005 (section 6 Clinical Studies) for further details.

In total (all studies), 11 subjects in the 120µg bivalent rLP2086 group reported SAEs that led to discontinuation from the study (controlled studies n=3, non-controlled studies n=8). In study B1971010, three bivalent 120µg rLP2086 subjects (motor vehicle accident, hydrocephalus, post-infectious arthritis) and no subjects in the control group discontinued from the study due to a SAE. Among the non-controlled studies, 1 subject from study B1971003 (pregnancy) and 7 subjects from study B1971012 (deep vein thrombosis, Type 2 diabetes mellitus, dermatitis contact, vertigo, decreased appetite, migraine, and Crohn's disease) were discontinued from the study due to a SAE.

One subject in the 200µg bivalent rLP2086 group (study B1971005) reported a SAE that led to discontinuation (depression).

Deaths
In total (all studies), one (1) bivalent rLP2086 participant (120µg) in study B1971010 died due to a motor vehicle accident.

8.4.5 Newly Diagnosed Chronic Medical Conditions

The definition of a newly diagnosed chronic medical condition (NDCMC) was similar in 4 studies for which NDCMCs were included in the safety evaluation (B1971011, B1971012, B1071010 and B1971042). NDCMCs were defined as diseases or medical conditions that were not identified prior to study entry and was expected to be persistent or otherwise long lasting in its effects.

Overall (7 studies), the percentage of subjects who reported a NDCMC was <1% in both the bivalent rLP2086 and control groups.

In the 4 controlled studies, 21 of 2566 (0.8%) bivalent rLP2086 participants and 10 of 1012 (1.0%) of control group participants were diagnosed with a NDCMC during the time period from vaccination #1 through the follow-up phase. NDCMCs that occurred in >1 bivalent rLP2086 participant included asthma (6 subjects [0.2%]) and migraine headache (2 subjects [0.1%]); 1 (0.10%) subject and 2 (0.2%) subjects in the control group were diagnosed with asthma and migraine headache, respectively. An additional nine bivalent subjects in non-controlled studies developed a NDCMC, of which >1 bivalent rLP2086 participant reported hypothyroidism (2 subjects) and scoliosis (2 subjects).

8.4.6 Neuroinflammatory and Autoimmune Conditions

Of 4576 subjects (all studies) who received the bivalent rLP2086 at any dose level and according to any schedule, 13 autoimmune conditions were reported in 13 individuals and one (1) participant reported a neuroinflammatory condition.

- Of the four studies that included a control group (B1971004, B1971005, B1971010, and B1971011),
  - 6 of the autoimmune conditions occurred among 2566 subjects (0.23%) who received the 120µg dosage of bivalent rLP2086 according to a 0, 2, 6-month schedule. The subset of 2566 subjects also included the participant with a neuroinflammatory condition (0.04%).
  - None of the 241 subjects who received 60µg or 200µg dosages of bivalent rLP2086 (studies B1971004 and B1971005) reported an autoimmune or neuroinflammatory condition.
- No autoimmune conditions (0%) or neuroinflammatory conditions were reported among the 1028 subjects who received ≥1dose of a control injection (i.e., saline and/or other non-Trumenba vaccine).
- The remaining 7 autoimmune conditions occurred among the 1769 subjects (0.40%) in studies with no control group (B1971003, B1971012, B1971042). All of the subjects received the 120µg formulation according to a 2-dose or a 3-dose schedule.

  Reviewer comment: Lipidated proteins may be associated with unknown or expected AEs. Bivalent rLP2086 is a lipidated protein vaccine.

In 4 studies, individuals with neuroinflammatory or autoimmune condition (studies B1971010, B1971011, B1971012, and B1971042) were not eligible (exclusion criterion) for study participation.

Case narratives

1. Psoriasis exacerbation: a 38 year old Caucasian female participant (study B1971003) with known history of psoriasis had an exacerbation 22 days after the 3rd bivalent rLP2086 vaccination. The event lasted until the end of the study (119 days). Autoimmune condition was not an exclusion criterion in this study.

2. Celiac disease exacerbation: a 22 year old Caucasian female participant (study B1971003) with known history of celiac disease had an exacerbation of gluten intolerance, which occurred 5 days after the 2nd bivalent rLP2086 vaccination. Her symptoms were categorized as mild, and resolved by the time of the telephone follow-up (38 days after vaccination 2).

