Application Type	Original Submission
STN	125549/0
CBER Received Date	16 June 2014
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Division / Office	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
Committee Chair	Drusilla L Burns, Ph.D. Chair, BLA Committee
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Priority Review	Breakthrough Therapy
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Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D., Team Leader
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	Estelle Russek-Cohen, Ph.D., Director, DB
Applicant	Wyeth Pharmaceutical Inc.
Established Name	Trumenba
(Proposed) Trade Name	*Neisseria meningitidis* Serogroup B bivalent rLP2086 vaccine
Pharmacologic Class	Meningococcal serogroup B Vaccine
Formulation(s), including Adjuvants, etc	Sterile liquid suspension of 60 µg of subfamily A and 60 µg of subfamily B rLP2086 (120 µg total protein) per 0.5 mL dose
Dosage Form(s) and Route(s) of Administration	0.5 mL single-dose pre-filled syringes with 60 µg of subfamily A and 60 µg of subfamily B rLP2086 (120 µg total protein) per 0.5 mL dose, to be injected intramuscularly
Dosing Regimen	3-dose series on a 0, 2, and 6 month schedule
Indication(s) and Intended Population(s)	For active immunization to prevent invasive meningococcal disease caused by N. *meningitidis* serogroup B in individuals aged 10 through 25 years.

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Glossary

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
BDR	blinded data review
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cLIA	competitive Luminex immunoassay
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCT	data collection tool
e-diary	electronic diary
EDMC	external data monitoring committee
ET	early termination
EU	European Union
FDA	Food and Drug Administration (United States)
fHBP	factor H binding protein
GCP	Good Clinical Practice
GMR	geometric mean ratio
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
hSBA	serum bactericidal assay using human complement
LLOQ	lower limit of quantitation
LOD	limit of detection
LP2086	lipoprotein 2086
MCAR	missing completely at random
MCV4	meningococcal conjugate vaccine
mITT	modified intent-to-treat
MI	multiple imputation
ML	maximum likelihood
MMRM	mixed-effects model with repeated measures
MnB	*Neisseria meningitidis* serogroup B
OMV	outer membrane vesicle
rLP2086	recombinant lipoprotein 2086
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
Tdap	tetanus, diphtheria, and acellular pertussis
ULOQ	upper limit of quantitation
US; USA	United States; United States of America

1. Executive Summary

1.1 Introduction

Pfizer submitted on June 16, 2014 the original Biologics License Application (BLA) STN BL 125549/0 under the Accelerated Approval licensure pathway for licensing the bivalent rLP2086 vaccine. The vaccine is intended for active immunization of individuals 10 through 25 years of age to prevent invasive meningococcal disease (IMD) caused by N. *meningitidis* serogroup B.

Need for accelerated approval is justified by recent domestic outbreaks of the MnB disease at Princeton University, New Jersey, and at the University of California Santa Barbara. These particular outbreaks prompted public health agencies to address the health crisis by using an investigational MnB vaccine that was under an Investigational New Drug application (IND).

The candidate bivalent rLP2086 vaccine, that targets MnB strains expressing subfamily A and B factor H binding proteins (fHBP), is currently being evaluated in on-going Phase 3 clinical trials under BB-IND 13812. The vaccine also received Breakthrough Therapy designation. According to the applicant, the following criteria necessary for Breakthrough Therapy designation have been met:

- The candidate MnB vaccine is intended to prevent a serious and life threatening condition.
- The available preliminary clinical evidence demonstrates that the vaccine may provide substantial improvement in intervention, compared to other, available disease treatment therapies.

1.2 Brief Overview of BLA Submission

The license application for use of the bivalent rLP2086 vaccine for individuals aged 10 to 25 years included safety and immunogenicity data generated from 7 clinical trials. A summary of the Phase 1/2 clinical studies can be found in Section 5.3 of this review. The main objectives of these 7 studies were to demonstrate that the candidate bivalent rLP2086 vaccine had ability to elicit serum bactericidal activity (as measured by serum bactericidal assay using human complement (hSBA)) for four primary strains indicated in the corresponding clinical studies and to show that the vaccine is safe.

1.3 Major Statistical Issues and Conclusions

In BLA 125549, the applicant presented safety and immunogenicity data from seven (B1971011, B1971012, B1971010, B1971005, B1971003, B1971004, and B1971042) Phase 1 and Phase 2 clinical trials that were carried out to demonstrate a positive benefit-risk profile of vaccination with the bivalent rLP2086 vaccine in individuals aged 10 through 25 years and to support US licensure of this vaccine

under the accelerated approval regulatory pathway. The statistical evaluation of the safety and immunogenicity of the three-dose regimen (on the 0-, 2- and 6-month schedule) of the recombinant lipoprotein 2086 vaccine (rLP2086) was based mainly on data collected in trials B1971011, B1971012, and B1971010, which the applicant considered to be the pivotal studies. A summary of the general information on the clinical studies is provided in Table 1. While all studies evaluated safety and immunogenicity of the bivalent rLP2086 vaccine, some other issues such as dose selection (trial B1971005), safety and immunogenicity of some other 2- and 3-dose schedules (trial B1971012), as well as concomitant use of rLP20806 with other vaccines (trials B1971010 and B1971011) were investigated also.

The quality of the submissions was sufficient to enable statistical evaluation. The analyses of data collected during the above mentioned studies led the statistical reviewers to draw the conclusions stated below.

Conclusions related to the immunogenicity

Evaluations of immune responses to the bivalent rLP2086 vaccine based on the immunogenicity data generated by seven Phase 1 and Phase 2 clinical trials submitted in this BLA are not intended to assess the breath of protection against MnB meningococcal disease the bivalent rLP2086 might confer. The foremost immunogenicity information regarding the immune responses to bivalent rLP2086 was generated by analyses related to five (5) co-primary endpoints (see Section 5.3 of this review) and four primary MnB test strains. Four (4) primary MnB test strains were selected to reflect the fact that the fHBP (factor H binding protein) sequence variants can be segregated into 2 immunologically distinct subfamilies A and B, and that 2 recombinantly produced LP2086 proteins from each subfamily A and B are represented in the vaccine.

It is worth noting that:

- ✓ The results related to the five co-primary endpoints considered in trials B1971011 and B19712 were consistent for these two clinical trials.
- ✓ The Phase 2 clinical trial B1971010 provided data that were used for an evaluation of the 4-fold rise endpoint that was part of the set of 5 co-primary endpoints. Conclusions obtained from the analyses of this endpoint were consistent with results from studies B1971011 and B1971012.
- ✓ Two studies (B1971011 and B1971010) provided data related to the concomitant use of Gardasil and Repevax (a diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine) vaccines in the adolescent population. The following issues are notable:
    - o The co-primary objectives regarding concomitant use of Gardasil and the bivalent rLP2086 vaccines were formally not achieved because not all 6 comparisons of the null hypothesis were rejected. The non-inferiority criterion was met for 5 comparisons. For the one null hypothesis that was not rejected, the lower limit of the 2-sided 95% CI for the HPV-18 GMR

was 0.62, only slightly below the pre-specified non-inferiority threshold of 0.67. The statistical reviewer defers to the medical reviewers regarding the clinical relevance of this finding.
    - The concomitant hypotheses related to Repevax were not considered in this review as they were not related to the objective of this submission.
- ✓ Study B1971012 provided immunogenicity data for different immunization schedules and dose numbers.
- ✓ Two studies (B1971042 and B1971004) provided supporting information on immune responses in populations older than 19 years.

Overall, 4459 subjects were randomized and were to be hSBA tested in three Phase 2 studies, B1971010, B1971011, and B1971012. Of the 4459 subjects, 2293 received at least 1 dose of the bivalent rLP2086 vaccine on the 0-, 2-, 6-month schedule and were included in the evaluable immunogenicity population. Among these 2293 subjects, a total of 1626 subjects (n=814 for vaccination group and n=812 for control group) were from study B1971011 carried out in the US.

The four studies which the applicant considers to be supportive studies included in the BLA are B1971003 (Phase 1/2), B1971004 (Phase 1), B1971005 (Phase 2), and B1971042 (Phase 2). A total of 657 subjects were vaccinated in these supportive studies, of which 524 and 133 received bivalent rLP2086 and control, respectively. The results from these supportive studies revealed that the rLP2086 vaccine elicited immune responses after 2 and 3 doses.

The pre-specified non-inferiority criteria for bivalent rLP2086 + Gardasil vaccination were met for 2 primary PMB80 (A22) and PMB2948 (B24) MnB test strains.

In summary*: Overall, based on 4 clinical trials which generated immunogenicity data in the indicated age range, it appears that three doses of the bivalent rLP2086 vaccine administered on the 0-, 2-, and 6-month schedule elicited immune responses expressed for four primary MnB test strains in healthy adolescents aged ≥ 11 to < 19 years. Immunogenicity data submitted by the applicant from three studies for subjects older than 18 years provided some additional information (about 72 subjects evaluated) supporting a similar conclusion for this older age group as well.*

Conclusions related to safety

- ✓ Overall the local and systemic reactogenicity events were more frequent among the rLP2086 vaccinees compared to the comparison subjects, but the majority of these events were reported to be mild or moderate in severity.
- ✓ The overall rates of AEs or SAEs among rLP2086 vaccinees were similar to those in the comparison group.
- ✓ A death occurred among vaccinees receiving 120 μg rLP2086, but it was due to traffic accident and considered not related to the vaccine by the investigator.

- ✓ Thirteen subjects reported autoimmune conditions and 1 subject wasdiagnosed with neuroinflammatory condition, among the 4576 subjects who received rLP2086, compared to no such conditions reported out of 1028 comparison subjects. However, statistical analysis did not detect evidence of excess risk among the rLP2086 vaccinees (RR 95% CI lower bound = 0.92; due to no cases among comparison subjects, the RR point estimate and its 95% CI upper bound are infinity). The majority (94.7%) of subjects received the 120 μg rLP2086 vaccine.
- ✓ For related AEs, the vaccinees receiving 120 μg rLP2086 showed higher rates compared to comparison subjects (RR=1.74, 95% CI lower bound=1.24).

In summary*: With the submitted data from Phase 1 and Phase 2 clinical trials, targeted comparisons were not always straightforward due to differing control regimens, despite common saline. Nevertheless, the submitted results by and large did not reveal excess risk in safety among subjects receiving the investigational rLP2086 vaccine compared to subjects considered as controls for comparison in the study. Whether or not the differing control regimens, despite common saline, made the comparison groups adequate controls is a clinical call to consider.*

2. Clinical and Regulatory Background

2.1 Background

The applicant has developed a novel investigational vaccine based on the bacterial surface-expressed, outer-membrane lipoprotein LP2086, which is also a factor H binding protein (fHBP). Development of the bivalent rLP2086 vaccine was conducted under IND 13812. Extensive discussions took place between Pfizer and CBER throughout the program development, and CBER's input and guidance were incorporated into the current Phase 2/3 clinical development program. The candidate bivalent rLP2086 vaccine is currently being evaluated in Phase 3 clinical trials under IND 13812.

2.2 Previous Human Experience with the Product

The clinical development of the bivalent rLP2086 vaccine began in 2006 with 3 early Phase 1 studies (Studies B1971007, B1971006, and 6108A1-500) in subjects aged 18 months to 36 months (99 subjects enrolled), 8 to 14 years (127 subjects enrolled), and 18 to 25 years (103 subjects enrolled).

2.4 Regulatory Activity Related to the Submission

Between April 2010 and the End of Phase 2 (EOP2) meeting in June 2012, many discussions and communications took place between Pfizer and CBER in an effort to define and reach agreement on licensing criteria for bivalent rLP2086. As a result of

these discussions, agreements on licensure criteria were reached. For assessment of bivalent rLP2086 vaccine responses, the primary MnB strains and the definitions of appropriate immune response endpoints were established.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

BLA 125549 was accepted as a Rolling BLA. The first rolling piece was received by CBER on May 8, 2014, and contained the complete non-clinical section of the application, the serological assay methods, and validation reports. The second rolling piece of BLA was received on May 12, 2014, and contained reports on five of seven clinical studies, datasets, and SAS programs. The third rolling piece was received on May 29, 2014, and contained CMC/facilities information. The final rolling piece, which initiated the review clock, was received on June 16, 2014, and included clinical study reports, datasets, SAS programs related to Phase 2 studies, and other required documents such as the Risk Management Plan, draft of label, draft of carton, and clinical summaries.

The quality of the submissions was sufficient to enable statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

As per the applicant, data submitted to this BLA were generated by seven clinical studies conducted in accordance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

This section is not applicable to this statistical review.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The statistical review of this BLA was divided between Dr. Barbara Krasnicka and Dr. Mridul Chowdhury. Issues related to the immunogenicity responses were reviewed by Dr. Krasnicka, while the safety aspects of vaccinations administered were reviewed by Dr. Chowdhury. Finally, synthesis of both segments of the review and the overall review documentation were performed and prepared by Dr. Krasnicka.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

The complete submission that contained clinical study reports (CSRs), SAS datasets, and other related materials was supplied by the applicant mainly in two steps (on May 12 and

June 16, 2014) and is located in BLA STN 125549/01 and 125549/04 (Amendments) in the EDR. All SAS datasets and programs were placed in Modules 5 of Amendments 01 and 04.

This statistical review evaluating the bivalent rLP2086 vaccine is based on the data for 7 studies, namely, studies B1971004, B1971005, B1971010, B1971011, B1971003, B1971012, and B1971042. For verification of the applicant's results, the statistical reviewers performed several statistical analyses on SAS datasets generated by the above mentioned studies.

This statistical review of BLA submission STN125549 is mainly based on the following volumes:
In Amendment 01:

- ✓ Module 5: The final protocols, SAPs, and clinical study reports for each of the five studies with adequate datasets and SAS programs.

In Amendment 04:

- ✓ Module 1: Administrative information and labeling.
- ✓ Module 2: Overviews of clinical efficacy and safety.
- ✓ Module 5: The final protocols, SAPs, and clinical study reports for each of the two studies with adequate datasets and SAS programs.

5.3 Overview of Clinical Trials/Studies

Seven (7) Phase 1/2 clinical trials, conducted with adolescents and adult subjects that used the final formulation of bivalent rLP2086 were included in this BLA. A summary of the basic information about the studies included in the submission is given in Table 1.

Table 1: General Information on the Submitted Studies

Study (Country)	Phase	Study Objectives	Study Population	Bivalent rLP2086 (Dosage)	Vaccine Schedule	# of subjects randomized
B1971003 (Aus)	1/2	To assess safety and immunogenicity of bivalent rLP2086	Young adults 18 to 40 years old	120 µg	Bivalent rLP2086 at 0, 1, 6-month.	60
B1971004 (US)	1	To assess safety and immunogenicity of bivalent rLP2086	Young adults 18 to 40 years old	60 µg, 120 µg, 200 µg	Bivalent rLP2086 at 0, 2, 6-month. Tdap at 0-month (saline at 2 and 6-month)	48
B1971005 (EU, Aus)	2	To assess safety and immunogenicity of bivalent rLP2086	Adolescents 11 to 18 years Old	60 µg, 120 µg, 200 µg	Bivalent rLP2086 at 0, 2, 6-month.	539

Study (Country)	Phase	Study Objectives	Study Population	Bivalent rLP2086 (Dosage)	Vaccine Schedule	# of subjects randomized
B1971010 (EU)	2	To assess safety and immunogenicity of bivalent rLP2086 when used with Repevax	Adolescents 11 to 19 years old	120 µg	Bivalent rLP2086 at 0, 2, 6-month. dTaP/IPV 0-month (saline at 2, 6-month)	749
B1971011 (US)	2	To assess safety and immune response to HPV without and with bivalent rLP2086 and to assess rLP2086 alone	Adolescents 11 to 18 years Old	120 µg	Bivalent rLP2086 at 0, 2, 6-month. HPV at 0, 2 ,6--month	2499
B1971012 (EU)	2	To assess safety and immunogenicity of bivalent rLP2086	Adolescents 11 to 19 years old	120 µg	Bivalent rLP2086 at 0, 1, 6-month; 0, 2, 6-month; 0, 4-month; 0, 4-month; 0, 6-month;	1713
B1971042 (US)	2	To assess safety and immunogenicity of bivalent rLP2086	Adults 18 to 65 years old	120 µg	Bivalent rLP2086 at 0, 2, 6-month.	13

Source: Clinical Overview, pages 36-37

All studies evaluated safety and immunogenicity of bivalent rLP2086. Additionally, the following issues were evaluated: (1) concomitant vaccinations (studies B1971010 and B1971011), (2) dose selection (study B1971005), and (3) safety and immunogenicity of various 2 and 3-dose schedules (study B1971012).

For the sake of better understanding of this statistical review, the following three important issues related to the evaluation of the immune response to the bivalent rLP2086 vaccine are worth noting:

(1) For the purpose of the Phase 3 studies, after long discussions between the FDA and the applicant, a main immunogenicity objective was specified. It relates to assessment of the immune responses induced by the rLP2086 vaccine, measured by hSBAs performed for MnB strains expressing LP2086 subfamily A and B proteins one month after the third vaccination dose. The assessment utilizes 5 co-primary endpoints. Four (4) of these 5 co-primary endpoints are vaccine-elicited 4-fold hSBA response to each of the 4 primary MnB test strains, and the fifth co-primary endpoint is a composite endpoint defined as hSBA responses $\geq$ LLOQs for all 4 primary MnB test strains combined.

For the sake of the main exploratory objective, the following parameters (proportions) were to be estimated:

a. (1)- (4) For each of four primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], proportion of subjects achieving at least 4-fold increase in hSBA titer from baseline to one month post third vaccination.

b. (5) Proportion of subjects achieving the composite hSBA response, as defined above, at one month after the third vaccination dose.

(2) For assessment of this main objective, immunogenicity data from three Phase 2 studies (B1971010, B1971011, and B1971012) conducted in adolescents were analyzed using the criteria agreed on by CBER and Pfizer for the pivotal Phase 3 adolescent Study B1971009.
(3) The hSBA titer was defined, using a "step titer" approach, as the highest 2-fold dilution of a serum sample that resulted in at least 50% reduction of bacteria in the assay.

In summary, based on the safety and immunogenicity data from seven Phase 1 and Phase 2 studies in adolescents, results of the statistical analyses related to safety and the main immunogenicity objective suggest trends of immune response to the bivalent rLP2086 vaccine as well as an acceptable safety profile. Pfizer aims to confirm these findings by the currently ongoing Phase 3 trials.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1: B1971011

Title of the clinical trial: "*A Phase 2, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of Gardasil (HPV) Vaccine and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥ 11 to <18"*

Study Initiation Date: September 28, 2011 (the first subject visit)
Study Completion Date: May 6, 2013 (the last subject visit)
Final Serology Date: December 18, 2013

6.1.1 History of Study Protocol

The final study protocol was submitted to CBER on August 12, 2010, and was followed by four amendments and 2 administrative changes made to the final amendment. Enrollment of subjects was initiated after submission of protocol Amendment 1. The four protocol amendments implemented many modifications to the study design such as:

- The external data monitoring committee (EDMC) charter was added.
- Inclusion/exclusion criteria were modified, e.g., an exclusion criterion related to allergen immunotherapy was added.
- Some details regarding designated bivalent rLP2086 strains, LLOQs for primary strains, criteria for each analysis population, and GMT calculations were added.
- Primary and secondary hypotheses, endpoints, and objectives were modified to reflect alignment with the overall vaccine development program.
- Visit numbers were added for clarity but did not modify existing time points.

- The Schedule of Activities and Study Procedures sections were revised by recording of previous events related to MCV4, Tdap, and other non-study vaccine administration.
- Subject withdrawal guidelines were clarified.
- Overall power for declaring non-inferiority was corrected.

The fourth version of the protocol was submitted to CBER on September 18, 2012. The study statistical analysis plan (SAP) was updated 7 times. The final version of the SAP is dated December 2, 2013, and incorporated all changes already implemented in the protocol amendments.

6.1.2 Objectives

The main objective of study B1971011 was to assess the safety, tolerability, and immunogenicity of concomitantly administered Gardasil and bivalent rLP2086 vaccines as compared to Gardasil or bivalent rLP2086 vaccines administered alone.

There were two co-primary immunogenicity objectives:

- To demonstrate that the immune response (based on geometric mean titer (GMT)) induced by Gardasil given with bivalent rLP2086 (Group 1) is non-inferior to the immune response induced by Gardasil alone (Group 3), as measured in both groups 1 month after the third vaccination (Visit 5) with Gardasil. Immune responses to all 4 components of Gardasil were assessed.
- To demonstrate that the immune response induced by bivalent rLP2086 given with Gardasil (Group 1) is non-inferior to the immune response induced by bivalent rLP2086 alone (Group 2), as measured in both groups by hSBA performed with two MnB test strains, one expressing LP2086 subfamily A and one expressing LP2086 subfamily B proteins, 1 month after the third vaccination (Visit 5) with bivalent rLP2086.

Primary Safety Objective was:

- To evaluate the safety profile of bivalent rLP2086, as measured by the proportions of subjects reporting local reactions, systemic events, and AEs.

The most important secondary objectives were:

- To describe the immune response to rLP2086 vaccine, as measured by hSBA performed with four MnB test strains, two expressing LP2086 (lipoprotein 2086 (referring to the recombinant fHBP or fHBP vaccine antigen)) subfamily A and two expressing LP2086 subfamily B proteins, 1 month after the third vaccination (Visit 5) with bivalent rLP2086 (Group 2).
- To describe the immune response to rLP2086 vaccine, as measured by hSBA performed with four MnB test strains, two expressing LP2086 subfamily A and two expressing LP2086 subfamily B proteins, 1 month after the second vaccination (Visit 3) with bivalent rLP2086 (Group 2).

The main immunogenicity exploratory objective related to immune response to the bivalent rLP2086 vaccine, as described by five immunogenicity co-primary endpoints, was pre-defined in the protocol. More information on the main immunogenicity objective can be found in Section 5.3 of this statistical review.

Detailed information on other secondary objectives can be found in Dr. Lucia Lee's clinical review. Endpoints considered in this study are discussed in Section 6.1.8 of this review.

6.1.3 Design Overview

Study B1971011 was a Phase 2, randomized, active-controlled, observer-blinded, multicenter clinical trial carried out in the US. Subjects were enrolled into the study if in good health, as judged by physical assessment and medical history, and if they met all inclusion criteria and none of the exclusion criteria. It was planned that approximately 2500 healthy adolescents age $\geq$ 11 to < 18 years at the time of study entry would be enrolled and randomized to one of 3 groups in a 2:2:1 (Group 1: Group 2: Group 3) ratio to receive bivalent rLP2086 + Gardasil, bivalent rLP2086 + saline, or saline + Gardasil, respectively. Vaccination schedules in each group are presented in Table 2.

Table 2: Study B1971011 Design

Month #	**Month 0**	**Month 2**	**Month 3**	**Month 6**	**Month 7**	**Month 12**
Visit #	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Group 1	rLP2086 + Gardasil®	rLP2086 + Gardasil®		rLP2086 + Gardasil®		Phone contact
Group 2	rLP2086 + Saline	rLP2086 + Saline		rLP2086 + Saline		Phone contact
Group 3	Saline + Gardasil®	Saline + Gardasil®		Saline + Gardasil®		Phone contact
Blood draw (all groups)	~20 mL		~20 mL		~20 mL	

Source: The applicant's table, B1971011 Protocol, page 9

The informed consent document and a complete medical history, as well as a complete physical examination, were collected and performed at Visit 1 before randomization and administration of the first study vaccination. At each of the vaccination visits (Visits 1, 2, and 4), subjects in Groups 1, 2, and 3 received one dose of bivalent rLP2086 + Gardasil, bivalent rLP2086 + saline, or saline + Gardasil, respectively.

The study staff dispensing and administering vaccines were unblinded, but all other study personnel, particularly individuals who evaluated subjects' safety, the principal investigator, and subjects were blinded.

Reviewer's comments

Study B1971011 was not primarily designed for assessments of safety and immunogenicity of the bivalent rLP2086 vaccine. Despite that, this Phase 2 study

demonstrated in an exploratory way functional immune responses to the bivalent rLP2086 vaccine for four primary MnB test strains.

6.1.4 Population

At the time of enrollment (baseline), the study population consisted of 11-18 year-old females and males

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and a legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in Dr. Lucia Lee's clinical review.

6.1.5 Study Treatments or Agents Mandated by the Protocol

The vaccination groups and the vaccination plan per study group are presented in Table 2 of this review.

The investigational products were supplied by the applicant and they were:

- ✓ The bivalent rLP2086 vaccine - a 0.5-mL dose formulated to contain 60 μg (total 120 μg) each of a purified subfamily A and a purified subfamily B rLP2086 protein, -----(b)(4)------ polysorbate 80, and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0.
- ✓ Gardasil® - Human Papillomavirus (HPV) Quadrivalent (Types 6, 11, 16, 18) Recombinant vaccine - a 0.5-mL dose.
- ✓ Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose.

The bivalent rLP2086 vaccine was administered intramuscularly by injecting 0.5 mL of vaccine into the upper deltoid muscle of the left arm (Groups 1 and 2). Gardasil® vaccine was administered intramuscularly into the upper deltoid muscle of the right arm (Groups 1 and 3). Saline was administered intramuscularly into the upper deltoid muscle of the right arm for Group 2 and into the upper deltoid muscle of the left arm for Group 3. Gardasil® dosing and preparation was according to the information stated in the product package insert.

Lot numbers of the investigational products are summarized in Table 3.

Table 3: Investigational Product Lot Numbers

Investigational Product	Manufacturer	Vendor Lot Number	Lot Number
Bivalent rLP2086	Pfizer	7-5104-013A	11-003091
Gardasil 10x 0.5mL Vials	Merck	0768Z	10-087622
Gardasil 10x 0.5mL Vials	Merck	0459AE	12-002982
Saline (0.9% sodium chloride)	Pfizer	7-8044-004A	11-002694

Source: The applicant's table, CSR, page 39

6.1.6 Sites and Centers

Multiple sites (63 sites) in the US participated in the study. One additional site (#1018) received investigational product but did not enroll any subjects.

6.1.7 Surveillance/Monitoring

The study was conducted by investigators contracted by and under the direction of the applicant. The investigators were responsible for adhering to the study procedures described in the protocol, in particular, for keeping records of the investigational products. Stanley Lawrence Block Jr, MD (Kentucky Pediatric/Adult Research) was responsible for investigators coordination.

All investigational products were packaged, labeled, and shipped by -------(b)(4)----------. Clinical laboratory assessments were performed by Pfizer Vaccine Research – High Throughput Clinical Testing, -------(b)(4)----------, and by ----------(b)(4)----------. Data management, data analyses, biostatistics, and medical writing were completed by the applicant or its designated representatives.

The final protocol, all amendments, and informed consent document (ICD) were reviewed and approved by the institutional review board(s) (IRBs) and/or independent ethics committee(s) (IECs) for each investigational center participating in the study.

6.1.8 Endpoints and Criteria for Study Success

In order to assess the immune responses to bivalent rLP2086 (Group 1 and Group 2) and Gardasil (Group 1 and Group 3) vaccines using hSBA and competitive Luminex immunoassays (cLIAs), respectively, blood samples (approximately 20 mL each) were drawn from each subject immediately before Vaccination 1, 28 to 42 days after Vaccination 2, and 28 to 42 days after Vaccination 3.

Study endpoints and parameters

Immunogenicity endpoints were:

- ✓ Titers at Baseline and 1 Month after the second and third vaccinations

- ✓ Seroconversion
- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ For the first co-primary objective and for subjects in Groups 1 and 3, the geometric mean titers (GMTs) for four HPV antigens (HPV-6, HPV-11, HPV-16, and HPV-18) were estimated utilizing titers measured at 1 Month (Visit 5) after the third vaccination with Gardasil®.
- ✓ For the second co-primary objective and for Groups 1 and 2, the hSBA geometric mean titers (GMTs) for the 2 primary strains (PMB80 [A22], PMB2948 [B24]), were estimated using titers measured at 1 Month after the third vaccination.
- ✓ Proportion of subjects who were at baseline seropositive for each of the four HPV antigens.
- ✓ Proportions of subjects with hSBA titers: equal to or greater than the lower limit of quantitation (LLOQ), ≥ 1:4, ≥ 1:8, ≥ 1:16, ≥ 1:32, ≥ 1:64, ≥ 1:128 for each of the 4 primary strains (PMB80 [A22], PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]) at each applicable blood draw time point.
- ✓ hSBA geometric mean titers (GMTs) for each of the 4 primary strains (PMB80 [A22], PMB2001 [A56], PMB2948 [B24], PMB2707 [B44]) at each applicable blood sampling time point.
- ✓ Proportions of subjects achieving at least 4-fold increase in hSBA titer from baseline to 1 month after the second and the third vaccinations (Visits 3 and 5).

For the sake of the main immunogenicity objective, i.e., for 5 co-primary immune response endpoints, the following parameters were defined:

(1) - (4) For each of four primary strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], proportion of subjects in Group 1 achieving at least 4-fold increase in hSBA titer from baseline to one month post third vaccination.

(5) Proportion of subjects in Group 1 achieving a composite hSBA response defined as hSBA titer ≥ LLOQ for all 4 primary strains combined at one month after the third vaccination.

Per definition, the 4-fold response took place if:

- o hSBA titer after vaccination was ≥ 1:16, for subjects with a baseline hSBA titer below LOD (i.e., with baseline hSBA titer < 1:4).
- o hSBA titer after vaccination was greater than or equal to four times the LLOQ, for subjects with a baseline hSBA titer ≥ LOD (i.e., with hSBA titer ≥ 1:4) but < LLOQ.
- o hSBA titer after vaccination was greater than or equal to four times the baseline titer, for subjects with a baseline hSBA titer ≥ LLOQ.

Safety endpoints

For each vaccine group, an assessment of vaccine safety was based on the following categories of safety measures:

- ✓ Immediate adverse events after each vaccination
- ✓ Solicited AEs (i.e., local and systemic reactions) and selected indicators of reactogenicity on the day of vaccination and on each of the following 7 days. (Please note that for bivalent rLP2086 and saline injections, local reactions (redness, swelling, and pain) were checked from the left arm.)
- ✓ Unsolicited AEs
- ✓ Medically significant AEs, i.e., AEs requiring, for instance, a physician's visit or an Emergency Department visit
- ✓ SAE data collected throughout the study period, i.e., from the first study vaccination (Visit 1) through 6 months after the third study vaccination (Visit 6).

More information on immunogenicity endpoints and parameters can be found in Section 2 (pages 21-24) of the study protocol.

6.1.9 Statistical Considerations and Statistical Analysis Plan

Hypotheses

The first co-primary objective was to demonstrate that the immune response induced by Gardasil® given with bivalent rLP2086 vaccine (Group 1) was non-inferior to the immune response induced by Gardasil® given alone (Group 3), as measured in Groups 1 and 3 at one month (Visit 5) after the third vaccination with Gardasil®.

The second co-primary objective was to demonstrate that the immune response induced by the bivalent rLP2086 vaccine given with Gardasil® (Group 1) was non-inferior to the immune response induced by the bivalent rLP2086 vaccine given alone (Group 2), as measured in Groups 1 and 2 by serum bactericidal assay using human complement (hSBA) performed with two MnB test strains, one expressing LP2086 subfamily A and one expressing subfamily B proteins, at one month after the third vaccination with the bivalent rLP2086 vaccine.

The following hypothesis was to be considered:

$$H_0 : \ln_{1.HPVi} - \ln_{3.HPVi} \leq -\ln 1.5 \text{ for any } i = 1, 2, 3, 4$$
$$\text{or } \ln_{1.hSBAj} - \ln_{2.hSBAj} \leq -\ln 1.5 \text{ for any } j = 1, 2$$

$$H_A : \ln_{1.HPVi} - \ln_{3.HPVi} > -\ln 1.5 \text{ for all } i = 1, 2, 3, 4$$
$$\text{and } \ln_{1.hSBAj} - \ln_{2.hSBAj} > -\ln 1.5 \text{ for all } j = 1, 2,$$

where $\ln_{1,HPVi}$ and $\ln_{3,HPVi}$ (i=1, 2, 3, 4) are the means of the natural logarithm transformed anti-HPV titers for the i^{th} HPV antigen in Group 1 and Group 3, respectively, and $\ln_{1,hSBAj}$ and $\ln_{2,hSBAj}$ (j=1, 2) are the means of the natural logarithm transformed hSBA titers for the j^{th} strain in Group 1 and Group 2, respectively. The primary strains (variants) were PMB80 (A22) and PMB2948 (B24) and four HPV antigens were HPV-6, HPV-11, HPV-16, and HPV-18.

Reviewer's comments

To evaluate two co-primary objectives, the applicant defined a single hypothesis which consisted of 6 comparisons formulated for four HPV antigens and two primary strains. The study overall Type I error was set at 2.5% (1-sided), and in order to declare success of this study, all 6 comparisons of the null hypothesis needed to be rejected. Please note that all alpha (Type I error) was spent on this analysis.

Statistical analysis

The following co-primary variables were used for testing of the hypothesis:

- Co-primary variables for the first co-primary objective were GMTs for four HPV antigens (HPV-6, HPV-11, HPV-16, and HPV-18) measured, for Groups 1 and 3, at 1 month after the third vaccination (Visit 5) with Gardasil. (Please note that both baseline seropositive and seronegative subjects were included in the comparisons.)
- Co-primary variables for the second co-primary objective were the hSBA GMTs for two primary MnB test strains PMB80 (A22) and PMB2948 (B24) measured, for Groups 1 and 2, at 1 month after the third vaccination (Visit 5) with bivalent rLP2086.

For the immunogenicity analyses, three analysis populations were defined:

(1) Evaluable immunogenicity population,
(2) Baseline HPV-seronegative evaluable immunogenicity population, and
(3) Modified intent-to-treat (mITT) population.

The evaluable immunogenicity population was used for the co-primary objectives and the post-Vaccination 3 immunogenicity objective and included subjects who: (1) received 3 doses of vaccine as per protocol specification, (2) had valid and determinate assay results for the proposed analysis, and (3) had no other major protocol violations. All randomized subjects who had at least 1 valid and determinate assay result related to a proposed analysis were included in the mITT population.

General information on assay measurements

The hSBAs were fully validated by Pfizer, and CBER approved the range of titers that could be quantified with acceptable linearity (relative accuracy/dilutional linearity) and precision. The assay range was defined as titers between the lower limit of quantitation (LLOQ) and the upper limit of quantitation (ULOQ), inclusive. Although the limit of detection (LOD) for all 4 primary MnB test strains was a titer equal to 1:4, other LLOQs for the 4 primary MnB test strains were established. The hSBA titers above the LLOQs were considered accurate. The LLOQs are listed in Table 4.

Table 4: The hSBA LLOQs for Four Primary MnB Test Strains

Strain	LLOQ
PMB80 (A22)	1:16
PMB2001 (A56)	1:8
PMB2948 (B24)	1:8
PMB2707 (B44)	1:8

Source: The applicant's table, SAP, page 28

When an hSBA titer was below the LLOQ, a titer value equal to half of the LLOQ was assigned for the purpose of GMT estimation. Due to this practice, estimates of GMTs may be biased; however, the applicant performed sensitivity analyses evaluating possible bias and did not find any influence of this practice on results.

The cLIA (competitive Luminex immunoassay) LLOQs for the HPV antigens were 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. For the estimation of GMTs for HPV antigens, assay results below LLOQ were also set to half of the LLOQ.

Statistical analysis

For the purpose of testing the hypothesis related to the non-inferiority objectives, the parameters:

- Geometric mean titer ratios (GMRs) (Group 1/ Group 3) for HPV-6, HPV-11, HPV-16, HPV-18 antigens
- GMRs (Group 1/Group 2) based on the hSBA titers for A22 and B24 strains,

and the corresponding 95% CIs were estimated utilizing data from Visit 5.

The logarithmically transformed assay results and the Student t distribution were utilized for the hypothesis testing, and statistical inferences were based on the confidence intervals of the GMRs.

Safety analysis

Safety data collected during the clinical study were summarized utilizing frequencies of events. No type I error was spent for the safety summaries.

6.1.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects were balanced across the three vaccination study groups. Gender ratios were similar across the vaccine groups. Males constituted 66.5% of the subjects (33.5% were females). The majority of subjects were white (81.6%). The younger age group (11 to < 15 years old) constituted 65.9% of the subjects. The mean age (± SD) at first vaccination was 13.6 (±1.92) years, while ages ranged from 11 to 17 years.

Disposition of subjects

A total of 2499 subjects were randomized and included in the Intent-to-treat (ITT) population. A summary of the randomized subjects' disposition is presented in Table 5.

Table 5: Disposition of Randomized Subjects

Disposition of Subjects	**Group 1** rLP2086 + Gardasil n(%)	**Group 2** rLP2086 + Saline n(%)	**Group 3** Saline + Gardasil n(%)	**Total** n(%)
Randomized	999	998	502	2499
Withdrawn before vaccination	6 (0.6)	8 (0.8)	1 (0.2)	15 (0.6)
Withdrawal before vaccination: No longer willing to participate in study	4 (0.4)	5 (0.5)	1 (0.2)	10 (0.4)
Withdrawal before vaccination: Does not meet entrance criteria	2 (0.2)	3 (0.3)	0 (0.0)	5 (0.2)
Withdrawal during vaccination phase: No longer wiling to participate in study	56 (5.6)	47 (4.7)	14 (2.8)	117 (4.7)
Withdrawal during vaccination phase: Lost to follow-up	29 (2.9)	32 (3.2)	14 (2.8)	75 (3.0)
Withdrawal during vaccination phase: No longer meets eligibility criteria	13 (1.3)	18 (1.8)	10 (2.0)	41 (1.6)
Withdrawal during vaccination phase: Other	12 (1.2)	13 (1.3)	5 (1.0)	30 (1.2)
Withdrawal during vaccination phase: Protocol violation	10 (1.0)	9 (0.9)	7 (1.4)	26 (1.0)
Withdrawal during vaccination phase: Adverse event	9 (0.9)	11 (1.1)	3 (0.6)	23 (0.9)
Completed Study	**848 (84.9)**	**841 (84.3)**	**438 (87.3)**	**2127 (85.1)**
Withdrawn after Visit 5	16 (1.6)	19 (1.9)	10 (2.0)	45 (1.8)
Completed 6 Month follow-up contact	875 (87.6)	879 (88.1)	448 (89.2)	2202 (88.1)

Source: Table based on the applicant's table (CSR, Page 63)

Of the 2499 randomized subjects, 2172 (86.9%) completed the vaccination phase of the study defined as a period from baseline to one month after the last vaccination, while 312 subjects withdrew during this vaccination phase. Subjects who withdrew from the vaccination phase were followed for safety purposes. The 6-month (after the last vaccination) follow-up telephone contacts were attempted, unless the subjects withdrew consent or were lost during the vaccination phase. A total of 2202 (88.1%) subjects completed the 6-month follow-up telephone contact.

Protocol deviations

As per the applicant's report, protocol deviations were identified throughout the study by monitoring the informed consent documentation, source documents, and other clinical trial–related documents. Protocol deviations were classified as major or minor. A major deviation was defined as one that could have a significant impact on the subject's immunogenicity result. All subjects with major protocol deviations were excluded from the evaluable immunogenicity population used for the immunogenicity analysis.

Of the 2499 subjects randomized into the study, 2049 (82.0%) were included in the evaluable immunogenicity population. Please note that immunogenicity analyses for different endpoints were usually based on special subsets of the evaluable immunogenicity population. Disposition of 450 (18.0%) subjects who were excluded from the evaluable immunogenicity population was as follows:

(1) 433 (17.3%) subjects did not have a scheduled pre-vaccination or post–vaccination 3 blood draw,
(2) 331 (13.2%) subjects did not have valid and determinate assay results at the pre-vaccination or post–vaccination 3 blood draw,
(3) 307 (12.3%) did not receive all vaccines,
(4) 81 (3.2%) subjects were not eligible or became ineligible for the study before or at the post–vaccination 3 blood draw,
(5) 26 (1.0%) subjects received prohibited vaccines or treatments, and
(6) 25 (1.0%) subjects had important protocol deviations.

Please note that many subjects were excluded due to multiple reasons.

It is worth noting that data for 160 subjects were unblinded at Site 1007. As per the applicant (CSR, page 65), "upon review, there were no changes made after unblinding to the safety data for the majority (n=109) of subjects, and for the remaining subjects (n=51), the safety information added after unblinding did not change the overall safety conclusions. Additional post hoc sensitivity analyses of immunogenicity data were performed by excluding subjects from this site from the evaluable immunogenicity population, and there was no impact on study conclusions."