3. Autoimmune thyroiditis: a 12 year old Caucasian female was evaluated for autoimmune conditions as part of an inpatient evaluation for Crohn's disease (she had been hospitalized ~3 weeks after the first bivalent rLP2086 vaccination for recurrent abdominal pain associated with fever (T39.0°C), loss of appetite, and loose stools; there was a family history of Crohn's disease). The participant was noted to have weight loss in the 2 years prior to the hospitalization, but no other symptoms suggestive of autoimmune thyroiditis were present and no laboratory investigations had been performed. Clinical laboratory results (available ~5 months after the 3rd bivalent rLP2086 vaccination) from an outpatient laboratory evaluation indicated an elevated TSH (30.7 µIU/mL;

reference range: 0.51-4.3 μIU/ml), decreased T4 (0.34 mg/L; reference range: 0.66-1.75 mg/L) and elevated anti-TPO antibody concentrations (275 IU/mL; reference range: 0-35 IU/mL). Informed consent was then obtained to assess thyroid function using the baseline (i.e. before the first dose of bivalent rLP2086) serum sample; the results were consistent with results from the outpatient evaluation. The subject withdrew from study B1971010 (fulfilled the exclusion criterion for an autoimmune condition).

4. Acute idiopathic thrombocytopenia purpura (ITP): an 11 year old Caucasian female developed petechiae on her torso and legs, which occurred 31 days after the 3rd bivalent rLP2086 vaccination. She was hospitalized the same day for further evaluation. She was afebrile and had no splenomegaly. Clinical laboratory results indicated a decreased platelet count (2 K/μL; normal range: 130-400 K/μL) in the serum and an absence of platelets in a bone marrow aspirate, but no other abnormalities. Her symptoms improved after a platelet transfusion and two courses of IVIG and corticosteroids. After a 30 day hospital stay, she went home and continued treatment with oral prednisone. Three weeks after hospitalization, the platelet count was within normal limits. Her past medical history was unremarkable, there was no prolonged bleeding following the 1st or 2nd bivalent rLP2086 vaccinations (study B1971010), and no concomitant medication use or receipt of a non-study vaccine during the study period.

5. Celiac disease: a 17 year old Caucasian female had a past medical history suggestive of celiac disease (positive serology for transglutaminase antibody (TTG) 3 years prior to study entry). She had no symptoms at study entry. The presence of dermatitis herpetiformis approximately 2 weeks after the 1st bivalent rLP2065 vaccination prompted an outpatient evaluation of the rash. A diagnosis of celiac disease was confirmed by intestinal biopsy (results available ~6 weeks after vaccination 1); elevated TTG antibody levels (2.22 U/ml; negative: <7 U/ml, positive: >10 U/ml); elevated endomysium antibodies (EMA) value of 40 (normal <1).

6. Post-infectious reactive arthritis: an 11 year old Caucasian male developed acute onset of interphalangeal joint swelling in both hands, which occurred 9 days after the 1st bivalent rLP2086 vaccination. Two days later, he developed persistent pain and swelling in his toe. He was hospitalized 15 days post-vaccination for further evaluation of arthritis. He had a history of pharyngitis one month prior to onset of symptoms. Inpatient laboratory results showed an elevated antistreptolysin O (ASO) titer of 414 IU/mL (reference range: <200 IU/mL) and group A beta-hemolytic streptococcus grew from a throat culture. After a 3 day hospital stay, the subject's joint swelling and pain resolved and he was discharged with a diagnosis of post-infectious arthritis. A follow-up examination with a rheumatologist revealed that no rheumatic disease was present. The subject withdrew from study B1971010 (fulfilled exclusion criterion for an autoimmune condition).

7. Sydenham's chorea: an 11 year old female (study B1971011 Group 1) developed involuntary jerky movements of the extremities and dysarthria, which occurred 17 days after the 2nd bivalent rLP2086 vaccination (concomitantly administered with HPV4) and lasted 4 days. She was evaluated by a neurologist, who noted the clinical findings described above. Laboratory results showed an elevated ASO titer of 389 IU/mL (normal: ≤150 IU/mL) and a positive rapid antigen strep test. She had no joint pain or rashes. An electrocardiogram (ECG) and echocardiogram were within normal limits. Her signs and symptoms of Sydenham's chorea gradually resolved.

8. IgA nephropathy: a 17 year old male (study B1971011 Group 2) developed dark urine one (1) day after vaccination visit 1 (bivalent rLP2086+saline). He was evaluated at the study site and noted to have a temperature of 38.6°C, mild leg pain, mild neck pain, and mild lower back pain. Three weeks after vaccination, he was noted to have persistent trace amounts of blood and protein in his urine.

Results from a percutaneous renal biopsy were consistent with IgA nephropathy. The subject withdrew from the study (fulfilled exclusion criterion for an autoimmune condition).

9. Crohn's disease: a 16 year old Caucasian female (study B1971012 Group 1) was newly diagnosed with Crohn's disease. She was hospitalized for persistent diarrhea, which started approximately 3 months after the 2nd bivalent rLP2086 vaccination and lasted five weeks. Results from a colonic biopsy were consistent with Crohn's disease. Her symptoms responded to treatment with mesalazine. She withdrew from the study (fulfilled exclusion criterion for an autoimmune condition). Telephone safety follow-up evaluation 2 months after study discontinuation indicated no significant findings.