Another Site, 1051, was terminated because of dissolution of the site management organization (SMO), "lack of further access to subject source information, and subsequent inability to execute study activities." Site 1051 was unable to completely recover source documentation after the discontinuation of operations of the SMO in August 2012. "Upon dissolution of the SMO, the principal investigator, in accordance with the sponsor's recommendation, immediately ceased enrollment (the last subject was enrolled in June 2012) and implemented a mitigation plan." All safety data reported from this site were included in the primary safety analysis. Moreover, to investigate possible bias in the overall safety conclusions caused by protocol deviations at Site 1051, the applicant performed sensitivity analyses in which safety data for this site were excluded. The analyses showed no impact of Site 1051 on the overall safety conclusions. The post-Vaccination 3 blood draw data were frequently missing at this site. Therefore, to fulfill the pre-defined SAP rules related to the definition of this population, none of the subjects enrolled at this site were included in the evaluable immunogenicity population.

Vaccination compliance

A summary of vaccination compliance by study visit is presented in Table 6.

Table 6: Numbers (%) of Subjects Who Received Study Vaccines

Vaccination Number	Vaccines	Group 1 N=999 n (%)	Group 2 N=998 n (%)	Group 3 N=502 n (%)
1	rLP2086 Gardasil Saline	992 (99.3) 992 (99.3) 0	990 (99.2) 0 990 (99.2)	0 501 (99.8) 501 (99.8)
2	rLP2086 Gardasil Saline	930 (93.1) 930 (93.1) 0	925 (92.7) 1 (0.1) 924 (92.6)	0 476 (94.8) 476 (94.8)
3	rLP2086 Gardasil Saline	871 (87.20 872 (87.3) 1 (0.1)	869 (87.1) 0 869 (87.1)	0 452 (90.0) 452 (90.0)

Source: The applicant's table (CSR, page 72)

About 88% of subjects received all study vaccines, but some administrations of vaccines did not comply with the study vaccination schedules. For instance, only 82.9%, 83.3%, and 87.1% of subjects in Groups 1, 2 and 3, respectively, followed the protocol-specified visit window requirement for Vaccination 3. However, despite vaccination window violations, subjects were not excluded from the evaluable immunogenicity population.

6.1.11 Immunogenicity Analyses

Datasets analyzed

Immunogenicity Modified Intention-to-treat (mITT) Population

Immunogenicity mITT population (2484 subjects; 99.4% of 2499 subjects randomized) consisted of all subjects who received a study vaccination and provided at least one evaluable post-baseline serum sample.

Evaluable Immunogenicity Population

The evaluable immunogenicity population consisted of all subjects who received correctly all relevant doses of vaccine, provided evaluable serum samples at the relevant time points, and had no major protocol deviations as defined prior to the database lock.

Detailed information on the evaluable immunogenicity population can be found in Section 6.1.10 of this review.

6.1.11.1 Analyses Related to Primary Endpoints

Primary immunogenicity hypothesis

The first co-primary objective related to HPV antigens was to demonstrate that the immune response induced by bivalent rLP2086 + Gardasil vaccination (Group 1) was

non-inferior to the immune response induced by saline + Gardasil (Group 3) vaccination, as measured in both groups at one month after the last dose of Gardasil (Visit 5).

Testing of the first section (i.e., related to the first co-primary objective) of the formal hypothesis employed estimates of the GMTs in Groups 1 and 3 for four HPV antigens. The corresponding Group 1 to Group 3 GMT ratios (GMRs) and their 2-sided 95% CIs were estimated. The non-inferiority margin criterion was 1.5-fold, which corresponds to a value of 0.67 for the lower limit of the 2-sided 95% CI of the GMR. Results of hypothesis testing related to the HPV antigens are presented in Table 7.

Table 7: Results of Testing the Primary Hypothesis Related to the HPV Antigens

Antigen	Group 1 # of subjects	Group 1 GMT	Group 3 # of subjects	Group 3 GMT	**Ratio**	**Ratio 95% CI**
HPV-6	813	451.8	423	550.3	**0.82**	**(0.72, 0.94)**
HPV-11	813	892.9	423	1084.3	**0.82**	**(0.74, 0.91)**
HPV-16	813	3695.4	423	4763.4	**0.78**	**(0.68, 0.88)**
HPV-18	813	744	423	1047.4	**0.71**	***(0.62, 0.81)***

Source: Based on the applicant's table, CSR, page 83

Testing of the hypothesis section related to the second co-primary objective was based on the evaluation of hSBA GMTs estimated for 2 primary MnB test strains (PMB80 [A22] and PMB2948 [B24]) at 1 month after the third dose of bivalent rLP2086 (Visit 5). Results of hypothesis testing related to two primary MnB test strains are presented in Table 8.

Table 8: Results of Testing the Primary Hypothesis Related to Response Induced by Bivalent rLP2086 Vaccine

Strain [Variant]	Group 1 # of subjects	Group 1 GMT	Group 2 # of subjects	Group 2 GMT	**Ratio**	**Ratio 95% CI**
PMB80 [A22]	803	53.3	801	57.8	**0.92**	**(0.85, 1.00)**
PMB2948 [B24]	788	25.8	793	28	**0.92**	**(0.84, 1.01)**

Source: The applicant's table, CSR, page 83

Reviewer's Comments

The non-inferiority criteria for comparisons of bivalent rLP2086 + Gardasil vaccination to saline + Gardasil vaccination or to bivalent rLP2086 + saline vaccination required that the lower limits of the 2-sided 95% CIs for the GMRs for antibodies to all four HPV antigens and for hSBA titers for 2 primary MnB test strains (A22 and B24) be greater than 0.67 at 1 month after Vaccination 3. Based on Tables 7 and 8, this pre-specified threshold was met for both MnB test strains and for 3 (out of 4) HPV antigens. But the lower limit of the 2-sided 95% CI for the HPV-18 GMR was 0.62, i.e., slightly below the pre-specified threshold of 0.67. Therefore, the non-inferiority criteria formally were not met because not all 6 comparisons of the null hypothesis were rejected. The statistical

reviewer defers to the medical reviewers regarding the implication of this narrow miss for the HPV-18 strain.

As per the applicant, results of testing the primary hypothesis based on the mITT population were similar to the results for the evaluable immunogenicity population. All HPV antigens and 2 MnB strains with the exception of HPV-18 met the 1.5-fold criterion.

6.1.11.2 Analyses Related to Secondary Endpoints

Results of the applicant's statistical analyses related to the secondary objectives can be found in the CSR, pages 84-98.

6.1.11.3 Analyses Related to Exploratory Endpoints

The main immunogenicity objective was to assess immune response to the bivalent rLP2086 vaccine using parameters related to 5 co-primary endpoints that were defined as follows:

> (1) to (4) For each of four primary MnB test strains (A22, A56, B24, and B44), proportion of subjects achieving at least 4-fold increase of hSBA from baseline to 1 month after the third vaccination, in Group 2.
> (5) Proportion of subjects achieving the composite hSBA response defined as hSBA titer ≥ LLOQ for all 4 primary MnB test strains combined, at one month after the third vaccination, in Group 2.

Detailed information on this objective can be found in Section 5.3 of this review.

The main immunogenicity objective was evaluated using thresholds established for the primary endpoints in Phase 3 clinical studies (e.g., Study B1971009) that investigate subjects in the same age range as study B1971011. The results for each co-primary endpoint were considered acceptable if the 95% CI Lower Limits for each co-primary endpoint were greater than the pre-specified thresholds presented in Table 9.

Table 9: Thresholds Related to the Main Immunogenicity Objective

Endpoint	Threshold
4-fold increase for PMB80 [A22]	75%
4-fold increase for PMB2001 [A56]	85%
4-fold increase for PMB2948 [B24]	65%
4-fold increase for PMB2707[B44)	60%
Composite Response (LLOQ)	75%

Source: The reviewer's table

The statistical analysis results for the main immunogenicity objective, i.e., for the proportions of subjects achieving an hSBA 4-fold rise in titer for each of the 4 primary

MnB test strains and for the proportions of subjects achieving the composite response, for the evaluable immunogenicity population are presented in Table 10.

Table 10: Results for the Main Immunogenicity Objective for Group 2 Based on the Evaluable Immunogenicity Population

Variables	Strain/Variant	# of subjects	Estimation of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	788	**86.4**	(83.8, 88.7)
hSBA Titer 4-fold rise	PMB2001 [A56]	730	95.3	(93.6, 96.8)
hSBA Titer 4-fold rise	PMB2948 [B24]	774	84.8	(82.0, 87.2)
hSBA Titer 4-fold rise	PMB2707 [B44]	788	80.7	(77.8, 83.4)
Composite hSBA response	For 4 primary strains	763	83.9	(81.1, 86.4)

Source: The reviewer's table based on the applicant's table, CSR, page 100

Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

*Note: The 4-fold increase is defined as follows: (1) For subjects with a baseline hSBA titer below the limit of detection (LOD, or an hSBA titer <1:4), a response is defined as an hSBA titer ≥1:16. (2) For subjects with a baseline hSBA titer ≥ LOD (ie, hSBA titer ≥1:4) and < lower limit of quantitation (LLOQ), a response is defined as an hSBA titer ≥4 times the LLOQ. (3) For subjects with a baseline hSBA titer ≥ LLOQ, a 4-fold response is defined as an hSBA titer ≥4 times the baseline titer***.***

Table 10 shows that for Group 2 (bivalent rLP2086 + saline), the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after Dose 3 were 86.4% for PMB80 [A22], 95.3% for PMB2001 [A56], 84.8% for PMB2948 [B24], and 80.7% for PMB2707 [B44], while 83.9% of subjects achieved the composite hSBA response (hSBA ≥ LLOQ for all 4 primary MnB test strains combined). Additionally, as per Table 10, all 95% lower confidence limits for 5 co-primary endpoints used for the main immunogenicity exploratory objective and for Group 2 exceeded the thresholds.

At CBER's request, the applicant performed an additional analysis in which a new definition for 4-fold rise for strain PMB80 [A22] was used. According to this new definition the 4-fold rise took place if:

- hSBA titer after vaccination was ≥ 1:64, for subjects with baseline hSBA titer below LLOQ (i.e., with baseline hSBA titer < 1:16).
- hSBA titer after vaccination was greater than or equal to four times the baseline titer, for subjects with a baseline hSBA titer ≥ LLOQ.

Results of the additional analysis are presented in Table 11.

Table 11: Proportion of Subjects with 4-Fold hSBA Titer Rise from Baseline, for Strain PMB80 [A22]

	# of subjects	Estimation of endpoint (%)	95% CI
1 Month after Vaccination 3	788	**55.2**	(51.7, 58.7)

Source: The reviewer's table based on the applicant's table, CSR, page 100

*Note: The 4-fold increase is defined as follows: (1) For Subjects with a baseline hSBA titer of < LLOQ, a 4-fold response is defined as an hSBA titer 4 times of the LLOQ (or ≥1:**64**). (2) For subjects with a baseline hSBA titer ≥ LLOQ, a 4-fold response is defined as an hSBA titer ≥4 times the baseline titer*

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By changing the definition of 4-fold rise, the proportion of subjects with 4-fold rise in hSBA titer from baseline changed drastically from 86.4% to 55.2%. For partial explanation of this result please see Table 12 that shows the GMTs and their 95% CIs for

subjects from Group 2. Please note that for strain PMB80 [A22] the GMT estimate is 57.8, and 84% of the subjects had titers below LLOQ at baseline.

Table 12: Estimates of hSBA GMTs for Group 2

Strain	Sampling Time Point	Number of Subjects	# of subjects below LLOQ	Estimation of GMT	95% CI
PMB80 [A22]	Before Vaccination 1	**799**	**668 (84%)**	9.9	(9.58, 10.33)
PMB80 [A22]	1 month after Vaccination 3	801	30 (4%)	57.8	(54.44, 61.44)
PMB2001 [A56]	Before Vaccination 1	740	671 (91%)	5	(4.75, 5.28)
PMB2001 [A56]	1 month after Vaccination 3	802	5 (1%)	128.2	(120.65, 136.27)
PMB2948 [B24]	Before Vaccination 1	793	738 (93%)	4.5	(4.35, 4.65)
PMB2948 [B24]	1 month after Vaccination 3	793	59 (7%)	28	(26.24, 29.87)
PMB2707 [B44]	Before Vaccination 1	805	785 (93%)	4.2	(4.10, 4.31)
PMB2707 [B44]	1 month after Vaccination 3	795	**114 (14%)**	31.9	(29.25, 34.82)

Source: The reviewer's table based on the applicant's tables from CSR, page 90 and 97

*Note: LLOQ = 1:16 for A22; LLOQ =1:8 for A56, B24, and B44. Titers below the LLOQ were set to 0.5*LLOQ for analysis.*

As per Table 12, please note that, one month after Vaccination 3, about 14% subjects had hSBA titer below LLOQ for strain PMB2707 [B44].

6.1.12 Subgroup Analyses

The applicant presented in the CSR, pages 269-276, results of statistical analyses related to possible influence of race (white, black, other) and age (strata 11-15 years, and 15-18 years) on immune responses to the bivalent rLP2086 vaccine at one month after the third vaccination. Based on results from these univariate analyses, no substantial differences in hSBA GMTs between the subgroups were revealed, but subjects in the younger age stratum had higher GMTs than subjects in the older stratum.

The proportions of subjects with hSBA titers ≥ LLOQ at 1 month after Vaccination 2 and Vaccination 3 were similar, within each study group, and for different age and race subgroups.

Table 13 summarizes results of statistical analyses performed to investigate possible influence of gender on the immune responses as expressed by GMTs and proportions of subjects with hSBA responses ≥ LLOQ after the 3rd dose of the bivalent rLP2086 vaccine.

Table 13: Numbers of Subjects with hSBA Titer ≥ LLOQ and Estimates of GMTs and the Corresponding 95% CIs at 1 Month after the 3rd Dose of the Bivalent rLP2086 Vaccine, for Two Genders and Group 2

A. Female

Strain	Sampling Time Point	Number of Subjects	# of subjects ≥ LLOQ	Estimation of GMT	95% CI
PMB80 [A22]	Before Vaccination 1	266	38 (14.3%)	9.6	(9.06, 10.23)
PMB80 [A22]	1 month after Vaccination 3	264	254 (96.2%)	53.4	(48.26, 59.08)

Strain	Sampling Time Point	Number of Subjects	# of subjects ≥ LLOQ	Estimation of GMT	95% CI
PMB2001 [A56]	Before Vaccination 1	241	29 (12%)	5.3	(4.81, 5.95)
PMB2001 [A56]	1 month after Vaccination 3	267	267 (100%)	117.5	(106.15, 130.04)
PMB2948 [B24]	Before Vaccination 1	265	9 (3.4%)	4.2	(4.07, 4.44)
PMB2948 [B24]	1 month after Vaccination 3	260	224 (86.2%)	22.6	(20.03, 25.43)
PMB2707 [B44]	Before Vaccination 1	269	6 (2.2%)	4.2	(4.02, 4.30)
PMB2707 [B44]	1 month after Vaccination 3	266	202 (75.9%)	23.8	(20.33, 27.95)

B. Male

Strain	Sampling Time Point	Number of Subjects	# of subjects ≥ LLOQ	Estimation of GMT	95% CI
PMB80 [A22]	Before Vaccination 1	533	97 (17.4%)	10.1	(9.63, 10.61)
PMB80 [A22]	1 month after Vaccination 3	537	517 (96.3%)	60.2	(55.79 64.86)
PMB2001 [A56]	Before Vaccination 1	499	40 (8.0%)	4.9	(4.57, 5.15)
PMB2001 [A56]	1 month after Vaccination 3	535	530 (99.1%)	133.9	(124.15, 144.49)
PMB2948 [B24]	Before Vaccination 1	528	46 8.7%)	4.2	(4.43, 4.37)
PMB2948 [B24]	1 month after Vaccination 3	529	510 (95.7%)	31.1	(28.83, 33.54)
PMB2707 [B44]	Before Vaccination 1	536	14 (2.7%)	4.2	(4.10, 4.37)
PMB2707 [B44]	1 month after Vaccination 3	529	479 (90.5%)	37	(33.39, 40.91)

Source: Table based on the applicant's tables, CSR, pages: 238, 239

Statistical analyses evaluating possible influence of gender on the immune responses (GMTs and proportions of subjects with hSBA Titer ≥ LLOQ) after the 3rd dose of the bivalent rLP2086 vaccine were post-hoc in nature. Therefore, the differences, if any, observed between the sub-groups should be interpreted accordingly.

Reviewer's comments and overall conclusions on immunogenicity results

- *The immunogenicity non-inferiority criteria for bivalent rLP2086 + Gardasil vaccines as compared to saline + Gardasil vaccines and as compared to the bivalent rLP2086 + saline vaccines were met for 2 primary MnB test strains and for HPV-6, HPV-11, and HPV-16 antigens, but the criterion for HPV-18 antigen was not quite met. For HPV-18, the lower limit of the 2-sided 95% CI for the GMR was 0.62, i.e., slightly below the pre-specified threshold of 0.67. Therefore, the alternative primary hypotheses formally were not supported. The statistical reviewer defers to the medical reviewers regarding the clinical relevance of this finding*

- *Due to the procedure of setting titers below LLOQ to 0.5*LLOQ, most of the hSBA GMTs were slightly overestimated. However, based on the applicant's sensitivity analyses (e.g., estimations of hSBA GMTs using maximum Likelihood Estimation or ANCOVA), this procedure did not impact the primary statistical results.*

- *Secondary and other analyses related to four primary MnB test strains showed no substantial differences between Groups 1 and 2, but hSBA GMTs and proportion of subjects with titers greater than LLOQ for Group 2 (rLP2086 + saline) were higher than for Group 1 (rLP2086 + Gardasil). However, it appears that Gardasil had no statistically meaningful influence on the immune response to the bivalent rLP2086 vaccine when these vaccines were given together.*

- *An exploratory analysis of 5 co-primary endpoints (related to the main exploratory objective) typical of those used in Phase 3 trials showed that the lower limits of the 95% CIs were greater after the third dose than the pre-defined thresholds for all 5 endpoints for Group 1 (bivalent rLP2086 + Gardasil) and Group 2 (bivalent rLP2086 + saline). Data generated by study B1971011 provided evidence that the bivalent rLP2086 vaccine elicits immune response expressed by four primary MnB test strains.*

- *Immunogenicity data for about 20% of the subjects are missing. Among these, 14% (138/998) of the subjects were withdrawn from the study during the vaccination period. Reasons for withdrawal are not clear.*

- *For Group 2 and after the third dose of the bivalent rLP2086 vaccine, there were 30, 5, 59, and 114 subjects with titers below the LLOQ (left-censored) for PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44] strains, respectively. In the case of the PMB2707 [B44] strain and one month after the second dose of vaccine, almost 43% (333/776) of the subjects had titers below the LLOQ.*

- *Evaluation of immune responses to the vaccine was based only on 4 primary MnB test strains. Therefore, data generated by this study do not provide apparent information on breath of protection against MnB meningococcal disease the bivalent rLP2086 vaccine might confer.*

6.1.13 Safety Analyses

Primary safety objective

The primary safety objective of this study was to evaluate the safety profile of bivalent 120 µg LP2086, as measured by the proportion of subjects reporting local reactions, systemic events, and adverse events (AEs).

Safety evaluation

A total of 2,499 subjects were randomized: 999 subjects to Group 1 (bivalent rLP2086 + Gardasil), 998 subjects to Group 2 (bivalent rLP2086 + saline), and 502 subjects to Group 3 (saline + Gardasil). Among the 2,499 randomized subjects, 15 subjects did not receive investigational vaccine; 1 randomized subject in Group1 received the wrong investigational products, from another study, at

visit 1 and withdrew. Thus, a total of 2,483 subjects comprised the safety population (N=992 for Group 1; N=990 for Group 2; N=501 for Group 3). The majority of the subjects were white (81.6%), non-Hispanic/non-Latino (82.6%), and 66.5% were male and 65.9% were 11 to < 15 years old.

Local Reactions

In the study, subjects reported local reactions at the injection site more frequently following administration of the bivalent rLP2086 vaccine (97.6% in Group 1 and 96.9% of in Group 2) compared to administration of saline (56.7% in Group 3 at the saline injection site) (Table 14). Pain was most commonly reported. Most local reactions were mild or moderate in severity.

Table 14: Subjects Reporting Local Reactions by Maximum Severity within 7 Days after Any Vaccination, Safety Population

Subjects	Group1 n[b](%)	Group1 95% CI[c]	Group2 n[b](%)	Group2 95% CI[c]	Group3 n[b](%)	Group3 95% CI[c]
# of subjects with known info after any vaccination	987	987	985	985	497	497
Pain at injection site - Any	959 (97.2)	(95.9, 98.1)	953 (96.8)	(95.4, 97.8)	272 (54.7)	(50.2, 59.2)
Pain at injection site - Mild	315 (31.9)	(29.0, 34.9)	303 (30.8)	(27.9, 33.7)	229 (46.1)	(41.6, 50.6)
Pain at injection site - Moderate	509 (51.6)	(48.4, 54.7)	524 (53.2)	(50.0, 56.4)	41 (8.2)	(6.0, 11.0)
Pain at injection site - Severe	135 (13.7)	(11.6, 16.0)	126 (12.8)	(10.8, 15.0)	2 (0.4)	(0.0, 1.6)
Redness[e] - Any	288 (29.2)	(26.4, 32.1)	287 (29.1)	(26.3, 32.1)	18 (3.6)	(2.2, 5.7)
Redness[e] - Mild	112 (11.3)	(9.4, 13.5)	123 (12.5)	(10.5, 14.7)	16 (3.2)	(1.9, 5.2)
Redness[e] - Moderate	141(14.3)	(12.2, 16.6)	129 (13.1)	(11.1, 15.4)	2 (0.4)	(0.0, 1.4)
Redness[e] - Severe	35 (3.5)	(2.5, 4.9)	35 (3.6)	(2.5, 4.9)	0 (0.0)	(0.0, 0.7)
Swelling[e] - Any	321 (32.5)	(29.6, 35.5)	330 (33.5)	(30.6, 36.5)	26 (5.2)	(3.4, 7.6)
Swelling[e] - Mild	166 (16.8)	(14.5, 19.3)	175 (17.8)	(15.4, 20.3)	20 (4.0)	(2.5, 6.1)
Swelling[e] - Moderate	144 (14.6)	(12.4, 16.9)	150 (15.2)	(13.0, 17.6)	6 (1.2)	(0.4, 2.6)
Swelling[e] - Severe	11 (1.1)	(0.6, 2.0)	5 (0.5)	(0.2, 1.2)	0 (0.0)	(0.0, 0.7)
Any Local	963 (97.6)	(96.4, 98.4)	954 (96.9)	(95.6, 97.9)	282 (56.7)	(52.3, 61.1)

Note: Subject 10851030 received wrong vaccines at Vaccination 2, Subject 10231026 received wrong vaccines at Vaccination 3, and Subject 10451006 received wrong vaccines at Vaccination 1. These subjects were excluded from the relevant safety population. Group1=120 µg rLP2086+Gardasil, Group2=120 µg rLP2086+Saline, Group3=Saline+Gardasil*

b. n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scale
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects
d. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
e. Mild = 2.5 to 5.0 cm, moderate = 5.5 to 10.0 cm, and severe is >10.0 cm.
f. Any local reaction = any pain at injection site, redness, or swelling.

Source: Full Clinical Study Report, B1971011, page 120-121

Systemic events

Of the systemic events reported by the rLP2086 vaccinees, headache, fatigue, and muscle pain were most common. For these respective events, the proportions

(95% CI) of subjects reporting were 73.4% (70.5%, 76.1%), 77.7% (75.0%, 80.3%), and 61.8% (58.7%, 64.8%) in Group 1; and 70.3% (67.3%, 73.1%), 73.6% (70.7%, 76.3%), and 58.4% (55.2%, 61.5%) in Group 2. In comparison, among subjects who received saline and Gardasil concomitantly (Group 3), these respective proportions were 60.6% (56.1%, 64.9%), 61.8% (57.3%, 66.1%), and 44.9% (40.4%, 49.4%). However, the overall proportion of subjects reporting any systemic events were 91.6% (89.7%, 93.2%) in Group1, 91.1% (89.1%, 92.8%) in Group 2, and 80.9% (77.1%, 84.3%) in Group 3. This indicates overall similarity of the systemic event profiles among the rLP2086 recipients despite their having co-administration of Gardasil (Group1) and Saline (Group 2). But the overall event frequencies in Group 1appeared somewhat higher compared to the comparison subjects in Group 3 (saline+Gardasil). The systemic events in all three groups were mostly mild and moderate in severity (Source: Full CSR, B1971011, page 392-393).

Adverse events during vaccination phase

A summary of adverse events during vaccination phase is provided in Table 15.

Table 15: Summary of Subjects Reporting at Least 1 AE during Vaccination Phase, Safety Population

AE Type	Group1 N=992 n(%)	Group1 N=992 95% CI	Group2 N=990 n(%)	Group2 N=990 95% CI	Group3 N=501 n(%)	Group3 N=501 95% CI
Any AE	435 (43.9)	(40.7, 47.0)	413 (41.7)	(38.6, 44.9)	248 (49.5)	(45.0, 54.0)
Mild	300 (30.2)	(27.4, 33.2)	266 (26.9)	(24.1, 29.7)	165 (32.9)	(28.8, 37.2)
Moderate	218 (22.0)	(19.4, 24.7)	216 (21.8)	(19.3, 24.5)	126 (25.1)	(21.4, 29.2)
Severe	48 (4.8)	(3.6, 6.4)	45 (4.5)	(3.3, 6.0)	18 (3.6)	(2.1, 5.6)

Group1=rLP2086+Gardasil, Group2=rLP2086+Saline, Group3=Saline+Gardasil; 95% CIs based on exact statistics.
N = number of subjects with known values after any vaccination.
n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales.
Source: Clinical Study Report, B1971011, page 140.

The proportion of subjects reporting at least 1 AE during the vaccination phase was 43.9% in group rLP2086+Gardasil and 41.7% in group rLP2086+Saline, compared to 49.5% in group Saline+Gardasil. Overall, the frequency of these AEs in the Saline+Gardasil group seemed slightly higher compared to the other two groups. Overall, there were no marked demographic subgroup differences by age, gender, or race, as shown in Table 16. The proportions of subjects reporting severe AEs were by and large similar across the three Groups and ranged from 3.6% to 4.8%. Most of these AEs, based on the AE severity level information provided, were mild or moderate.

Table 16: Subjects Reporting at Least 1 AE during Vaccination Phase by Demographic Subgroups, Safety Population

Demographic Subgroup	Group1 N	Group1 n(%)	Group2 N	Group2 n(%)	Group3 N	Group3 n(%)
Age 11 to <15 yrs	642	282 (43.9)	652	274 (42.0)	343	173 (50.4)
Age 15 to <18 yrs	350	153 (43.7)	338	139 (41.1)	158	75 (47.5)
Female	337	151 (44.8)	327	131 (40.1)	169	87 (51.5)
Male	655	284 (43.4)	663	282 (42.5)	332	161 (48.5)
White	824	369 (44.8)	787	333 (42.3)	414	203 (49.0)
Black	118	38 (32.2)	149	55 (36.9)	56	33 (58.9)
Other	50	28 (56.0)	54	25 (46.3)	31	12 (38.7)

Group1=rLP2086+Gardasil, Group2=rLP2086+Saline, Group3=Saline+Gardasil; 95% CIs based on exact statistics.
N = number of subjects with known values after the vaccination.
n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales.
Source: Clinical Study Report, B1971011, page 515-528.

SAEs

Throughout the study, a total of 32 (1.3%) subjects reported serious AEs (SAEs), with 12 (1.2%) subjects from Group 1, 16 (1.6%) subjects from Group 2, and 4 (0.8%) subjects from Group 3 (Clinical Study Report, B1971011, Table 40, page 168). In an overall comparison (28/1982 vs 4/501), an excess risk of SAEs in rLP2086 over control was not noted (RR=1.77, 95% CI: (0.67, 6.74)). Of the 32 reported subjects with SAEs, 4 subjects had SAEs in the infections/infestations category, 7 subjects had SAEs that belonged to injury/poisoning/procedural-complications, and 10 subjects had SAEs of psychiatric disorders. The SAEs included 2 autoimmune cases, one case of Sydenham's chorea in group rLP2086+Gardasil group and one case of IgA nephropathy in group rLP2086+Saline. Both of these cases were claimed as clinically not related to the investigational vaccine by the investigator. The study reported no death.

Reviewer's safety conclusions

In this study, local reactions (i.e., pain, etc., at injection site) and systemic events (i.e., headache, fatigue, and muscle pain, etc.) were reported more frequently among the rLP2086 vaccinees, compared to subjects in the Control arm where saline and Gardasil were co-administered. Additionally, among the rLP2086 vaccinees, those who had co-administration of Gardasil had comparable proportions reporting reactogenic incidents compared with those who were co-administered saline. Most of the reactogenic incidents were reported as mild or moderate in clinical severity.
The proportions of subjects reporting severe AEs were by and large similar across the study's three Groups and ranged within 3.6% - 4.8%. The similarity held regardless of the demographic subgroups of age, gender, and race.

The study included two autoimmune cases, one being a case of Sydenham's chorea in group rLP2086+Gardasil group, with the other one being a case of IgA nephropathy in the group rLP2086+Saline. The applicant claimed that both of these cases were not related to the investigational vaccine. The study reported no death.

In general, an overall excess of risk in safety among the rLP2086 vaccinees relative to the control subjects was not discernible.

6.2 Trial #2: B1971012

Title of the study: *"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"*

Study Initiation Date: March 3, 2011 (the first subject visit)
Study Completion Date: September 18, 2012 (the last subject visit)
Final Serology Date: August 30, 2013

6.2.1 History of Study Protocol and Changes in the Conduct of the Study

The original study protocol was submitted to CBER on April 20, 2010, and was followed by four amendments and one document related to the administrative changes made to the final amendment. Enrollment of subjects was initiated after submission of protocol Amendment 1.
The first amendment to the protocol implemented modifications to the study design such as:

- The primary objective and endpoints were changed
- Inclusion/exclusion criteria were modified
- Statistical sections were updated to reflect changes.

The second (July15, 2011) and the third (April 23, 2012) amendments addressed changes in methods of data collection for safety and immunogenicity endpoints.

The fourth amendment submitted to CBER on September 24, 2012, introduced the following changes:

- An immunogenicity exploratory objective and endpoints consistent with the Phase 2/3 program was added, and
- Safety endpoints were updated to be consistent with the Phase 3 program.

The study statistical analysis plan (SAP) was updated 3 times.

It is worth noting an event which interrupted the study conduct. Study injections were temporarily paused on July 1, 2011, during investigation of a "suspected unexpected

serious adverse reaction" (SUSAR) identified for a 15-year-old female subject. The subject was hospitalized after she developed severe chills, headache, and vertigo approximately 70 minutes after receiving her second dose of bivalent rLP2086. The applicant's risk management committee (RMC) reviewed the case and recommended resumption of study vaccination. The EDMC agreed with the recommendation of the RMC that vaccinations were safe to resume without a change to the benefit-risk profile. Subsequently, a decision was made on July 13, 2011, to resume study immunizations. However, per European regulations, resumption of the study could occur only after a successful submission and approval of a substantial amendment, which would allow the resumption of the study to occur 2 to 3 months after the study pause. Because of the study pause and the time required to obtain EU approval for the study restart of the study, a minority of subjects did not receive their vaccinations at Visits 2 or 3. The study was restarted following implementation of the substantial protocol amendment which extended the dosing visit time windows to allow subjects impacted by the delay to remain in the study.

6.2.2 Objectives

Primary objective:

- ✓ To assess the immune response induced by the bivalent rLP2086 vaccine, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins 1 month after the third vaccination with bivalent rLP2086, in Group 1 subjects (0-, 1-, and 6-month vaccine schedule).

- ✓ To assess the immune response induced by the bivalent rLP2086 vaccine by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins 1 month after the third vaccination with bivalent rLP2086, in Group 2 subjects (0-, 2-, and 6-month vaccine schedule).

Secondary objectives:

- ✓ To assess the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins 1 month after the second vaccination with bivalent rLP2086, in Group 3 subjects (0- and 6-month vaccine schedule).

- ✓ To describe the immune response, as measured by serum bactericidal assay performed with MnB strains expressing LP2086 subfamily A and B proteins throughout the entire study period, among all groups subjects.

Primary safety:

- ✓ To evaluate the safety profile of bivalent rLP2086, as measured by the incidence rates of local reactions, systemic events, and AEs

Main immunogenicity exploratory objective:

- ✓ To assess the immune response described by 4-fold response and a composite response, as measured by hSBA performed with 4 primary MnB test strains, 2 expressing LP2086 subfamily A and 2 expressing LP2086 subfamily B proteins, one month after the third dose of the bivalent rLP2086 vaccine. More details on the main immunogenicity objective can be found in Section 5.3 of this review.

6.2.3 Design Overview

Study B1971012 was a Phase II, randomized, placebo-controlled, single-blind, multicenter trial carried out in the European Union. Subjects were randomly assigned to 5 groups in a 3:3:3:2:1 ratio (Group 1 : Group 2 : Group 3 : Group 4 : Group 5) to receive study vaccination as per the study design presented in Table 17. It was planned that approximately 1716 subjects (20 subjects per site) would be enrolled in this clinical trial at approximately 86 sites. Subjects were stratified into 2 age groups: ≥ 11 to < 14 and ≥ 14 to < 19 years at the time of enrollment.

Table 17: Study B1971012 Design

Group #	Visit 1 Month 0	Visit 2 Month 1	Visit 3 Month 2	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 7	Visit 7 Month 12
Group 1	rLP2086	rLP2086	Saline		rLP2086		Phone contact
Group 2	rLP2086	Saline	rLP2086		rLP2086		Phone contact
Group 3	rLP2086	Saline	Saline		rLP2086		Phone contact
Group 4	rLP2086	Saline	rLP2086		Saline		Phone contact
Group 5	Saline	Saline	rLP2086		rLP2086		Phone contact
Blood draw (all groups)	20 mL		20 mL	20 mL		20 mL	

Source: The applicant's table, CSR, page 28

The maximum duration of subject participation in the study was approximately 17 months (including a telephone contact 6 months after the last study vaccination). Collection of 20mL of blood from all subjects was performed before Vaccination 1, before Vaccination 3, 1 month after Vaccination 3, and 1 month after Vaccination 4.

Study subjects were blinded with respect to their allocation to vaccine groups. However, investigators and the applicant knew the allocation of all subjects throughout the study.

Reviewer's comments

The objective of study B1971012 was to assess the safety, tolerability, and immunogenicity of the bivalent rLP2086 vaccine administered in a healthy adolescent population according to some dose schedules. The dose schedules were: (1) 0-, 1-, and 6-month, or (2) 0-, 2-, and 6-month, or (3) 0- and 6-month, or (4) 0- and 2-month, or (5) 2- and 6-month. Based on results generated by this and other studies, the applicant

decided that the optimal schedule for vaccination with the bivalent rLP2086 vaccine would be 0, 2, and 6 months. This schedule would be subsequently indicated in the label. Therefore, this review is focused on Group 2 data, i.e., on immunogenicity responses to the bivalent rLP2086 vaccine administered according to the 0-, 2-, and 6-month schedule.

6.2.4 Population

At the time of enrollment (baseline), the study population consisted of 11-19 year-old females and males

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and/or a legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

The complete list of inclusion and exclusion criteria can be found in the Dr. Lucia Lee's clinical review.

6.2.5 Study Treatments or Agents Mandated by the Protocol

Vaccination plan per study group is presented in Table 14 of this review.

The investigational products were supplied by the applicant and they were:

- The bivalent rLP2086 vaccine - a 0.5-mL dose formulated to contain 60 μg (120 μg total) of purified subfamily A and a purified subfamily B rLP2086 proteins, --------(b)(4)-------polysorbate 80, and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0
- Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose.

6.2.6 Sites and centers

Study B1971012 was undertaken by Wyeth, a Pfizer company, and conducted at 60 sites in Czech Republic, Denmark, Finland, Germany, Poland, Spain, and Sweden. One additional study center (site 1019, located in Spain) received the investigational product but did not enroll any subjects.

6.2.7 Surveillance/Monitoring

The study was conducted by investigators contracted by and under the direction of the applicant. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of the investigational product, and for ensuring accurate completion of the CRFs and data collection tools (DCTs) supplied by

the applicant. Timo Vesikari, MD, Director of Vaccine Research Center Clinics (University of Tampere, Finland) was responsible for coordination of investigators.

The final protocol, all amendments, and informed consent document (ICD) were reviewed and approved by the institutional review board(s) (IRBs) and/or independent ethics committee(s) (IECs) for each of the investigational center participating in the study.

According to the applicant, the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All local regulatory requirements, in particular those affording greater safety protections to trial participants, were followed.

6.2.8 Endpoints and Criteria for Study Success

For assessment of the immunogenicity response to the bivalent rLP2086 vaccine, functional antibodies were evaluated using 4 primary MnB test strains. The four primary MnB test strains expressing LP2086 subfamily A and B variants were PMB80 [A22], PMB2001 [A56], PMB2707 [B44], and PMB2948 [B24].

Immunogenicity endpoints were:

- ✓ Titers at baseline and 1 month after the second and the third vaccinations
- ✓ Four-fold response.

Immunogenicity parameters were:

- ✓ hSBA geometric mean titers (GMT) for each of the 4 primary strains at each blood sampling time point
- ✓ Proportions of subjects with hSBA titer ≥ LLOQ for each of the 4 primary strains at each blood sampling time point
- ✓ Proportions of subjects with hSBA titers ≥ 1:4, ≥ 1:8, ≥ 1:16, ≥ 1:32, ≥ 1:64 at each blood sampling time point.

Definition of the endpoint related to the main immunogenicity objective can be found in Section 6.1.8 of this review.

6.2.9 Statistical Considerations and Statistical Analysis Plan

The endpoints related to the first and secondary co-primary objectives were the proportions of subjects in Group 1 and Group 2 with hSBA titer ≥ LLOQ, for each of the 4 primary strains, measured 1 month after the third vaccination with the bivalent rLP2086 vaccine.

Primary immunogenicity hypotheses

The formal hypotheses for study Group 1 and 2 are:

H_0: $p_{A56} \leq 50\%$, or $p_{A22} \leq 50\%$, or $p_{B24} \leq 50\%$ or $p_{B44} \leq 50\%$

H_a: $p_{A56} > 50\%$ and $p_{A22} > 50\%$ and $p_{B24} > 50\%$ and $p_{B44} > 50\%$,

where p_{A56}, p_{A22}, p_{B24}, and p_{B44}, defined as the response rates, are the proportions of subjects with hSBA titer ≥ LLOQ about thirty days after the third vaccination, for the 4 primary test strains and for a given group (Group 1 or 2).

The hypothesis test was 1-sided, with alpha 0.0125 for both co-primary objectives. There were 4 strains to be tested for co-primary endpoints within each co-primary objective. In order to declare success within each co-primary objective, the null hypotheses have to be rejected for all 4 strains.

As per the protocol, when the primary objective is not achieved, then all analyses related to the first secondary objective would be presented but no inferences based on these analyses would be made. All other immunogenicity analyses as well as safety data were summarized descriptively.

Reviewer's comments

(1) Per protocol, LLOQ for four strains was defined as 1:8. However, after the primary analysis was completed, the applicant was informed by CBER that LLOQ should be 1:16 for PMB80 [A22]. The statistical reviewer performed analyses and concentrated on the results received under assumption that LLOQ for PM80 [A22] was 1:16.

(2) The main objective of Phase 2 trial B1971012 was to enhance knowledge about the immune responses to the bivalent rLP2086 vaccine for 4 primary test strains. As the immune responses for primary test strains were not fully known at the beginning of the trial, the thresholds used in the immunogenicity hypotheses were defined in the protocol at low levels (50%). The statistical reviewer defers to others members of the review team regarding whether these thresholds represent adequate measurements for immune responses.

(3) Assessment of the immune response to the bivalent rLP2086 vaccine could be drawn only based on the results received from performing statistical analysis on data generated by the B1971012 clinical trial (Groups 1 and 2) regarding the main immunogenicity exploratory endpoints.

6.2.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects were balanced across the five vaccination study groups. Gender ratios were similar across the vaccine groups. Males constituted about 50% of subjects. The majority of subjects were white (99%). The older age group (14 to < 19 years old) constituted 63.3% of subjects. The mean age (± SD) at the first vaccination was 14.4 (±2.20) years, while the age range was 11 to 18 years.