10. Rheumatoid arthritis: an 18 year old Caucasian female had medical history of joint pain (thumb, both wrists) approximately 7 months prior to study enrollment. As a participant in study B1971012 (Group 2), she received a bivalent rLP2086 dose, then a saline injection, then a second bivalent rLP2086 dose at monthly intervals. She developed thumb pain 2 weeks after the saline injection, which resolved after 13 days. She experienced recurrent thumb pain, which started four weeks after the 2nd bivalent rLP2086 vaccination and resolved 3 months later. A diagnosis of rheumatoid arthritis was confirmed by a rheumatologist, and she started treatment with methotrexate and prednisolone. The subject withdrew from the study (fulfilled exclusion criterion for an autoimmune condition).

11. Basedow-Graves disease (hyperthyroidism): a 15 year old Caucasian male was asymptomatic at study entry and subsequently diagnosed with Basedow-Graves disease (hyperthyroidism) during the study. The participant had presented to the outpatient clinic, 84 days after bivalent rLP2086 vaccination 1, with a one month history of tremors and a submandibular lump. The autoimmune condition was determined retrospectively to be a pre-existing condition, based on thyroid function results performed with the baseline (i.e. before the first dose of bivalent rLP2086) serum sample. The subject withdrew from study B1971012 (fulfilled exclusion criterion for an autoimmune condition). Safety follow-up by telephone call was made approximately 5 months after study discontinuation indicated no significant findings.

12. Hypothyroidism: a 16 year old Caucasian female was asymptomatic at study entry and subsequently diagnosed with hypothyroidism during the study. Approximately 3 weeks after the 1st bivalent rLP2086 vaccination, the subject began to experience mild fatigue. Results from an outpatient evaluation showed an elevated TSH (5.63 mU/L; normal range: 0.5-3.6 mU/L), normal T4 (13 pmol/L; normal range: 11-19 pmol/L), and elevated anti-TPO antibody concentrations (1100 IU/mL; normal range: <60 IU/mL). The autoimmune condition was determined retrospectively to be a pre-existing condition, based on thyroid function results performed with a baseline serum sample, which were consistent with results from the outpatient evaluation. The subject withdrew from study B1971012 (fulfilled exclusion criterion for an autoimmune condition).

13. Hypothyroidism: a 18 year old Caucasian female was asymptomatic at study entry and subsequently diagnosed with hypothyroidism during the study. The study investigator noted that the subject began to experience fatigue 5 months after the 2nd bivalent rLP2086 vaccination. The autoimmune condition was determined retrospectively to be a pre-existing condition, based on results performed with a baseline serum sample.

14. Bell's palsy: a 16 year old male (study B1971011 Group 2) developed moderate facial paralysis 32 days after vaccination visit 2 (bivalent rLP2076+saline) and received a 2-day course of prednisone. Clinical laboratory tests (available six days after the onset of symptoms) and were positive for Lyme disease. He began a 28-day course of doxycycline and symptoms resolved completely. He received

the 3rd bivalent rLP2076 vaccination approximately one month after symptoms had resolved, had no recurrence of symptoms, and subsequently completed the study.

The applicant concluded that (a) there was no significant difference between the proportions of subjects with autoimmune (0.23%) or neuroinflammatory (0.04%) conditions in bivalent rLP2086 and control group recipients among the 4 controlled studies (6 autoimmune cases and 1 neuroinflammatory case in 2566 bivalent rLP2086 subjects); (b) bivalent rLP2086 was not the causative agent, since most of the conditions existed prior to study entry.

The applicant provided background rates for each of the autoimmune conditions using healthcare claims data from age-matched population from the ----b(4)---------- or from the published literature. The –b(4)---- contained healthcare claims data from >10 million active members in healthcare organizations in the US. The 95% CIs for the estimated rates of each autoimmune condition reported in bivalent rLP2086 study population (CBER-generated analyses) overlapped with the 95% CIs for the background rates for the corresponding autoimmune conditions, suggesting that the occurrence of autoimmune or neuroinflammatory conditions among bivalent rLP2086 vaccinees was not significantly greater the background rates for the corresponding conditions in the general population of adolescents and young adults. Please see the CBER pharmacovigilance reviewer's memo for further details.

In a separate CBER-generated analysis, the maximum risk of autoimmune or neuroinflammatory conditions was calculated for the overall population of rLP2086 vaccinees (14 cases in 7 studies) compared to control group participants (95% CI lower bound of the relative risk ratio = 0.92) and for the bivalent rLP2086 subset population in controlled studies (7 cases in 4 studies) (95% CI lower bound of the relative risk ratio = 0.76).