Disposition of subjects

A total of 1714 subjects were enrolled in this study and included in the safety analyses. Of the 1714 subjects, 1 subject was not randomized. Almost all the remaining randomized subjects were included into the Intent-to-treat (ITT) population. A summary of the randomized subjects' disposition is presented in Table 18.

Table 18: Disposition of Subjects (Vaccine Groups as Randomized)

Disposition of Subjects	**Group 1** Schedule 0,1,6 n(%)	**Group 2** Schedule 0,2,6 n(%)	**Group 3** Schedule 0,6 n(%)	**Group 4** Schedule 0,2 n(%)	**Group 5** Schedule 2,6 n(%)
Randomized	427	430	427	286	143
Withdrawal during vaccination phase - No longer wiling to participate in study	19 (4.4)	17 (4.0)	14 (3.3)	13 (4.5)	10 (7.0)
Withdrawal during vaccination phase - Protocol violation	7 (1.6)	5 (1.2)	8 (1.9)	1 (0.3)	1 (0.7)
Withdrawal during vaccination phase - Withdrew consent	3 (0.7)	4 (0.9)	7 (1.6)	3 (1.0)	4 (2.8)
Withdrawal during vaccination phase - Adverse event	6 (1.4)	4 (0.9)	5 ((1.2)	4 (1.4)	0
Withdrawal during vaccination phase - Protocol violation	3 (0.7)	1 (0.2)	2 (0.5)	0	1 (0.7)
Withdrawal during vaccination phase - Other	4 (0.9)	4 (0.9)	4 (0.9)	2 (0.7)	3 (2.1)
Study Completed	**385 (90.2)**	**395 (91.9)**	**386 (90.4)**	**261 (91.3)**	**123 (86.0)**

Source: Statistical reviewer's table based on the CSR, page 58, Table 9

Of the 1713 randomized subjects, 1550 (90.5%) completed the study, 159 (9.3%) withdrew during the vaccination phase, and 1645 (96.0%) completed the 6-month follow-up telephone call. The 6-month follow-up telephone calls were attempted for all subjects who had received at least 1 study vaccination, including subjects who withdrew during the vaccination phase, unless they had withdrawn consent.

Protocol deviations

As per the applicant's report, protocol deviations were identified by the site monitors and were documented in the designated clinical trial management system. At the end of the

study, protocol deviations were also identified from the clinical trial database. Protocol deviations were classified as major or minor. Major deviation was defined as one that could have a significant impact on the subject's immunogenicity results.

A total of 1711 subjects (99.9% of 1713 randomized subjects) were included in the mITT (modified intent-to-treat) population. Of the 2 subjects (0.1%) excluded from the mITT population, 1 was in Group 1 and 1 was in Group 3. Subjects were excluded for not having at least 1 valid and determinate assay result. Because of the pause that took place during the B1791012 study course (see 6.2.1 of this review), the study schedules were not followed for some subjects. For example, some subjects did not receive their vaccinations at the pre-specified Visits 2 and 3. The main safety analysis was performed taking into account injection administered groups not randomized groups.

6.2.11 Immunogenicity Analyses

Immunogenicity Evaluable Population

Due to the study pause, for the purpose of the immunogenicity analyses, four immunogenicity populations were established:

- Evaluable immunogenicity population
- Per-schedule evaluable immunogenicity population
- Per-schedule immunogenicity population, and
- Out-of-schedule subset population.

Evaluable immunogenicity population consisted of subjects who: (1) were eligible and randomized, (2) received all doses of bivalent rLP2086 at per randomization group scheduled visits, (3) had the pre-vaccination blood draw prior to the first dose of bivalent rLP2086 and had the (1-Month) blood draw 28 to 42 days after the last bivalent rLP2086 vaccination, (4) had valid and determinate assay results for the proposed analyses, (5) had received no prohibited vaccine or treatment, and (6) had no other major protocol violations as determined by the applicant's global medical monitor.

Per-Schedule Evaluable Immunogenicity Population, subset of the evaluable immunogenicity population, consisted of subjects who received the bivalent rLP2086 vaccine "as randomized and scheduled."

Per-Schedule Immunogenicity Population consisted of subjects who received all doses of bivalent rLP2086 according to the protocol-specified time windows, regardless of the randomization group assignment. An immunogenicity analysis was performed for this population regardless of the randomization group assignment. A total of 892 subjects (52.1%) were included in the per-schedule immunogenicity population.

Out-of-Schedule Subset Population consisted of all subjects who were included in the mITT (modified intend-to-treat) population, but not included in the per-schedule evaluable immunogenicity population.

Numbers of subjects included in different immunogenicity populations are summarized by group in Table 19.

Table 19: Immunogenicity Populations

Populations	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	Group 4 n(%)	Group 5 n(%)
Randomized	427 (100%)	430 (100%)	427 (100%)	286 (100%)	143 (100%)
mITT	426 (99.8)	430 (100)	426 (99.8)	286 (100)	143 (100)
Evaluable immunogenicity population	365 (85.5)	360 (83.7)	371 (86.9)	241 (84.3)	113 (79.0)
Per-schedule evaluable immunogenicity population	**193 (45.2)**	**165 (38.4)**	**209 (48.9)**	**173 (60.5)**	**82 (57.3)**
Per-schedule immunogenicity population	202 (47.3)	170 (39.5)	249 (58.3)	182 (63.6)	89 (57.3)
Out-of-schedule subset population	233 (54.6)	265 (61.6)	217 (50.8)	113 (39.5)	61 (42.7)

Source: Reviewer's table based on the CSR, page 70

As per Table 19, a total of 1711 subjects (99.9% of 1713 subjects randomized) were included in the mITT population. But only 822 subjects (47.99%) were included in the per-schedule evaluable immunogenicity population. Of these, 193 (45.2%) were in Group 1, 165 (38.4%) in Group 2, 209 (48.9%) in Group 3, 173 (60.5%) in Group 4, and 82 (57.3%) in Group 5.

6.2.11.1 Analyses of Primary Endpoint(s)

Reviewer's comments

The per-schedule evaluable immunogenicity population was the primary population used for the assessments of the immune responses to three doses of the bivalent rLP2086 vaccine. Subjects were included in the per-schedule evaluable immunogenicity population if the bivalent rLP2086 vaccine was administered "as randomized and scheduled." Subjects were excluded from the per-schedule evaluable immunogenicity population if they were not included in the evaluable immunogenicity population and they did not receive all doses of the bivalent rLP2086 vaccine according to the protocol-specified time windows.

Primary immunogenicity hypotheses

Numbers (%) of subjects with hSBA titer ≥ LLOQ one month after Dose 3 of the bivalent rLP2086 vaccine are summarized in Table 20.

Table 20: Numbers (%) of Subjects with hSBA Titer ≥LLOQ One Month after the Third Dose of the Bivalent rLP2086 Vaccine – Per-schedule Evaluable Immunogenicity Population

Strain	Group 1 Number of Subjects	Group 1 # of subjects ≥LLOQ	Group1 97.5% CI	Group 2 Number of Subjects	Group 2 # of subjects ≥LLOQ	Group2 97.5% CI
PMB80 [A22]	189	174 (92%)	(87, 96)	165	161 (98%)	(93, 100)
PMB2001 [A56]	193	192 (100%)	(97, 100)	165	162 (98%)	(94, 100)
PMB2948 [B24]	187	162 (87%)	(80, 92)	163	148 (91%)	(84, 95)
PMB2707 [B44]	188	165 (88%)	(81, 93)	161	135 (84%)	(76, 90)

Source: Based on the applicant's Table 16, CSR, page 76

Table 20 demonstrates that the lower limits of the 97.5% CIs of the estimated proportions of subjects achieving an hSBA titer ≥ 1:8 after 3 doses of the bivalent rLP2086 vaccine for all strains (PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44]) and Groups 1 (0-, 1-, and 6-month schedule) and 2 (0-, 2-, and 6-month schedule) were greater than 50%. Therefore, the two null co-primary hypotheses can be rejected.

To demonstrate that the study pause did not have impact on the results for the two co-primary hypotheses, the applicant performed analyses showing that results from testing these hypotheses on the per-schedule evaluable, evaluable, and per-schedule immunogenicity populations were similar.

6.2.11.2 Analyses Related to Exploratory Endpoints

The main immunogenicity objective was to assess immunogenicity response to the bivalent rLP2086 vaccine using parameters related to 5 co-primary endpoints that were defined as follows:

(1) to (4) For each of four primary MnB test strains (A22, A56, B24, and B44), proportion of subjects in Group 2 achieving at least 4-fold increase of hSBA from baseline to 1 month after the third vaccination.

(5) Proportion of subjects in Group 2 achieving the composite hSBA response, i.e., achieving hSBA titer ≥ LLOQ for all 4 primary MnB test strains combined, one month after the third vaccination.

Detailed information on this objective can be found in Sections 5.3 and 6.1.11.3 of this review.

Results of the statistical analysis for the main immunogenicity objective, i.e., for proportions of subjects achieving at least 4-fold hSBA titer rise separately for each of the 4 primary MnB test strains and for the proportion of subjects achieving the composite response for the per-schedule evaluable immunogenicity population are presented in Table 21. The main immunogenicity objective was evaluated only for Groups 1(0-, 1-, and 6-month schedule) and 2 (0-, 2-, and 6-month schedule).

Table 21: Results for the Main Immunogenicity Objective after the 3rd Vaccination for the Per-schedule Evaluable Immunogenicity Population

For Group 2 (0-, 2- and 6-month schedule)

Variables	Strain/Variant	# of subjects with valid hSBA	Estimation of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	162	87.7	(81.6, 92.3)
hSBA Titer 4-fold rise	PMB2001 [A56]	160	93.8	(88.8, 97.0)
hSBA Titer 4-fold rise	PMB2948 [B24]	161	78.3	(71.1, 84.4)
hSBA Titer 4-fold rise	PMB2707 [B44]	159	78.6	(71.4, 84.7)
Composite hSBA response		159	81.8	(74.9, 87.4)

For Group 1 (0-, 1- and 6-month schedule)

Variables	Strain/Variant	# of subjects with valid hSBA	Estimation of endpoint (%)	95% CI
hSBA Titer 4-fold rise	PMB80 [A22]	183	77.6	(70.9, 83.4)
hSBA Titer 4-fold rise	PMB2001 [A56]	182	91.2	(86.1, 94.9)
hSBA Titer 4-fold rise	PMB2948 [B24]	185	74.1	(67.1, 80.2)
hSBA Titer 4-fold rise	PMB2707 [B44]	188	80.9	(75.5, 86.2)
Composite hSBA response		178	83.9	(73.7, 85.9)

Source: The reviewer's table based on the applicant's table, Clinical Study Report Addendum, page 86

Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

Table 21 demonstrates that the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after Dose 3 were similar for Groups 1 and 2, despite different vaccination schedules. For Group 2 (schedule 0, 2, and 6 months), the proportions were 87.7% for PMB80 [A22], 93.8% for PMB2001 [A56], 78.3% for PMB2948 [B24], and 78.6% for PMB2707 [B44], while 81.8% of subjects achieved the composite hSBA response (hSBA ≥ LLOQ for all 4 primary MnB test strains combined). Additionally, as per Table 21, for four co-primary endpoints used for the main immunogenicity exploratory objective and for Group 2, all 95% lower confidence limits exceeded the thresholds (see section 6.1.11.3). The composite hSBA response (hSBA ≥ LLOQ for all 4 primary MnB test strains combined) missed marginally the threshold. However, the 95% lower confidence limit for the composite hSBA response endpoint calculated based on the per-schedule (as randomized) evaluable immunogenicity population exceeded the threshold > 75%.

6.2.12 Subgroup Analyses

According to the applicant's subgroup analyses by gender for the evaluable immunogenicity population, proportions of subjects achieving hSBA titers ≥ 1:8 were similar for both genders.

Based on the subgroup analysis by age stratum, the ≥ 11- to < 14-year-old cohort tended to have lower proportion of subjects with hSBA titers ≥ 1:8 at baseline and slightly higher responses after the third dose than subjects in the ≥ 14- to <1 9-year-old cohort. It can be concluded from Tables 22 and 23 that age stratum may have an influence on the immunogenicity responses to three doses of the bivalent rLP2086 vaccine.

Table 22: Proportions of Subjects Achieving ≥ 4-fold Rise and the Composite Response for Age Stratum 11 to < 14 years, Group 2 (0, 2, 6 months), and Evaluable Immunogenicity Population

A. Proportions of Subjects Achieving ≥ 4-fold Rise

Strain	Number of Subjects	# of subjects with ≥ 4-fold rise	Estimation of endpoint	95% CI
PMB80 [A22]	128	116	90.60%	(84, 95)
PMB2001 [A56]	125	120	96.00%	(91, 99)
PMB2948 [B24]	131	107	81.70%	(74, 88)
PMB2707 [B44]	127	108	85.00%	(78, 91)

B. Composite hSBA Response (hSBA titer ⩾ LLOQ for All 4 Primary Strains)

Number of Subjects	# of subjects with ≥ LLOQ for all strains	Estimation of endpoint	95% CI
126	105	83.30%	(76, 89)

Source: Clinical Study Report Addendum, pages 143-145

Table 23: Proportions of Subjects Achieving ≥ 4-fold Rise and the Composite Response for Age Stratum 14 to < 19 years, Group 2 (0, 2, 6 months), and Evaluable Immunogenicity Population

A. Proportions of Subjects Achieving ≥ 4-fold Rise

Strain	Number of Subjects	# of subjects with ≥ 4-fold rise	Estimation of endpoint	95% CI
PMB80 [A22]	221`	177	80.10%	(74, 85)
PMB2001 [A56]	222	207	93.20%	(89, 96)
PMB2948 [B24]	219	157	71.70%	(65, 78)
PMB2707 [B44]	222	177	80.00%	(74, 85)

B. Composite hSBA Response (hSBA titer ⩾ LLOQ for All 4 Primary Strains)

Number of Subjects	# of subjects with ≥ LLOQ for all strains	Estimation of endpoint	95% CI
219	177	80.80%	(75, 86)

Source: Clinical Study Report Addendum, pages 146-147

For the evaluable immunogenicity population, Group 2 (0, 2, and 6 months), and 5 co-primary endpoints used for the main objective, it can be concluded from Tables 22 and 23 that the younger group of subjects tended to have slightly higher responses to the 3–dose vaccination.

Reviewer's comments and overall conclusions on immunogenicity results related to study B1971012

- *An unexpected serious adverse reaction (SUSAR) occurred during the B1791012 study course, and the study conduct was interrupted. The study per-protocol schedules were not followed for some subjects. For example, some subjects did not receive their vaccinations at the pre-specified Visits 2 or 3. The study was restarted after implementation of a substantial protocol amendment. Due to this interruption, some different immunogenicity populations were defined. The statistical reviewer's focus was on immunogenicity analyses performed on the per-schedule evaluable immunogenicity population for Groups 1 and 2. The per-schedule immunogenicity population consisted of only about 40% of the total study population, but the study pre-specified procedures were followed strictly for these subjects.*
- *The main objective of Phase 2 trial B1971012 was to enhance knowledge about the immune responses to the bivalent rLP2086 vaccine for 4 primary test strains. As the immune responses for primary test strains were not fully known at the beginning of the trial, the thresholds used in the immunogenicity hypotheses were defined in the protocol at low levels (50%). The statistical reviewer defers to others members of the review team regarding whether these thresholds represent adequate measurements for immune responses.*
- *Assessment of the immunogenicity response to the bivalent rLP2086 vaccine could be drawn based on the results received from performing statistical analysis only on data generated by the B1971012 clinical trial (Groups 1 and 2) regarding the main immunogenicity endpoints.*
- *To show that the study pause did not have substantial impact on the conclusion derived from the data generated by study B1971012, the applicant performed many statistical analyses utilizing four immunogenicity populations (per-schedule immunogenicity population, evaluable immunogenicity population, and per-schedule evaluable immunogenicity population as well as out-of-schedule subset population) and showed that statistical results did not depend on the population used for analysis, i.e., they were similar for different immunogenicity populations.*
- *Data generated by study B1971012 indicated that the bivalent rLP2086 vaccine elicited immunogenicity responses expressed for the four primary MnB test strains.*

6.2.13 Safety Analyses

Primary safety objective

To evaluate the safety profile of bivalent 120 µg rLP2086, as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

Safety evaluation

Local Reactions

Subjects reported pain at the injection site more frequently following administration of the bivalent rLP2086, followed by redness and swelling, and the pattern held regardless of the vaccination schedules, 0-, 1-, 6-month (Group 1) or 0-, 2-, 6-month (Group 2). For any pain, redness, and swelling, the percentages (95% CIs) of subjects reporting these were, respectively, 98.8% (97.3%, 99.6%), 30.0% (25.7%, 34.6%), and 36.9% (32.4%, 41.6%) in Group1. In Group 2, these corresponding percentages were 98.8% (97.2%, 99.6%), 30.9% (26.5%, 35.6%), and 33.8% (29.3%, 38.6%). Most local reactions were mild or moderate in severity (source: CSR, B1971012, pages 104-105).

Systemic events

Of the systemic events reported by the 120 µg rLP2086 vaccinees, headache, fatigue, and muscle pain were most common. For these respective events, the proportions (95% CI) of subjects reporting were 74.4% (70.0%, 78.5%), 78.9% (74.7%, 82.7%), and 54.7% (49.8%, 59.5%) from Group 1 subjects; and 73.2% (68.6%, 77.4%), 76.6% (72.2%, 80.6%), and 52.9% (48.0%, 57.8%) from Group 2 subjects. These results suggest overall similarity of the systemic event profiles of the rLP2086 recipients in the two groups (source: CSR, B1971012, pages 124-125).

Adverse events during vaccination phase

A summary of adverse events during the vaccination phase is provided in Table 24 for all 5 dose regimens used (Group 1, Group 2, Group 3, Group 4, and Group 5).

Table 24: Summary of Subjects Reporting at Least 1 AE during the Vaccination Phase, Safety Population

Subjects/Adverse Event Type	**Group 1** Schedule 0,1,6 n(%)	**Group 2** Schedule 0,2,6 n(%)	**Group 3** Schedule 0,6 n(%)	**Group 4** Schedule 0,2 n(%)	**Group 5** Schedule 2,6 n(%)
Number of subjects in safety population	426	414	451	277	144
Any Adverse Event	157 (36.9)	148 (35.7)	160 (35.5)	99 (35.7)	54 (37.5)
Mild Adverse Event	112 (26.3)	109 (26.3)	118 (26.2)	67 (24.2)	43 (29.9)
Moderate Adverse Event	68 (16.0)	61 (14.7)	62 (13.7)	36 (13.0)	17 (11.8)
Severe Adverse Event	10 (2.3)	10 (2.4)	4 (0.9)	8 (2.9)	0 (0.0)

Source: Clinical Study Report, page 149.

The proportion of subjects reporting at least 1 AE during the vaccination phase was 36.9% in Group 1 and 35.7% in Group 2. These proportions ranged from

35.5% to 37.5% in the remaining 3 groups, suggesting no overall variation across the 5 Groups. The AEs reported were mostly mild or moderate.

Severe AEs

Throughout the study, severe AEs were reported by 10 (2.3%) subjects from Group 1, 10 (2.4%) subjects from Group 2, 4 (0.9%) subjects from Group 3, 8 (2.9%) subjects from Group 4, and none from Group 5 (source: CSR, B1971012, Table 24, page 149). No differences in these AEs were discernible among the 5 rLP2086 regimen groups [P-value = 0.082, Fisher-Freeman-Halton's Exact test (-----(b)(4)----)].

Autoimmune conditions

The study included 5 subjects diagnosed with autoimmune conditions during the study: Crohn's disease (in Group 1 [120 µg bivalent rLP2086 using a 0, 1, 6-month schedule]), rheumatoid arthritis (in Group 2 [120 µg bivalent rLP2086 using a 0, 2, 6-month schedule]), Basedow's disease (in Group 3 [120 µg bivalent rLP2086 using a 0 and 6-month schedule]), and hypothyroidism (2 subjects in Group 4 [120 µg bivalent rLP2086 using a 0 and 2-month schedule]). All 5 conditions were considered by the applicant to be not related to study vaccination. The study reported no death (source: Summary of Clinical Safety, page 31).