8.5 Safety Conclusions

The safety of bivalent rLP2086 vaccine was evaluated in 7 clinical studies (B1971003, B1971004, B1971005 stage 1, B1971010, B1971011, B1971012 and B1971042). The overall population of bivalent rLP2086 participants were 56.1% male, primarily Caucasian (90.8%); 58.1% of subjects were age 11 to ≤14 years, 40.0% were age 15 to ≤18 years and 2.0% were older than age 18 years.

Of the studies that included a control group, 120μg bivalent rLP2086 was more reactogenic than a saline injection (studies B1971005 stage 1, B1971010 and B1971011) or Tdap (study B1971004). Injection site pain was the most frequent solicited local adverse reaction reported by participants in both the 120μg bivalent rLP2086 and control groups. Headache, fatigue and generalized muscle pain were the most commonly reported solicited systemic adverse reactions. Overall, the percentage of subjects in the 120μg bivalent rLP2086 group and the control group who reported SAEs throughout the study (time interval from the day of the first vaccination through the follow-up phase) was 1.7% and 1.6%, respectively, which was within reported SAEs rates for other adolescent vaccines.

Among bivalent rLP2086 participants 11 to ≤18 years of age, there were no notable differences in frequencies of solicited local reactions sub-stratified by age 11 to ≤14 and 15 to ≤18 years, and a trend towards lower frequencies of systemic reactions after the first vaccination among subjects 15 to ≤18 years of age vs. subjects 11 to ≤14 years of age for fever (T ≥38.0C; 3.0 vs. 8.2), chills (23.1% vs. 32.1%) and antipyretic use (20.8% vs. 30.2%). The rates of unsolicited AEs and SAEs among the two subgroups were similar. The safety of bivalent rLP2086 in adults was generally acceptable.

Gender differences for certain solicited local and systemic adverse reactions were noted among adolescents. In US study B1971011, approximately 10-15% lower in male participants for swelling at the rLP2086 injection site (e.g., after the first vaccination: 19.0% vs. 26.9%), headache (e.g., after the first

vaccination: 50.8% vs. 63.2%) and fatigue (after the second vaccination: 40.3% vs. 58.8%). Rates of unsolicited AEs and SAEs rates were similar.

Autoimmune and Neuroinflammatory Conditions
A total of 13 cases of autoimmune disease and 1 neuroinflammatory condition were reported among 120μg bivalent rLP2086 subjects in the 7 clinical studies. Lipidated proteins may be associated with unknown or unexpected AEs.

- The types of autoimmune and neuroinflammatory conditions reported in the studies were medical conditions that commonly occur in adolescents and young adults. More than one subject with a thyroid disorder was identified; however, autoimmune hypothyroidism is one of the most common autoimmune conditions and the onset of symptoms is typically during adolescence. The disease presentation and clinical course of autoimmune and neuroinflammatory conditions in bivalent rLP2086-vaccinated subjects did not differ from corresponding conditions among adolescents and young adult populations described in the medical literature.
- For 9 of the 14 cases identified among bivalent rLP2086 participants, a single case of a specific autoimmune or neuroinflammatory condition was reported in the study population. A rate analysis for a single case may not be informative, other than to note that the cases might not be frequent in the study population. For autoimmune conditions in which more than one case was reported, CBER-generated analyses indicated that the 95% CIs for rates observed in the study population and corresponding 95% CIs for the background rates (estimated from event rates calculated from a healthcare claims database or obtained from the published literature) in an age-matched population for the same autoimmune condition overlapped. The 95% confidence intervals for each AE rate in the study population were wide due to the small number of cases.
- A DMC that routinely reviewed safety data from the phase 2 studies included in the BLA and that currently reviews safety data from ongoing phase 3 studies recommended: (a) in general, follow-up evaluations to assess long term outcomes of autoimmune or neuroinflammatory events in subjects for whom an autoimmune or neuroinflammatory condition was identified during the study (b) all bivalent rLP2086 clinical studies that are ongoing or planned could proceed without modification (with regard to evaluations of autoimmune and neuroinflammatory conditions).
- In this reviewer's opinion,
  - There was no conclusive evidence of excess risk of autoimmune or neuroinflammatory conditions among the overall population of bivalent rLP2086 vaccinees.
  - Reasons for the observed imbalance between autoimmune and neuroinflammatory cases identified among the bivalent rLP2086 and control group participants are not straightforward. Increased numbers of reported subjects with autoimmune diseases might have in part corresponded to stimulated reporting. Safety evaluations in studies B1971011, B1971012 and B1971010 included a prompt for the investigator to inquire about autoimmune and neuroinflammatory conditions at each study visit, an extensive list of MedDRA terms used to identify possible cases in the clinical database, and an extensive work-up to confirm diagnoses.
  - The majority of the cases were conditions that were confirmed by laboratory evidence that the disease existed prior to study entry. The possibility that bivalent rLP2086 vaccination precipitated symptoms of autoimmune disease in individuals who were asymptomatic at the time of study entry is inconclusive, as the number of cases identified was small and the time interval for follow-up was short (6 months).