Reviewer's safety conclusion

No differences were discernible with respect to severity of local reactions, systemic events, and unsolicited AEs, when the bivalent 120 µg rLP2086 was administered in 2 or 3 doses involving 5 schedules. Five autoimmune conditions were reported, but were claimed by the applicant to be unrelated to study vaccine. Overall, an imbalance of safety outcomes across the 5 groups was not discerned.

6.3 Trial #3: B1971010

Title of the study: "*A Phase 2, randomized, placebo-controlled, single-blind trial to assess the safety, tolerability, and immunogenicity of Repevax® and Bivalent rLP2086 vaccine when administered concomitantly in healthy subjects aged ≥11 to <19 years*"

Study Initiation Date: March 18, 2011 (the first subject visit)
Study Completion Date: February 19, 2013 (the last subject visit)
Final Serology Date: August 30, 2013

6.3.1 History of Study Protocol

The final study protocol dated July 22, 2010 was modified by 4 amendments and one administrative change. The four protocol amendments implemented many modifications of the study design. For example:

- Inclusion/exclusion criteria were updated.

- Exploratory immunogenicity objectives and endpoints were added.
- The definition of the study end was changed.
- Safety endpoints were updated to be consistent with Phase 3 program.

Enrollment to and vaccinations administered in the study were paused temporarily during the evaluation of a SUSAR (see Section 6.2.1) in another ongoing study (see Section 6.2.1 related to study B1971012). They were resumed at approximately the same time as study B1971012 was resumed. The study pause caused delays in some subjects' vaccination visits and the originally planned dosing schedules for some subjects were not adhered to. The study was restarted following the implementation of a substantial protocol amendment (Amendment 2), which extended the dosing visit time windows to allow subjects impacted by the delay to remain in the study.

6.3.2 Objectives

The main immunogenicity objective of study B1971010 was to demonstrate that the immune responses induced by Repevax given concomitantly (Group 1) with the bivalent rLP2086 vaccine were non-inferior to the immune responses induced by Repevax alone (Group 2) when responses were measured 1 month after Vaccination 1.

There were also some secondary immunogenicity objectives. The most important was:

- To describe the immune response to the bivalent rLP2086 vaccine, as measured by hSBA performed with 4 primary MnB test strains (2 expressing a LP2086 subfamily A protein and 2 expressing a LP2086 subfamily B protein), one month after the third vaccination with bivalent rLP2086. Serum samples from approximately 50% of subjects were hSBA tested with respect to PMB80 [A22] and PMB2948 [B24] and the other 50% of serum samples were tested with respect to PMB2001 [A56] and PMB2707 [B44].

The primary safety objective was defined as follows:

- To evaluate the safety profile of bivalent rLP2086, as measured by the proportions of subjects reporting local reactions, systemic events, and AEs.

The main immunogenicity exploratory objective related to the immune responses to the bivalent rLP2086 vaccine (see Section 5.3 of this review) could not be considered in this study, because hSBA testing for all four primary MnB strains was not performed in all study subjects.

Endpoints considered in this review for study B1971010 are discussed later in Section 6.3.8.

Detailed information on other objectives can be found in Dr. Lucia Lee's clinical review.

6.3.3 Design Overview

Study B197010 was a Phase 2, randomized, placebo-controlled, single-blind, multicenter trial in which subjects of age ≥ 11 to < 19 years were randomly assigned in a 1:1 ratio to Group 1 and Group 2. It was planned that approximately 750 subjects (on average, 22 subjects per site) would be enrolled into this clinical trial at approximately 34 sites. The study design is presented in Table 25.

Table 25: Study B1971010 Design

Group #	Month 0 Visit 1	Month 1 Visit 2	Month 2 Visit 3	Month 3 Visit 4	Month 4 Visit 5	Month 5 Visit 6	Month 12 Visit 7
Group 1	rLP2086 + Repevax® Blood draw	Blood draw	rLP2086	Blood draw	rLP2086	Blood draw	Phone contact
Group 2	Saline+Repevax® Blood draw	Blood draw	Saline	Blood draw	Saline	Blood draw	Phone contact

Source: Clinical Study Report, page 26

A total of 753 subjects were enrolled in this study and were included in the analyses performed for this study report. Of the 753 subjects, 4 were not randomized because of a site error and the remaining 749 were randomized and included in the ITT population. Of these 749 subjects, 373 subjects were in Group 1 (bivalent rLP2086 + Repevax) and 376 subjects were in Group 2 (saline + Repevax).

6.3.4 Population

At the time of enrollment (baseline), the study population consisted of 11 to 19 year-old females and males

- ✓ Who provided evidence of a personally signed and dated informed consent document (ICD) indicating that the subject and/or the legally authorized representative were informed of all pertinent aspects of the study, and
- ✓ Who were healthy as determined by medical history, physical examination, and judgment of the investigator.

6.3.5 Study Treatments or Agents Mandated by the Protocol

Vaccination plan per study group is presented in Table 21 of this review.

The investigational products were supplied by the applicant and the administered products were:

- o The bivalent rLP2086 vaccine - a 0.5-mL dose formulated to contain 60 μg (120 μg total) of purified subfamily A and purified subfamily B rLP2086 proteins, ----------(b)(4)---------- polysorbate 80, and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0

- Sterile normal saline solution for injection (0.9% sodium chloride) - a 0.5-mL dose.
- Repevax® (a diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine) – a low dose as per vaccine label.

6.3.6 Sites and Centers

Study B1971010 was conducted at 34 sites in Finland, Germany, and Poland.

6.3.7 Surveillance/Monitoring

According to the applicant, the study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of the investigational products, and for ensuring accurate completion of the CRFs and data collection tools (DCTs) supplied by the applicant. Timo Vesikari, MD, Director of Vaccine Research Center Clinics (University of Tampere, Finland) was responsible for coordination of investigators.

6.3.8 Endpoints and Criteria for Study Success

Note: The immune responses to Repevax were not considered and reviewed in this statistical review as they are not relevant to this BLA. Only assessments of the immune responses to the bivalent rLP2086 vaccine are reported in the following sections.

For evaluation of the observed immune response to the bivalent rLP2086 vaccine, functional antibodies were evaluated using 4 primary MnB test strains. The four primary MnB test strains expressing LP2086 subfamily A and B variants were PMB80 [A22], PMB2001 [A56], PMB2707 [B44], and PMB2948 [B24].

Immunogenicity endpoints considered by the reviewer were:

- ✓ Titers at baseline and 1 month after the second and the third vaccinations
- ✓ 4-fold rise

Immunogenicity parameters considered by the reviewer were:

- ✓ hSBA geometric mean titer (GMT) for each primary strain measured at each blood sampling time point
- ✓ Proportions of subjects with hSBA titer ≥ LLOQ for each primary strain measured at each blood sampling time point.

6.3.9 Statistical Considerations and Statistical Analysis Plan

The primary hypotheses and statistical decision rules related to immunogenicity of Repevax were not relevant to the objective of this BLA. Therefore, they were not considered in this review.

All immunogenicity analyses related to the bivalent rLP2086 vaccine and safety data for this study are summarized in this review descriptively.

It is important to note that the study team was provided with separate subject listings for hSBA testing on A22/B24 and on A56/B44 strains, respectively. Fifty percent of subjects from Groups 1 and 2 were tested with respect to strains PMB80 [A22] and PMB2948 [B24], while the remaining 50% subjects from Groups 1 and 2 were tested for primary strains PMB2001 [A56] and PMB2707 [B44]. All tests were performed pre-vaccination (baseline), post-Vaccination 1 and post-Vaccination 3.

6.3.10 Study Population and Disposition

Demographic characteristics

At baseline, demographic and other characteristics of the enrolled subjects, e.g., gender ratios, were balanced across the two vaccination study groups. Males constituted about 51% of the subjects. The majority of subjects were white (99%). The younger age group (11 to < 14 years old) constituted about 58% of the subjects. The median age at first vaccination was 13 years, while the age range was 11 to 18 years.

Disposition of subjects

A summary of the randomized subjects' disposition is presented in Table 26.

Table 26: Disposition of Randomized Subjects

Subject Disposition	**Group 1** rLP2086 Repevax n(%)	**Group 2** Saline Repevax n(%)
Randomized	373	376
Withdrawn	42 (11%)	29 (7.5%)
Withdrawn during vaccination phase – No longer willing to participate in study	18 (4.8)	10 (2.7)
Withdrawn during vaccination phase – Protocol violation	9 (2.4)	7(1.9)
Withdrawn during vaccination phase – Withdrew consent	3 (0.7)	4 (0.9)
Withdrawn during vaccination phase – Adverse event	8 (2.1)	0 (0.0)
Lost to follow-up	4 (1.1)	5 (1.3)
Study Completed	**330 (88.5)**	**347 (92.3)**

Source: The reviewer's table based on the applicant's table, CSR, page 52

Number of subjects who were withdrawn from the study during the vaccination phase was higher for Group 1 (41 subjects (11%)) than for Group 2 (28 subjects (7.4%)).

Of the 749 randomized subjects (4 subjects were vaccinated but not randomized), 677 subjects received at least one study vaccine, did not prematurely discontinue the study, and provided safety information at the scheduled follow-up telephone call.

A total of 748 subjects (99.9% of 753 enrolled subjects) were included in the mITT (modified intent-to-treat) population.

All 753 subjects enrolled in this study were included in the safety analyses.

Protocol deviations

Because of the study pause and the related protocol amendment, the vaccination windows were changed. Only 59.2% and 57.6% of randomized subjects in the bivalent rLP2086 + Repevax group and 64.6% and 61.7% of randomized subjects in the Saline + Repevax group followed the original protocol-specified visit window requirement for the Vaccination 2 and Vaccination 3 visits, respectively. A total of 31.4% and 29.2% of randomized subjects in Group 1 and 30.1% and 28.5% of randomized subjects in Group 2 followed the extended visit window requirement (Amendment 2) for the Vaccination 2 and Vaccination 3 visits, respectively.

Per each blood draw visit, there were about 10% of subjects who did not follow the protocol-specified visit window requirement of 1 month after vaccination.

6.3.11 Immunogenicity Analyses

Immunogenicity Evaluable Population

Immunogenicity populations considered in this review are presented in Table 27.

Table 27: Immunogenicity Populations

Population	**Group 1** # of subjects(%)	**Group 2** # of subjects (%)
Randomized	373	376
mITT	372 (99.7)	376 (100)
Post-vaccination 3 evaluable immunogenicity population	307 (82.3)	330 (87.8)

Source: The reviewer's table based on the applicant's table, CSR, pages 63

The applicant defined the post-Vaccination 3 evaluable immunogenicity population for the purpose of analyses specifically related to vaccination with the bivalent rLP2086.

Post-Vaccination 3 evaluable immunogenicity population consisted of subjects who: (1) were eligible and randomized, (2) received all investigational products at Visit 1, Visit 3, and Visit 5 as per study schedule, (3) had the pre-vaccination blood draw prior to the first dose of bivalent rLP2086 and had the blood draw 28 to 42 days after the last vaccination with bivalent rLP2086, (4) had valid and determinate assay results for the proposed analyses, (5) had received no prohibited vaccine or treatment, and (6) had no other major protocol violations as determined by the clinicians.

Modified Intent-To-Treat (mITT) population consisted of all subjects who: (1) were eligible and randomized, (2) had at least 1 valid and determinate assay result related to a proposed analysis.

A total of 637 (85.0% of 749) subjects (307 in Group 1 and 330 in Group 2) were included in the post-Vaccination 3 evaluable immunogenicity population.

6.3.11.1 Descriptive Analyses of Immunogenicity Endpoint(s)

Two types of analyses, namely, related to:

(1) proportion of subjects with an hSBA titer ≥ LLOQ, and
(2) proportion of subjects with ≥ 4-fold rise

are considered in this review.

The numbers (%) of subjects included in the post-Vaccination 3 evaluable immunogenicity population who had an hSBA titer ≥ LLOQ for the primary MnB test strains are presented in Table 28. Please note that the LLOQ for PMB80 [A22] strain was hSBA titer 1:16, while the LLOQ for all other MnB test strains was hSBA titer 1:8.

Table 28: Numbers (%) of Subjects with hSBA Titer ≥ LLOQ, Post-Vaccination 3 Evaluable Immunogenicity Population

Strain	Group 1 Number of with valid hSBA titers	Group 1 # of subjects with observed titer ≥LLOQ	Group1 95% CI
PMB80 [A22]	158	151 (96%)	(91, 98)
PMB2001 [A56]	148	148 (100%)	(97, 100)
PMB2948 [B24]	157	152 (97%)	(93, 99)
PMB2707 [B44]	146	119 (82%)	(74, 87)

Source: The reviewer's table based on the applicant's table, CSR, page 76

The proportions of subjects achieving hSBA titer ≥ LLOQ at 1 month after Vaccination 3 were 95.6%, 100%, 96.8%, and 81.5% for strains PMB80[A22], PMB2001[A56], PMB2948[B24], and PMB2707[B44], respectively.

Numbers (%) of subjects achieving at least 4-fold rise in hSBA titer at 1 month after Vaccination 3 (Visit 6) for the 4 primary MnB test strains are presented in Table 29.

Table 29: Numbers (%) of Subjects Achieving ≥4-Fold Rise in hSBA Titer, Post-Vaccination 3 Evaluable Immunogenicity Population

Strain/Variant	Group 1 # of subjects with valid hSBA at both baseline and Visit 6	Group 1 # of subjects achieving ≥ 4-fold rise in hSBA titer	95% CI
PMB80 [A22]	153	134 (87.6%)	(81, 92)
PMB2001 [A56]	136	126 (92.6%)	(87, 96)
PMB2948 [B24]	156	126 (80.8%)	(74, 87)
PMB2707 [B44]	143	111 (77.6%)	(70, 84)

Source: The reviewer's table based on the applicant's table, CSR Addendum, page 6

As shown in Table 29, 87.6%, 92.6%, 80.8%, and 77.6% of the subjects from Group 1 and the post-Vaccination 3 evaluable immunogenicity population achieved ≥ 4-fold rise in hSBA titer for PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44] strains, respectively. As per the applicant, the proportions of subjects achieving 4-fold rise in hSBA titer from baseline to one month after Dose 3 were similar for the post-Vaccination 3 evaluable immunogenicity and mITT populations.

6.3.12 Subgroup Analyses

According to the applicant, no apparent differences were detected in the subgroup analyses of the proportions of subjects with hSBA titers ≥ LLOQ performed by age stratum (11-14, > 14 -18), sex, race, and country.

Reviewer's comments and overall conclusions on immunogenicity results related to study B1971010

Data generated by study B1971010 indicated that the bivalent rLP2086 vaccine elicited measurable immune responses expressed for four primary MnB test strains. However, results of evaluations of the immune responses after three doses of the bivalent rLP2086 vaccine should be interpreted in light of the following considerations:

- *Immune responses to vaccination with the bivalent rLP2086 vaccine were not tested and evaluated in the same subjects for all four primary MnB test strains. Fifty percent of the subjects were tested for hSBA titers against A22/B24 variants and the remaining 50% of the subjects were tested for titers against A56/B44 variants.*
- *The first dose of the bivalent rLP2086 vaccine was given concomitantly with Repevax vaccine.*
- *Evaluations of immune responses to four primary MnB test strains are exploratory in nature.*

6.3.13 Safety Analyses

Primary safety objective

To evaluate the safety profile of bivalent rLP2086 as measured by the incidence rates of local reactions, systemic events, and AEs.

Safety evaluation

Local reactions

The subjects reported pain at the injection site more frequently after administration of the bivalent rLP2086 vaccine, followed subsequently by redness and swelling. For any pain, redness, and swelling, the percentages (95% CIs) of subjects reporting these events were, respectively, 98.1% (96.2%, 99.2%), 30.0% (25.4%, 35.0%), and 33.0% (28.5%, 38.3%) in Group 1, and 64.8% (59.8%, 69.6%), 5.0% (3.1%, 7.7%), and 8.2% (5.6% , 11.4%) in Group 2. Most local reactions were mild or moderate in severity. Overall, 98.4% (96.5%, 99.4%) of subjects in Group 1 receiving rLP2086 reported local reactions of any type, compared to 65.9% (60.9%, 70.6%) in Group 2 receiving Saline (CSR, B1971010, page 91-92).

Systemic events

Of the systemic events reported by the rLP2086 vaccinees, headache, fatigue, and muscle pain were most common. For these events, the overall proportions (95% CI) of subjects reporting were, respectively, 83.9% (79.8%, 87.5%), 85.0% (81.0%, 88.5%), and 60.9% (55.7%, 65.8%) from Group 1 subjects; and 74.3% (69.6%, 78.7%), 79.6% (75.2%, 83.6%), and 52.4% (47.2%, 57.5%) from Group 2 subjects (CSR, B1971010, page 97-102). There appeared to be an overall higher incidence of headache, fatigue, and muscle pain in Group 1 subjects compared to Group 2.

Adverse events during vaccination phase

Of 374 subjects, 37.4% (32.5%, 42.6%) reported at least 1 AE during the vaccination phase in Group 1, compared to 40.2% (35.2%, 45.3%) of 378 subjects in Group 2. Despite this overall similarity of proportions of subjects with at least 1 AE between the two groups, the proportions with at least 1 severe AE were 2.7% (1.3%, 4.9%) (n=10) in Group 1 and 0.5% (0.1%, 1.9%) (n=2) in Group 2 (CSR, B1971010, page 118) suggesting a higher proportion of subjects with severe AEs in Group1. Severe AEs were mostly in the category of infections and infestations (CSR, B1971010, pages 107-110, 117-118).

SAEs

Overall, a total of 15 subjects reported serious AEs during the vaccination phase, with 11 (2.9%) (95% CI: (1.5%, 5.2%)) subjects being from Group 1, and 4 (1.1%) (95% CI: (0.3%, 2.7%)) subjects from Group 2 (source: CSR, B1971010, page 127). To state

briefly, the SAEs reported by the 11 subjects in Group 1 included idiopathic thrombocytopenic purpura, vertigo positional, arthritis infective, cellulitis, gastroenteritis, sinusitis, tonsillitis, road traffic accident, headache, hydrocephalus, and depression. Those reported by the 4 subjects in Group 2 included appendicitis, peritonsillar abscess, hip fracture, joint dislocation, syncope, drug abuse, and ruptured ovarian cyst. The SAEs were determined by the investigator to be not related to the investigational product. A death due to traffic accident was reported in the study.

During the study, 4 subjects were diagnosed with autoimmune conditions, all in Group 1 receiving the investigational vaccine. The conditions were considered to be not related to rLP2096 by the investigator, with some described as pre-existing cases based on baseline serum.

Reviewer's safety conclusions

The study shows that an overall higher proportion of subjects vaccinated with rLP2086 (Group 1) experienced local reactions compared to those who received Saline (Group 2). Most local reactions were mild or moderate in severity, with pain at injection site reported most frequently.

The study suggests a tendency for overall higher incidence of headache, fatigue, and muscle pain in Group 1 compared to Group 2, but statistical significance was not asserted.

The study reported a higher rate (2.7%) of severe AEs in Group 1, and these were mostly in the category of infections and infestations.

The reported SAEs and autoimmune conditions in 4 subjects were claimed to be not related to the investigational vaccine by the investigator. A death occurred due to a traffic accident.

In general, an overall imbalance in safety between the rLP2086 vaccinees and Control subjects could not be discerned.

6.4 Supportive Studies

General information

Four supportive studies B1971003 (Phase 1/2), B1971004 (Phase 1), B1971005 (Phase 2), and B1971042 (Phase 2) were included in BLA 125549.0. Overall, 657 subjects were vaccinated in these 4 supportive studies, including 524 with bivalent rLP2086 and 133 with control. Of the 524 subjects vaccinated with the bivalent rLP2086, 283 received at least 1 dose of 120 μg of bivalent rLP2086.

There were 288 (43.8%) male and 369 (56.2%) female subjects between 11 and 62 years of age (mean = 17.0 years). The majority of the subjects were white (n=624, 95.0%) followed by black (n=16, 2.4%), other race (n=9, 1.4%), and Asian (n=8, 1.2%).

Note: Studies B1971003, B1971004, and B1971005 were conducted when the applicant's final agreement with CBER on the primary MnB test strains and immunogenicity endpoints was not yet reached.