- The benefit of bivalent rLP3086 vaccination outweighs the risk of developing an autoimmune or neuroinflammatory disease.

9. ADDITIONAL CLINICAL ISSUES

9.1 Pediatric Study Plan

The following plan was approved by the pediatric review committee (PeRC):

- The requirement for studies in children ages 0 to 12 months was waived, due to adverse safety outcomes observed in infants. In study B1971008, 90% of infants who received ½ the dosage amount (60μg) of the final formulation and 64% of infants who received 1/6th the dosage amount (20μg) of the final formulation, respectively, developed fever (T>38.0°C) after the first dose. The DMC recommended that further vaccinations in both dosage groups be discontinued. The safety data from this study was included in section 8.4 of the package insert.

- The requirement for studies in children ages 1 year to <10 years was deferred because the vaccine is ready for use in individuals 10 to <25 years of age and the studies in children age 1 to <10 years have not been completed. The applicant plans to conduct phase 2 studies B1971017 (ages 2 years to 10 years) and B1971035 (ages 1 year to 2 years) to assess the safety and immunogenicity of bivalent rLP2086 and the optimal dosage for children 1 year to 2 years of age. A phase 3 study is planned pending data from the phase 2 studies.

- Clinical data from studies B1971011, B1971012, B1971010 and B1971005 support the safety and immunogenicity of bivalent rLP2086 in individuals ages 11 to <18 years.

- Extrapolation of safety and immunogenicity to children age 10 years is supported by the safety and immunogenicity profile observed in children ages 11 to <18 years.

9.2 Human Reproduction and Pregnancy Data

No adverse effects on embryo-fetal development or pre- or post-natal development were shown in animal reproductive and developmental toxicity studies and there have been no clinical trials conducted in pregnant women, which support a Pregnancy Category B.

Although pregnancy was an exclusion criterion, 7 female participants were inadvertently vaccinated while pregnant. Only 1 of the cases had a known adverse outcome (spontaneous abortion) 84 days post-vaccination (gestational age unknown), which was unrelated to 120ug bivalent rLP2086 vaccination. Of the remaining 6 cases, 3 pregnancies resulted in normal births for subjects who received 120μg bivalent rLP2086 + HPV4 (n=1) and 120 μg bivalent rLP2086 (n=2), 2 were reported as elective terminations, and for 1 case the subject received bivalent rLP2086 but the pregnancy outcome was not known.

The applicant plans to conduct an observational study in the post-marketing period (study B1971052) using electronic healthcare data to assess pregnancy outcomes and birth outcomes in women who were exposed or not exposed to bivalent rLP2086 during pregnancy. The outcomes assessed include live birth, spontaneous abortion, stillbirth, and major congenital abnormalities. Data analyses include incidence and risk ratios for pregnancy outcomes, prevalence and prevalence ratios for birth outcomes and stratified analyses by covariates (sociodemographics, maternal comorbidities, maternal prenatal behaviors, concomitant medication/vaccination, pregnancy history and healthcare utilization).

9.3 Aspects of the Clinical Evaluation Not Previously Covered

9.3.1 Breadth of Coverage Strategy

The overall plan to evaluate the breadth of protection afforded by the bivalent rLP2086 vaccine is as follows:

(a) 109 MenB strains were tested using pooled human serum, which was able to kill approximately 82% of isolates obtained from CDC ABC surveillance and national laboratories in Europe.[5] The test strains differed with respect to clonal complex, Por A subtype, fHBP subfamily, fHBP subgroup and variant. The level of protein expression for each strain was quantitated, using a –b(4)----- antibody to fHBP. The –b(4)----------of 64 of the strains was then compared to the susceptibility of the strain to killing. Strains with –b(4)- above a threshold level were generally susceptible to the pooled serum. Approximately one third were below the threshold value, of which approximately 50% of the strains were susceptible to killing by pooled serum.