6.4.1 Study B1971003

Title: *"An open-label safety and blood collection study in MnB rLP2086 vaccinated healthy adult volunteers for immunological assay development"*

Objectives

- ✓ The primary objective of this study was to obtain large blood volumes from volunteer donors that were vaccinated with 120 µg of Meningococcal serogroup B (MnB) recombinant lipoprotein 2086 (rLP2086) vaccine, for use in serological assay development.
- ✓ The safety objective of this study was to assess the safety and tolerability of 120 µg of MnB rLP2086 in healthy adults aged 18 to 40 years.
- ✓ An exploratory objective of this study was to assess the immunogenicity of 120 µg of rLP2086 vaccine, as measured by serum bactericidal assay (SBA) and/or levels of antibody specific to rLP2086 antigens.

Study design

Study B1971003 was a Phase 1/2 multicenter, single-arm, uncontrolled, open-label safety and assay development study. A total of 60 healthy Australian adults aged 18 to 40 years were enrolled in the study and received 120 µg rLP2086 vaccine on the 0-, 1-, 6-month schedule.

Whites constituted 93.3% of the subjects, females 73.3%, non-Hispanic (100%), and the mean ± standard deviation age was 28.6 ± 6.74 years. About 92% of the subjects received all 3 doses of 120 µg of the bivalent rLP2086.

Immunogenicity conclusions

- ✓ Most subjects did not have measurable SBA activity before their first dose of vaccine.
- ✓ Responses related to strain PMB1745 [A05], as measured by the proportion of subjects with SBA titers ≥ 1:4, were 74.5% after 2 doses and approximately 94% after 3 doses.

- ✓ Responses related to strain PMB17 [B02], as measured by the proportion of subjects with SBA titers ≥ 1:4, were 69.6% after 2 doses and approximately 94% after 3 doses.
- ✓ More than 85% of the subjects achieved a post-dose 3 SBA titer of ≥ 1:32 for both strains tested.

Reviewer's immunogenicity comments

Results from the immunogenicity analyses performed in study B1971003 revealed that the rLP2086 vaccine elicited immune responses after 2 and 3 doses.

Safety results

Pain at injection site was the most (98.3%) commonly reported local reaction by subjects within 7 days after any dose. Most local reactions were mild and no subject reported severe pain. Of the systemic events within 7 days of any dose, fatigue (71.7%) and headache (75.0%) were most frequently reported, followed by muscle pain (53.3%). These too were mild or moderate in clinical intensity. No severe systemic events were reported post Dose 1 or post Dose 2, although one subject reported 4 severe systemic events post Dose 3 (B1971003 Synopsis, page 9).

Adverse events

Overall, 46 (76.7%) subjects reported AEs. AEs were most frequently observed in the categories of infections and infestations (n = 24, 40.0%) and nervous system disorders (n = 7, 11.7%). Upper respiratory tract infection (31.7%), headache (10.0%), and gastroenteritis (6.7%) were the most reported individual AEs.

Six (10%) subjects reported severe AEs, including suicide attempts by one subject, during the vaccination phase. No subject died during the study. Two (2) subjects reported autoimmune conditions (one case with psoriasis and the other with celiac disease). Both were confirmed as pre-existing prior to enrollment.

Reviewer's safety conclusions

Pending the clinical adjudication of the two reported autoimmune cases that the applicant claimed were due to pre-existing conditions prior to enrollment, the study's most common reactogenicity events (pain at injection site, headache, fatigue, and muscle pain) were mostly mild or moderate by clinical assessment and did not suggest concern about tolerability of the 120 μg bivalent rLP2086 dose administered using a 0, 1, 6-month schedule.

6.4.2 Study B1971004

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

General information

Study B1971004-US was designed to evaluate the safety and tolerability of 60, 120, and 200 μg of rLP2086 vaccine in healthy adults aged 18 to 40 years. The clinical trial was a single-center, randomized, open-label, active- and placebo-controlled, parallel-group trial in healthy adults. Approximately 48 healthy adult subjects 18 to 40 years of age were randomized in a 1:1:1:1 ratio to receive: (1) three intramuscular (IM) injections of 60 μg, 120 μg, or 200 μg of the bivalent rLP2086 vaccine, or (2) the control regimen, i.e., Tdap vaccine (Adacel), during the first visit and then placebo during the next vaccination visits.

The initial vaccination schedule of 0, 2, 6 months was altered to 0, 2, 6 to 9 months because of a study pause. The second vaccination and the third vaccination took place approximately 2 months (51 to 70 days) after the first vaccination and approximately 4 to 7 months (106 to 238 days) after the second vaccination, respectively.

On October 22, 2009, this study was paused temporarily after a serious adverse event (SAE), that met a protocol-defined study stopping rule, was reported in study B1971005. During the B1971004 study pause, 12 subjects received Vaccination 3, but the pause delayed vaccinations of the remaining study subjects. Hence, the time window for the third vaccination schedule was updated in the protocol (Amendment 3) to 4 to 7 months after Dose 2.

The study population consisted of male and female subjects aged 18 to 40 years, with the mean age of 28.8 years and the standard deviation 6.72 years. Most subjects were white (79.2%) and female (60.4%).

Subjects were to participate in the study for approximately 8 months.

Study objectives

The study objectives were:

1. To assess the safety and tolerability of 60-, 120-, and 200-μg doses of rLP2086 vaccine
2. To assess the immunogenicity of 60-, 120-, and 200-μg doses of rLP2086 vaccine, as determined by quantitation of immunoglobulin G (IgG), subfamily A and B, titers elicited by the rLP2086 vaccine in healthy adults 18 to 40 years of age.

Disposition of subjects

Of the 189 subjects who signed ICFs, due to many laboratory abnormalities, only 48 subjects were randomized into 4 groups: 12 subjects into the 60-µg rLP2086 vaccine group, 12 subjects into the 120-µg rLP2086 vaccine group, 12 subjects into the 200-µg rLP2086 vaccine group, and 12 subjects into the control group.

Fourteen subjects (30%) withdrew from the study. One subject withdrew because of an adverse event (mild gastritis), which the investigator considered not related to the rLP2086 vaccine.

Immunogenicity evaluation

The primary immunogenicity endpoints were the rLP2086-specific IgG results. IgG responses to LP2086 subfamily A and B proteins were assessed using a ---(b)(4)--- assay. IgG titers were expressed in arbitrarily assigned ---(b)(4)--- units. Based on the immunogenicity results presented in the CSR, increases in IgG GMTs could be observed for both subfamilies A and B proteins after administration of the rLP2086 vaccine at the 60-, 120-, or 200-µg dose levels. For the treatment groups, GMTs for subfamilies A and B after Doses 2 and 3 were higher than at baseline.

Safety evaluation

A higher proportion of subjects receiving rLP2086 reported local reactions at the injection site, compared to subjects who received Adacel at Dose 1 and to subjects receiving saline at Doses 2 and 3. For systemic events, the higher frequency was seen as well among the rLP2086 vaccinees compared to the control group. Fatigue, headache, and muscle pain were most commonly reported. These events were mostly mild or moderate in severity.

The study did not encounter any death or autoimmune or neuroinflammatory AEs.

Reviewer's safety conclusions

The majority of the reactogenicity events reported were mild to moderate and did not appear to suggest a general imbalance with regard to tolerability of the bivalent rLP2086 vaccine, as used in this study.

6.4.3 Study B1971005

Title: "A randomized, single-blind, placebo-controlled, Phase 2 trial of the safety, immunogenicity, and tolerability of meningococcal serogroup B (MnB) rLP2086 vaccine at doses of 60 µg, 120 µg, and 200 µg in healthy adolescents aged 11-18 years"

General information

Clinical trial B1971005 was a randomized, single-blind, placebo-controlled trial in adolescents aged 11 to 18 years to assess safety, tolerability, and immunogenicity of the bivalent rLP2086 vaccine (doses 60 μg, 120 μg, and 200 μg) administered on the 0-, 2-, and 6-month schedule. A total of 536 subjects received rLP2086 vaccine or placebo. Of this number, 415 subjects (22, 198, and 195 in the 60 μg, 120 μg, and 200 μg groups, respectively) received at least 1 dose of the rLP2086 vaccine. The study was conducted in Australia (133 subjects), Spain (144 subjects), and Poland (172 subjects). The control regimen was normal saline.

The study has been conducted in 2 stages:

- Stage 1 was designed to assess the safety and immunogenicity of the bivalent rLP2086 vaccine and to provide a basis for the dose level selection for the next set of studies.
- Still ongoing Stage 2 of the study was designed to evaluate the duration of the meningococcal group B (MnB)-specific immune responses for up to 4 years after the third vaccination.

Stage 1 was carried out in two steps. During Step 1, small groups of subjects received 1 dose of 60, 120, or 200 μg of rLP2086 vaccine and safety of the single dose was evaluated by a project independent safety review team (PISRT) which was responsible for deciding whether "to continue dosing to the expanded cohorts consisting of the control, 120-μg, and 200-μg groups."

As of July 6th, 2010, 99 subjects were enrolled into Step 1 and 440 in "the expanded enrollment phase" (Step 2). Based on data from Stage 1, the applicant chose the 120-μg dose level for the next planned Phase 2 and 3 studies.

Some changes were introduced into the clinical trial B1971005 protocol during the study conduct, namely:

- The stopping rules for moderate systemic reactions and chills at any severity were removed
- Timing of the 3rd vaccination was broadened to 9 months. The vaccination schedule was changed to 0, 2, and 6 to 9 months.
- The time window for the immunogenicity bleeds post-dose 3 was broadened from 2 to 3 months.

Changes of vaccination time and windows for immunogenicity bleeds were caused by a study pause imposed due to a vaccination related SAE and the subsequent safety evaluation. This pause delayed visits for Vaccination 3.

Study objectives

The study objectives were:

- To select "optimal" dose of rLP2086 vaccine

- To assess safety and tolerability of 60-, 120-, and 200-µg doses of rLP2086 vaccine in healthy subjects aged 11 to 18 years
- To evaluate the immunogenicity of 60-, 120-, and 200-µg doses of rLP2086 vaccine in healthy subjects aged 11 to 18 years.

Disposition of subjects

A total of 539 subjects (99 enrolled into the sentinel cohort phase and 440 enrolled into the expanded enrollment phase) were enrolled in Stage 1 of the trial. The initial study sites were located in Australia and then trial was expanded to include additional countries (Spain and Poland). The disposition of subjects is presented in Table 30.

Table 30: Disposition of Subjects in Study B1971005

Subject Disposition	**Group 1** Control n(%)	**Group 2** 60 µg n(%)	**Group 3** 120 µg n(%)	**Group 4** 200 µg n(%)
Randomized	121	22	198	198
Vaccinated - Dose 1	121 (100.0)	22 (100.0)	198 (100.0)	195 (98.5)
Vaccinated - Dose 2	118 (97.5)	22 (100.0)	194 (98.0)	189 (95.5)
Vaccinated - Dose 3	116 (95.9)	21 (95.5)	191 (96.5)	183 (92.4)
Post dose 3 immunogenicity analysis population	**79 (65)**	**21 (95)**	**114 (58)**	**104 (53)**

Source: The reviewer's table based on the applicant tables, CSR, pages 48 and 94

It can be concluded from Table 30 that the post-dose 3 immunogenicity analysis was based on about 59% (318/539) of the study population.

Immunogenicity evaluation

Immunogenicity of the vaccine was assessed using hSBA performed with two MnB indicator test strains PMB1745 (A05 variant) and PMB17 (B02 variant), as well as with 4 primary SBA test strains: PMB3302 (A04 variant), PMB1256 (B03 variant), PMB2001 (A56 variant), and PMB2707 (B44 variant).

The LLOQs for the hSBAs were 1:9, 1:10, 1:18, 1:9, 1:12 and 1:7 for strains PMB1745, PMB17, PMB3302, PMB1256, PMB2001, and PMB2707, respectively. Titers above the LLOQ for the IgG assay and hSBAs were considered accurate and their quantified values were reported. Values below the LLOQ were set to 0.5×LLOQ for the purpose of the analysis.

A summary of post-dose 3 immunogenicity results for Group 3, based on the GMTs, is presented in Table 31.

Table 31: Meningococcal hSBA GMTs for Stage 1, Group 3, and mITT Population

Variant/Strain	Group 3 - 120 µg Number of subjects with valid hSBA titers	Group 3 - 120 µg Estimation of GMT	Group 3 - 120 µg 95% Confidence Interval
A04 (PMB3302)	108	177.4	(156.1, 201.6)
A05 (PMB1745)	114	165.0	(137.5, 197.9)
A56 (PMB2001)	114	181.5	(151.7, 217.0)
B02 (PMB17)	113	57.5	(47.5, 69.5)
B03 (PMB1256)	86	50.9	(36.8, 70.4)
B44 (PMB2707)	115	56.0	(44.2, 70.9)

Source: Clinical Study Report, page 73

GMTs after Dose 3 were generally higher than GMTs after Dose 2.
Post–dose 3 GMTs for the 60-µg, 120-µg, and 200-µg dose levels were as follows:

165.2, 177.4, and 188.6, respectively, for PMB3302 (A04 variant),
99.3, 165.0, and 167.5, respectively, for PMB1745 (A05 variant),
120.5, 181.5, and 172.0, respectively, for PMB2001 (A56 variant),
67.2, 57.5, and 58.2, respectively, for PMB17 (B02 variant),
24.9, 50.9, and 39.5), respectively, for PMB1256 (B03 variant), and
39.4, 56.0, and 58.6, respectively, for PMB2707 (B44 variant).

Reviewer's immunogenicity comments and conclusion

It appears that this study design used an adaptive method. The sponsor did not specify when and why the 60 µg group was excluded from the "expanded enrollment." However, subjects from the 60 µg group (Step 1 of Stage 1; 22 subjects enrolled into this group) received the full series of vaccinations with rLP2086 vaccine at months 0, 2, and 6 and were covered by the full follow-up.

In summary, hSBA results from Stage 1 of this study demonstrated generally greater responses with increasing dose levels, but the magnitudes of the immune responses for the 120 µg and 200 µg doses were similar. In two cases, the 120 µg dose elicited slightly higher responses than the 200 µg dose. It is unknown whether changes in the conduct of the study and the analyses to be performed, as well as the amount of missing immunogenicity outcomes, could have introduced bias into the study results.

Safety evaluation

Local reactions

Among local reactions within 7 days of any dose, pain at the injection site was commonly reported. Proportions of subjects reporting pain ranged from 68% to 89% across the rLP2086 doses and vaccinations (CSR, B1971005, page 83). In the placebo group, pain was reported by 14.8% - 16.8% of subjects across all three vaccinations. Most local reactions reported were mild or moderate in severity and had short median duration of less than 4.5 days.

Systemic events

The systemic events generally occurred with higher frequencies in the rLP2086 groups compared to the placebo subjects, with fatigue, headache, and muscle pain being most common. For these three respective event types, the 120 μg rLP2086 vs placebo comparison of rates at dose 3 were (33.3%, 16.5%), (35.4%, 24.3%), and (26.5%, 4.3%), respectively (CSR, B1971005, page 89). The majority of systemic events were mild or moderate, with a median duration of 1.0 to 6.0 days.

Adverse events during vaccination phase

The study reported 23 subjects having severe AEs among the 415 rLP2086 vaccinees, while 6 subjects out of 121 in the Control group (source: Reviewer's compilation from Table 10-7, CSR, B1971005, page 101) reported severe AEs (RR=1.12, 95% CI: (0.49, 3.32)). For 120 μg rLP2086 vaccinees, in particular, based on the comparison 8/198 vs 6/121, the RR was 0.81 (95% CI: (0.29, 2.52)), thus not suggesting risk imbalance between study groups. No subject reported a life-threatening AE.

SAEs

Nineteen subjects reported SAEs. Except for one case (anaphylaxis, which resolved), the investigator determined the SAEs to be unrelated to rLP2086.

Reviewer's safety conclusion

An imbalance of severe SAEs between the rLP2086 vaccinees and control subjects was not apparent. SAEs in general were claimed unrelated to rLP2086 by the investigator.

6.4.4 Study B1971042

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"

Primary objectives

Immunogenicity

- ✓ "To describe the immune response, as measured by serum bactericidal assay using human complement (hSBA) performed with 4 primary Neisseria meningitidis serogroup B (MnB) test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein," 1 month after the third vaccination with bivalent rLP2086.

Safety

- ✓ To describe the safety profile of bivalent rLP2086, as measured by local reactions, systemic events, AEs, SAEs, newly diagnosed chronic medical conditions, medically attended AEs, and immediate AEs.

Study design

Study B1971042 was a Phase 2, single-arm, open-label trial to assess the safety, tolerability, and immunogenicity of 120 µg of bivalent rLP2086 vaccine administered in laboratory personnel (inclusive of Pfizer staff) ≥18 to ≤ 65 years of age. The subjects received 120 µg of bivalent rLP2086 vaccine on the 0-, 2-, 6-month schedule. The number of subjects actually enrolled (N=13) was less than expected (N~70).

Subject disposition and Demography

Of the 13 subjects enrolled in this study, 7 (53.8%) completed the vaccination phase. All 13 subjects received Vaccination 1, 8 (61.5%) subjects received Vaccination 2, and 7 (53.8%) subjects received Vaccination 3.

Six subjects (46.2%) withdrew during the vaccination phase. Of these, 3 subjects no longer met eligibility criteria (upon review they met exclusion criterion of a pre-existing autoimmune condition), and according to the investigator, 2 subjects withdrew consent due to reasons unrelated to AEs and 1 subject was lost to follow-up. As per the applicant, no subjects were withdrawn from the study due to an AE.

The majority of subjects in the study were white (76.9%) and female (69.2%). The mean age was 44.4 years (range 24 to 62 years).

Immunogenicity evaluation

Of the 13 subjects enrolled in the study, only 6 (46%) were included in the evaluable immunogenicity population.

- ✓ All these 6 subjects had hSBA titers ≥ LLOQ for PMB2948 [B24] after Vaccination 1 and for PMB2001 [A56] after Vaccination 2.
- ✓ None of the subjects had an observed hSBA titer ≥ LLOQ for all 4 primary MnB test strains combined at baseline (before Vaccination 1).
- ✓ An hSBA titer fold rise ≥ 4 from baseline to 1 month after Vaccination 3 was achieved for PMB80 [A22] and PMB2001 [A56] strains by 5 subjects, for PMB2948 [B24] strain by 4 subjects, and for PMB2707 [B44] strain by 3 subjects.
- ✓ Three of 5 subjects achieved a composite hSBA response hSBA ≥ LLOQ for all 4 primary strains combined.

Reviewer's immunogenicity conclusion

Based on the immunogenicity results, subjects responded to vaccinations with increased immune response accompanying increased vaccine doses. However, it is difficult to draw a definitive conclusion from results of this study due to a small number (6) of evaluable subjects and the non-randomized study design.

Safety evaluation

All subjects who received at least 1 dose of bivalent rLP2086 were included in the safety analysis. However, please note that safety data were available for 13 subjects after vaccination 1, 8 subjects after vaccination 2, 7 subjects after vaccination 3, and for 10 subjects in the follow-up phase.

In the safety population, pain at the injection site, fatigue, and muscle pain were the most common events, and generally were of mild or moderate character. No SAEs were reported during the study. No autoimmune or neuroinflammatory conditions were reported. One subject reported a newly diagnosed chronic medical condition of gouty arthritis, but the applicant did not consider it to be an SAE flag in the clinical narrative (CSR, B1971042, page 130).

Reviewer's safety conclusion

Overall, the study revealed generally mild or moderate types of reactogenicity events, and no occurrence of autoimmune/ neuroinflamatory condition or death was encountered. Therefore, no general safety concern regarding the rLP2086 vaccine arose from this study; however, the sample size was very small.

7. Integrated Overview of Efficacy

7.1 Background

The statistical evaluation of the safety and immunogenicity of three doses of the bivalent rLP2086 vaccine administered on the 0-, 2-, and 6-month schedule was based on data collected during seven Phase 1 and Phase 2 clinical trials. An extended summary of the general information on these clinical studies is provided in Table 32 (see Section 8.1). While all studies evaluated safety and immunogenicity of the bivalent rLP2086 vaccine, some other issues such as dose selection (trial B1971005), safety and immunogenicity of other 2- and 3-dose schedules (trial B1971012), as well as concomitant use of rLP20806 with other vaccines (trials B1971010 and B1971011) were also investigated.