(b) Individual sera were assessed against multiple MenB strains. The proportion of individuals with a $\geq$4-fold increase in hSBA titer (post-vaccination compared to pre-vaccination titer) or the proportion of participants with a hSBA titer $\geq$1:8 were estimated for each strain tested. Response rates were as low as 60% for some strains with –b(4)- above the designated threshold. Susceptibility to killing appeared to be variant-dependent, although even strains expressing the same variant were not equally susceptible to killing. However, strain susceptibility to bactericidal killing was hierarchical based on the observed 4-fold response rate, i.e., serum of vaccinated individuals that contained fHBP antibodies which were bactericidal against less susceptible strains was predictive of serum bactericidal killing of more susceptible strains. Thus, inferences about vaccine effect could be made based on the ability of fHBP antibodies in the serum from vaccinated individuals to kill strains that were characteristic of the variant they were intended to represent.

(c) Primary strains: hSBA responses using four primary MenB strains (PMB2948 [variant B24], PMB80 [variant A22], PMB2707 [variant B44], PMB2001 [variant A56]) provide the principal data to support vaccine effectiveness in the context of accelerated approval. The primary strains were selected based on epidemiologic relevance and shown by the applicant to be typical of strains expressing the same variant with regard to the –b(4)-. The primary strains account for >90% of MenB strains circulating in the US and Europe (see subpart a). In the US, A22 and B24 are the most prevalent variants found to be expressed on disease-causing MenB strains. The primary strains altogether represent four of the six fHBP phylogenetic variant subgroups.

(d) Secondary strains: confirmatory studies in post-marketing period will be conducted to assess hSBA responses following bivalent rLP2086 vaccination using an additional 10 MenB strains that represent a range of genetically diverse fHBPs in the US. Immunogenicity data from these studies to verify and describe the clinical benefit Trumenba further, by demonstrating vaccine effectiveness against meningococcal B strains that represent an extended range of antigenically diverse fHBP variants, would fulfill the requirements for postmarketing confirmatory study(ies) under the accelerated approval regulations.

9.3.2 Bactericidal Activity of Individual Post-vaccination Sera in hSBA Assays Using Strains from Meningococcal B Outbreaks at US Universities

Individual serum samples from adolescents in study B1971012 who were vaccinated with 2 or 3 doses of bivalent rLP2086 were tested by the applicant in hSBA assays using isolates from meningococcal B outbreaks reported in 2013 at two US universities. Isolates from the two universities were strains that expressed variants B24 and B153, respectively. Bactericidal activity of antibodies in the post-vaccination serum samples was measurable in a dose-dependent manner.

10. CONCLUSIONS

The clinical data submitted in this BLA support the safety and immunogenicity of bivalent rLP2086 vaccine for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B, when administered as a 3-dose series at 0, 2 and 6 months in individuals 10 to ≤25 years of age.

The clinical data included in the BLA support accelerated approval of Trumenba in accordance with statutory regulations [21 CFR 601.41]. Demonstration of effectiveness was based on the ability of bivalent rLP2086 to induce bactericidal antibodies (surrogate marker) to fHBP and measured by hSBA assays using four primary meningococcal group B test strains.

- The primary strains that were selected included fHBP variants from both subfamilies (A and B), including the most prevalent variants expressed on MenB disease isolates in the US (B24 and A22) and also took into account the susceptibility of the strains to bactericidal killing based on the amount of fHBP expressed on the bacterial surface.
- The following surrogate endpoints were evaluated in support of US licensure under accelerated approval:
  - The proportion of participants with a ≥4-fold increase in hSBA titers (from pre-vaccination 1 to post-vaccination 3) to each of the four primary MenB test strains, and
  - The proportion of participants with a hSBA titer ≥ LLOQ of the assay to four primary strains (composite response).
- In three phase 2 adolescent studies, the hSBA responses following vaccination at 0, 2, and 6 months, as assessed by the endpoints described above, were adequate. There were no substantial differences in hSBA responses in gender or age stratified analyses. The hSBA responses in young adults were generally similar to corresponding responses in adolescents. Extrapolation of safety and effectiveness of bivalent rLP2086 from adolescents to children 10 to <11 years of age is supported because the course of the disease, immune responses to vaccination, and safety profile of the vaccine are expected to be sufficiently similar in these two age groups.
- The diversity of circulating *N. meningitidis* causing endemic disease in the US is attributed in part to the genetic sequence diversity and variable expression of surface proteins, including fHBPs. As a condition for accelerated approval, studies are being conducted to evaluate the breadth of coverage by assessing hSBA responses in adolescents and young adults with the four primary strains and hSBA responses with a panel of ten secondary strains. The design of the studies is acceptable to verify and describe the anticipated clinical benefit of the vaccine. The studies are ongoing. See section 11.5 *Recommendations for Postmarketing Actions.*

Immunogenicity data from evaluations of other parameters (e.g. GMT for each strain) also supported the overall conclusions about the immunogenicity of bivalent rLP2086. in addition, the applicant tested serum samples from adolescents who had been vaccinated in clinical trials with bivalent rLP2086 in hSBA assays using isolates from meningococcal B outbreaks reported in 2013 at two US universities. Bactericidal activity of antibodies in the post-vaccination serum samples was measurable in a dose-dependent manner, which further supported the immunogenicity of bivalent rLP2086 against epidemiologically relevant strains in the US.

The safety of bivalent rLP2086 was supported by data from 7 clinical studies in approximately 4580 bivalent rLP2086 participants. Bivalent rLP2086 was reactogenic relative to the study product used for comparison (e.g., saline, HPV4). Gender (higher frequencies in female participants) and age (less frequent in adolescents 15 to <18 vs. 11 to <15 years of age) differences were less than gender and age differences observed with HPV4 vaccine, which is routinely administered in the US. The frequencies of SAEs among the bivalent rLP2086 and control groups were similar. The occurrences of autoimmune and

neuroinflammatory conditions reported in the study population were within the background rates in adolescents and young adults for the respective autoimmune and neuroinflammatory conditions. Continued assessment of potential safety issues during the post-marketing period will include a review of safety data from approximately 10,000 bivalent rLP2086 participants from four additional randomized, controlled studies that are completed or near completion and ongoing assessment of safety data from the pharmacovigilance program.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Please see Table 11.

Table 11. Risk-Benefit Consideration

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Neisseria meningitidis* is a significant cause of meningitis and sepsis worldwide; the majority of meningococcal disease is caused by 5 serogroups, including serogroup B. A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss) and approximately 10% of cases are fatal. • The incidence of invasive meningococcal disease is highest in infants, and second peak occurs in adolescents and young adults.	• Invasive disease due to serogroup B *Neisseria meningitidis* is a serious and potentially life-threatening condition. • Adolescents and young adults are at risk to develop invasive meningococcal disease.
Unmet Medical Need	• At present, no meningococcal B vaccines are licensed or available in the US. • Available therapy for prevention of invasive meningococcal disease includes antibiotic chemoprophylaxis. However, disease manifestations are prevented only if individuals at risk are identified in a timely manner.	• Bivalent rLP2086 would be the first group B meningococcal vaccine licensed and available in the US.
Clinical Benefit	• Immunogenicity data from studies in adolescents and young adults supported the effectiveness of bivalent rLP2086 (120µg) administered as a 3-dose series (0, 2 and 6 months), as measured by hSBA responses using 4 primary MenB strains. • No immunological interference with MenB hSBA responses and to 3 of 4 HPV types was observed when bivalent rLP2086 was administered concomitantly with HPV4 (Gardasil; types 6, 11, 16 and 18). The non-inferiority criterion (1.5 fold differences in GMT ratio) for HPV-18 was not met (lower bound of the 95% CI for the GMT ratio was 0.62). In the last 10 years, no breakthrough infections due to HPV-18 have been reported among HPV4-vaccinated individuals.	• In the context of the accelerated approval pathway, the studies included in the BLA support the effectiveness of bivalent rLP2086 for individuals 10 to $\leq$25 years of age.
Risk	• One participant (200µg dosage) of 4576 bivalent rLP2086-vaccinated individuals developed signs and symptoms of anaphylaxis. • Bivalent rLP2086 is reactogenic. Pain at the injection site, fatigue, headache, muscle pain and chills were common solicited adverse reactions. Most reactions were mild or moderate. • In the 4 controlled studies, the incidences of SAEs among the bivalent rLP2086 and control groups were similar. • Autoimmune and neuroinflammatory conditions were reported in 13 and 1 bivalent rLP2086 participants, respectively. There was no conclusive evidence of excess risk of autoimmune or neuroinflammatory conditions among the overall population of bivalent rLP2086 vaccinees (14 cases in 7 studies) compared to control group participants.	• The safety profile of bivalent rLP2086 is acceptable.
Risk Management	• See risk section described above.	• The potential for anaphylactic reactions and information regarding reactogenicity were adequately described in the package insert. • The proposed plans for monitoring potential safety issues (routine pharmacovigilance, review of safety data from studies B1971015, B1971009, B1971014 and B1971016), vaccine effectiveness (population-based surveillance in collaboration with CDC, characterizing new emerging variants), vaccine failure (routine pharmacovigilance), and safety in pregnancy (clinical study) are acceptable.

11.2 Recommendations on Regulatory Actions

In the opinion of this reviewer, the immunogenicity and safety data submitted in this application support the approval of this BLA.

11.3 Recommendations on Postmarketing Actions

Post-marketing requirements

- In accordance with the accelerated approval regulations, confirmatory studies in the post-marketing period are being conducted to verify and describe further the clinical benefit of bivalent rLP2086 against meningococcal B strains that encompass a broader diversity of epidemiologically relevant fHBP variants in the US.
  - Study B1971009 (10 to 19 years of age)
  - Study B1971016 (18 to 26 years of age)

- In accordance with PREA requirements, studies being conducted to assess the safety and effectiveness in children 1 year to 10 years of age include
  - Study B1971017: 2 years to 10 years of age (phase 2)
  - Study B1971035: 12 months to 24 months of age (phase 2)
  - A phase 3 study in children 1 year to 10 years of age

Post-marketing commitments

- The applicant commits to providing final study reports for
  - Study B1971014: a study to further describe the safety of bivalent rLP2086 in individuals 10 to 26 years of age.
  - Study B1971015: a study to assess the safety and immunogenicity when bivalent rLP2086 is given concomitantly with Tdap and meningococcal (serogroups ACWY) conjugate vaccines.
  - Study B1971052: a study to assess the risk of pregnancy-associated adverse events and birth outcomes following vaccination with bivalent rLP2086.

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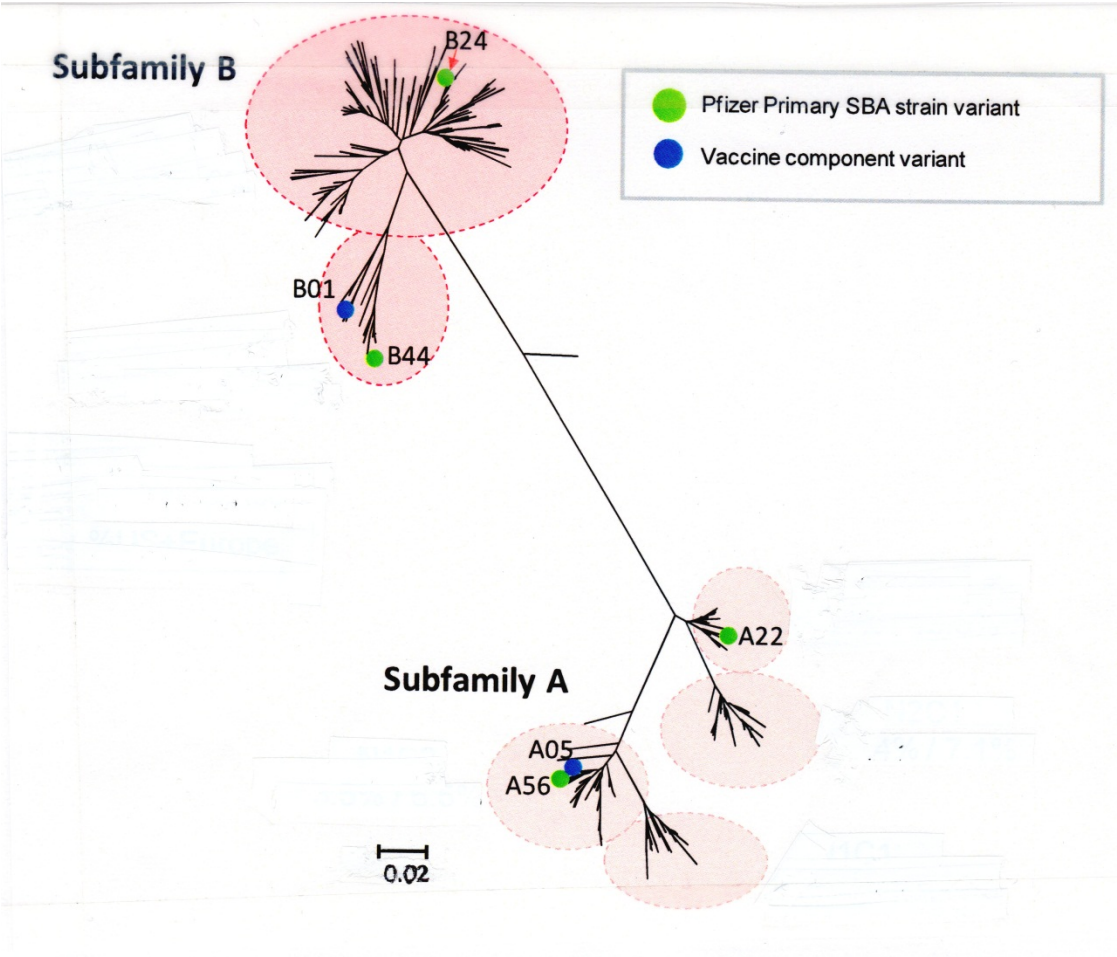
APPENDIX 1

Figure 1. Phlyogenetic Tree Showing Vaccine fHBP Antigens and fHBP Variants Expressed by Primary Meningococcal B Test Strains-

This figure is a fHBP phylogenetic tree showing the relationship between the primary MenB test strains and vaccine antigens..



Source: Adapted from vr-vtr-10156.pdf, Figure 5, page 15.