A total of 5604 subjects were vaccinated, of which 4576 received at least 1 injection with the investigational bivalent rLP2086 vaccine, at some dose level

and vaccination schedule. Table 34 (see Section 8.1) provides a disposition of the 4576 subjects who received at least one dose of the bivalent rLP2086 vaccine of the final formulation at any dose level and any schedule. The remaining 1028 subjects were in comparison groups and received saline alone (studies B197004, B1971005) or saline with concomitant Repevax (study B1971010) or Gardasil (study B1971011) vaccines. Use of different control regimens, despite the same saline, made the comparison across studies not straightforward.

Integrated demographic results of pooled data submitted are presented in Table 33 (see Section 8.1 of this review).

7.2 Overview of Efficacy

In BLA 125549, the applicant presented immunogenicity data from seven (B1971011, B1971012, B1971010, B1971005, B1971003, B1971004, and B1971042) Phase 1 and Phase 2 clinical trials that were carried out to demonstrate a positive benefit-risk profile of vaccination with the bivalent rLP2086 vaccine in individuals aged 10 through 25 years. The immunogenicity assessment of the three-dose regimen (on the 0-, 2-, and 6-month schedule) of the bivalent rLP2086 vaccine was based mainly on data collected in trials B1971011, B1971012, and B1971010. The foremost immunogenicity information regarding the immune responses to bivalent rLP2086 was generated by exploratory analyses related to 5 co-primary endpoints and four primary MnB test strains. Four of the co-primary endpoints were defined as at least 4-fold rise in hSBA titer from baseline to 1 month after Dose 3 of bivalent rLP2086 for each of four MnB test strains. The fifth co-primary endpoint was the composite endpoint defined as hSBA titer ≥ LLOQ for all 4 primary MnB test strains combined, 1 month after Dose 3 of bivalent rLP208 vaccine. These 5 co-primary endpoints, also being used in the ongoing Phase 3 clinical trials, were assessed in 2 Phase 2 studies, B1971011 and B1971012, while 4 of the co-primary endpoints were assessed in an additional Phase 2 study, B1971010. These three Phase 2 studies used the 120 μg dose of bivalent rLP2086 on the 0-, 2-, 6-month schedule.

Overall, 4459 subjects were randomized and planned to have hSBA tests in three Phase 2 studies B1971010, B1971011, and B1971012, which the applicant considered to be the pivotal studies. Of the 4459 subjects, 2293 received at least 1 dose of bivalent rLP2086 on the 0-, 2-, 6-month schedule and were included in the evaluable immunogenicity population. Among these 2293 subjects, a total of 1626 subjects (n=814 for vaccination group and n=812 for control group) were from study B1971011 carried out in the US.

Analyses of data generated by B1971011 and B1971012 studies for 5 co-primary endpoints showed that after the third dose, the lower limits of the 95% CIs for hSBA titers were above acceptable levels (i.e., above 80% for study B1971011) and results were consistent across these two studies. Additionally, results were comparable across studies for the immunogenicity parameters such as:

(1) Proportions of subjects achieving hSBA titer ≥ LLOQ for each of the 4 primary MnB test strains

(2) hSBA geometric mean titers (GMTs) for each of the 4 primary MnB test strains

(3) Proportions of subjects with hSBA titers ≥ 1:4, ≥ 1:8, ≥ 1:16, ≥ 1:32, ≥ 1:64, and ≥1:128 for each of the 4 primary MnB test strains.

The following remarks related to particular trials are worth noting:

Clinical trial B1971011

- ✓ The immunogenicity non-inferiority criteria for comparisons of the bivalent rLP2086 + Gardasil vaccines to saline + Gardasil vaccines and to the bivalent rLP2086 + saline vaccines were met for 2 primary MnB test strains and for HPV-6, HPV-11, and HPV-16 antigens, but the criterion for the HPV-18 antigen was not quite met. For HPV-18, the lower limit of the 2-sided 95% CI for the GMR was 0.62, i.e., slightly below the pre-specified threshold of 0.67. Therefore, the alternative primary hypotheses formally were not supported. However, the statistical reviewer defers to the medical reviewers regarding the clinical relevance of this finding.
- ✓ An analysis of 5 co-primary endpoints related to the main exploratory objective, and typical of those used in Phase 3 trials, showed that the lower limits of the 95% CIs for all 5 endpoints were greater after the third dose than the pre-defined thresholds for Group 1 (bivalent rLP2086 + Gardasil) and Group 2 (bivalent rLP2086 + saline).
- ✓ Assessments of the immune responses after three doses of the bivalent rLP2086 vaccine were performed only for 4 primary MnB test strains. Therefore, data generated by this study do not provide apparent information on the breath of protection against MnB meningococcal disease the bivalent rLP2086 vaccine might confer.
- ✓ Data generated by study B1971011 provided evidence that the bivalent rLP2086 vaccine elicited immune responses expressed for four primary MnB test strains.

Clinical trial B19712

- ✓ The main objective of Phase 2 trial B1971012 was to enhance knowledge about the immune responses to the bivalent rLP2086 vaccine for 4 primary test strains. As the immune responses for primary test strains were not fully known at the beginning of the trial, the thresholds used in the immunogenicity hypotheses were defined in the protocol at low levels (50%). The statistical reviewer defers to others members of the review team regarding whether these thresholds represent adequate measurements for immune responses.
- ✓ Trial B1971012 provided immunogenicity data for some immunization schedules and dose numbers.

- ✓ An unexpected serious adverse reaction (SUSAR) occurred during the B1791012 trial course, and the study conduct was interrupted. The study per-protocol schedules were not followed for some subjects. Due to the pause, the statistical reviewer focused on immunogenicity analyses performed on the per-schedule evaluable immunogenicity population (see definition in Section 6.2 of this review) for Groups 1 and 2. The per-schedule immunogenicity population consisted of only about 40% of the total study population, but the study pre-specified procedures were followed strictly for these subjects.
- ✓ Data generated by clinical trial B1971012 indicated that the bivalent rLP2086 vaccine elicited immune responses expressed for 4 primary MnB test strains.

Clinical trial B1971010

- ✓ The trial provided data related to concomitant vaccination with Repevax vaccine in the adolescent population. However, the concomitant hypotheses related to Repevax were not considered in this review as they were not related to the objective of this submission.
- ✓ Results of evaluations of the immune responses after three doses of the bivalent rLP2086 vaccine were based on evaluation of the 4-fold rise endpoint that was part of 5 co-primary endpoints. The results should be interpreted in light of the following considerations:
    - o Immune responses to vaccination with the bivalent rLP2086 vaccine were not tested and evaluated in the same subjects for all four primary MnB test strains. Fifty percent of the subjects were tested for hSBA titers against A22/B24 variants, and the remaining 50% of the subjects were tested for titers against A56/B44 variants.
    - o The first dose of the bivalent rLP2086 vaccine was given concomitantly with Repevax vaccine.
- ✓ Data generated by trial B1971010 indicated that the bivalent rLP2086 vaccine elicited measurable immune responses expressed for four primary MnB test strains.

The four supportive (i.e., not pivotal) studies included in the BLA were B1971003 (Phase 1/2), B1971004 (Phase 1), B1971005 (Phase 2), and B1971042 (Phase 2). These studies provided additional supporting information, for example, on immune responses in populations aged 19 years or older. A total of 657 subjects were vaccinated in these 4 supportive studies, 524 and 133 of whom received bivalent rLP2086 and control, respectively.

Different dose regimens and hSBA responses, mainly to 120 μg and 200 μg dose levels of bivalent rLP2086, were tested in study B1971005. As the immune responses and the safety profile of the 120 μg dose appeared to be optimal from the safety and immunogenicity perspectives, all subsequent studies were conducted at this dose level.

The results from the supportive studies revealed that the rLP2086 vaccine elicited immune responses after 2 and 3 doses.

7.3 Efficacy Conclusions

Data generated by 7 clinical trials and submitted in the BLA provide preliminary evidence supporting the immunogenicity of the bivalent rLP2086 vaccine administered in individuals 10 through 25 years of age. In particular, data generated by US clinical trial B1971011 provided substantial evidence, based on 5 co-primary endpoints, that the bivalent rLP2086 vaccine elicited immune responses expressed for four primary MnB test strains. Among the 7 clinical trials, multiple analyses, that utilized such parameters as proportions of subjects achieving hSBA titer ≥ LLOQ, hSBA GMTs, and proportions of subjects achieving 4-fold response for each primary MnB test strain, showed that the immunogenicity results were comparable across studies.

8. Integrated Overview of Safety

8.1 Safety Design, Data and Subject Disposition

For this BLA, the clinical safety of the investigational product, the recombinant lipoprotein 2086 vaccine (rLP2086), with proposed indication for active immunization to prevent invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroup B (MnB) in individuals aged 10 years or more, was investigated in 5604 subjects in 7 completed Phase 1 and Phase 2 clinical trials and studies. An overview of the studies used in this BLA is presented in Table 32 below.

Table 32: Completed Phase 1 and Phase 2 Studies Used in Safety Evaluation

Studies	Region	Age Group (Years)[a]	Study Size N ($n_{rLP2086}$)†	Design (doses and vaccination schedule)
B1971003*	Aus	≥18 to ≤40	60 (60)	Single-group, uncontrolled, open-label study -120 µg rLP2086 (0,1,6-month)
B1971004*	US	≥18 to ≤40	48 (36)	Randomized, open-label, active- and placebo-controlled study 60µg, 120µg, 200µg (0,2,6-month) Saline (0,2,6-month; plus Adacel [Tdap] at month 0)
B1971005*	EU/Aus	≥11 to ≤18	536 (415)	Randomized, single-blind, placebo-controlled study 60µg, 120µg, 200µg (0,2,6-month) Saline (0,2,6-month)
B1971010	EU	11-18	752 (374)	Randomized, placebo-controlled, single-blind study Group 1: 120 µg rLP2086 (0,2,6-month) + Repevax (0-month) Group 2: Saline (0,2,6-month) +Repevax (0-month)
B1971011	US	11-17	2483 (1982)	Randomized, active-controlled, observer-blinded study Group 1: 120 µg rLP2086 +Gardasil (0,2,6-month) Group 2: 120 µg rLP2086 +Saline(0,2,6-month) Group3: Saline +Gardsil (0, 2,6-month)

Studies	Region	Age Group (Years)[a]	Study Size N ($n_{rLP2086}$)†	Design (doses and vaccination schedule)
B1971012	EU	11-18	1712[b] (1696)	Randomized, placebo-controlled,[c] single-blind study Group 1: 120 µg rLP2086 (0,1,6-month) Group 2:120 µg rLP2086 (0,2,6-month) Group 3: 120 µg rLP2086 (0,6-month) Group 4: F15120 µg rLP2086 (0,2-month) Group 5: 120 µg rLP2086 (2,6-month)
B1971042	US	≥18 to ≤65	13 (13)	Single-group, uncontrolled, open-label trial 120 µg rLP2086 (0,2,6-month)
All combined	-	-	5604 (4576)	-

Abbreviations: N = number of subjects with known values; Tdap = tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine; Aus = Australia; EU = European Union; US = United States.
a. Age at enrollment. Subjects could have aged beyond the enrollment age for subsequent injections
b. Includes 16 subjects who received only saline, and who are not included in overall rLP2086 exposure
c. Saline administered to maintain the single blind; hence each study injection was controlled although the study is not a controlled study
**Subjects with autoimmune conditions were allowed to enroll. †Subjects with any rLP2086 exposure are included within braces, with the remaining 1028 subjects used as control*
Source: Summary of Clinical Safety, page 14-15; and "rLP2086 Autoimmune Case Discussion, Cases included in June 2014 BLA" Sponsor's Communication to CBER, June 2014.

A total of 5604 adolescents and adults were vaccinated: of these, 4576 subjects received at least one dose of rLP2086, and 1028 control subjects received saline alone or saline co-administered with other vaccines (Tdap, Repevax, Gardasil).

The safety analyses for the pooled safety data were performed by rLP2086 dose (60 µg, 120 µg, and 200 µg). Table 33 shows numbers of subjects receiving different rLP2086 doses and controls in the 7 studies.

Table 33: Number of Subjects Receiving Different rLP2086 Doses and Control in 7 Studies

Study	Control # of subjects	rLP2086 60 µg # of subjects	rLP2086 120 µg # of subjects	rLP2086 200 µg # of subjects	All rLP2086 # of subjects
B197004	12	12	12	12	36
B197005	121	22	198	195	415
B197010	378		374		374
B197003			60		60
B197012	16*		426 (0-,1-,6-month) 414 (0-,2-,6-month) 451(0-,6-month) 277 (0-,2-month) 128* (2†-,6-month)		1696
B197011	501		992 + 990 =1982		1982
B197042			13		13
Total	1028	34	4335	207	4576

**16 subjects who received only saline were not included in overall rLP2086 exposure, reducing the exposure to128 subjects from 144 subjects.*
Source: Summary of Clinical Safety, page 14-15, and B1971012, Clinical Study Report, Page 28.

It is evident from Table 33 that the120 µg dose was used in all seven studies, B1971003, B1971004, B1971005, B1971010, B1971011, B1971012, and B1971042, while the 60 µg and 200 µg doses were utilized in studies B1971004 and B1971005. In study B1971010, subjects received Repevax at month 0, in addition to rLP2086 at months 0, 2, 6, and in study B1971011, subjects received Gardasil (Group 1) or Saline (Group 2) in addition to rLP2086 at months 0, 2, 6.

In the text that follows, the assembly of all 5604 subjects who participated in the 7 clinical trials and studies and were included in the safety analyses will be called the pooled safety population.

Table 34 provides a disposition of the 4576 subjects who received at least one dose of the bivalent rLP2086 vaccine of the final formulation at any dose level and any schedule.

Table 34: Disposition of Vaccinated Subjects, Pooled (7 Studies) Safety Population

Subject Disposition	**rLP2086 120 µg n (%)**	**rLP2086 60 µg n (%)**	**rLP2086 200 µg n (%)**	**Total n (%)**
Vaccination - Dose 1[a]	4335 (100.00)	34 (100.00)	207 (100.00)	4576 (100.00)
Vaccination - Dose 2	4052 (93.47)	32 (94.12)	200 (96.62)	4284 (93.62)
Vaccination - Dose 3	3099 (71.49)	29 (85.29)	192 (92.75)	3320 (72.55)
Completed vaccination phase[b]	3868 (89.23)	29 (85.29)	192 (92.75)	4089 (89.36)
Withdrawn during vaccination phase	467 (10.77)	5 (14.71)	15 (7.25)	487 (10.64)
Withdrawal during vaccination - No longer willing to participate in study	186 (4.29)	0 (0.00)	0 (0.00)	186 (4.06)
Withdrawal during vaccination - Lost to follow-up	73 (1.68)	1 (2.94)	0 (0.00)	74 (1.62)
Withdrawal during vaccination - Protocol deviation	53 (1.22)	0 (0.00)	1 (0.48)	54 (1.18)
Withdrawal during vaccination - Adverse event	50 (1.15)	0 (0.00)	2 (0.97)	52 (1.14)
Withdrawal during vaccination - Other	36 (0.83)	0 (0.00)	4 (1.93)	40 (0.87)
Withdrawal during vaccination - No longer meets eligibility criteria	35 (0.81)	0 (0.00)	0 (0.00)	35 (0.76)
Withdrawal during vaccination - Withdrew consent	19 (0.44)	0 (0.00)	0 (0.00)	19 (0.42)
Withdrawal during vaccination - Subject request	3 (0.07)	3 (8.82)	1 (0.48)	7 (0.15)
Withdrawal during vaccination - Withdrawal by subject	2 (0.05)	0 (0.00)	4 (1.93)	6 (0.13)
Withdrawal during vaccination - Investigator declined further study participation	4 (0.09)	0 (0.00)	0 (0.00)	4 (0.09)
Withdrawal during vaccination - Parent/Legal guardian request	1 (0.02)	1 (2.94)	2 (0.97)	4 (0.09)
Withdrawal during vaccination - Investigator request	2 (0.05)	0 (0.00)	1 (0.48)	3 (0.07)
Withdrawal during vaccination - Withdrawal due to pregnancy	2 (0.05)	0 (0.00)	0 (0.00)	2 (0.04)
Withdrawal during vaccination -	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.02)

Subject Disposition	rLP2086 120 µg n (%)	rLP2086 60 µg n (%)	rLP2086 200 µg n (%)	Total n (%)
Subject death				
Study Completed	3820 (88.12)	29 (85.29)	191 (92.27)	4040 (88.29)
Withdrawn after vaccination phase	48 (1.11)	0 (0.00)	1 (0.48)	49 (1.07)
withdrawal after vaccination phase - Lost to follow-up	33 (0.76)	0 (0.00)	0 (0.00)	33 (0.72)
withdrawal after vaccination phase -Other	8 (0.18)	0 (0.00)	0 (0.00)	8 (0.17)
withdrawal after vaccination phase - Subject request	3 (0.07)	0 (0.00)	0 (0.00)	3 (0.07)
withdrawal after vaccination phase -Investigator request	2 (0.05)	0 (0.00)	0 (0.00)	2 (0.04)
withdrawal after vaccination phase - No longer willing to participate in study	2 (0.05)	0 (0.00)	0 (0.00)	2 (0.04)
withdrawal after vaccination phase - Adverse event	0 (0.00)	0 (0.00)	1 (0.48)	1 (0.02)
6-Month follow-up telephone contact attempt[c]	4083 (94.19)	22 (64.71)	186 (89.86)	4291 (93.77)
Completed 6-mo follow-up telephone contact	4010 (92.50)	22 (64.71)	186 (89.86)	4218 (92.18)

a. *The values in this row are used as the denominators for percentages.*
b. Defined as from the first dose of study vaccine till 1-month after dose 3. For B1971004, 1-month after dose 3 is also the end of the study visit.
c. A telephone contact was to be attempted on all subjects 6 months after their last dose, unless they withdrew consent or lost to follow up during vaccination phase. Study B1971004 was not designed to have 6-month follow-up call, and subjects were not included in the count of this row.
Source: Integrated Summary of Safety, page 23.

While these data are designated as the overall safety data in the BLA, the applicant presented the core safety data to be from subjects who received the rLP2086 vaccine in the 120µg dose using a 0-, 2-, 6-month schedule in 4 randomized, controlled, Phase 1 and Phase 2 clinical studies. These studies are B1971004, B1971005, B1971010, and B1971011; their safety data are shown in Table 37 below. The safety data from other studies, B1971003, B1971012, and B1971042, as they were open label and non-controlled, were considered by the applicant as supportive.

In this review, however, all subjects receiving at least 1 dose of rLP2086 were included in the overall safety evaluation, thus including the 1769 subjects from the uncontrolled studies (38.7% of the total vaccinated subjects). Additionally, the core studies' control subjects had differing control regimens [e.g., saline alone (B197004, B1971005), or saline with co-administration of Repevax (B1971010) or Gardasil (B1971011) vaccine] across studies, making it unclear whether these subjects in combination would be appropriate control for the above mentioned core studies. Thus, given the heterogeneity of the control regimens, this safety review compared all vaccinated subjects (whether in a controlled study or not) to all control subjects. In the following sections, an integrated analysis of safety from all 7 studies is presented, followed by a summary of the 4 controlled core safety studies, and study-specific brief analyses on safety.

The safety data were collected from the parents/guardians, adult subjects, or by the investigator via clinical interviews or physician examinations. The reactogenicity data included both local reactions and systemic events recorded daily into electronic diaries for 7 days after each dose. The unsolicited AEs and

SAEs were collected by the investigators based on clinical evaluation of the subjects, as well as information provided to investigators by the parents/guardians, through 6 months after the last vaccination.

The studies were not powered for safety comparisons. Moreover, results are best viewed as descriptive, and any references to statistical significance should not be interpreted inferentially since no pre-specified hypotheses are being tested.

Demographic characteristics of overall safety data

A summary of demographic characteristics of subjects who were included in the pooled safety population is provided in Table 35.

Table 35: Demographic Characteristics, Pooled Safety Population

Population Demographics	rLP2086 120 µg n(%)	rLP2086 60 µg n(%)	rLP2086 200 µg n(%)	Total n(%)
Number of subjects	4335	34	207	4576
Gender - Male	2455 (56.6)	17 (50.0)	95 (45.9)	2567 (56.1)
Gender - Female	1880 (43.4)	17 (50.0)	112 (54.1)	2009 (43.9)
Race - White	3928 (90.6)	28 (82.4)	200 (96.6)	4156 (90.8)
Race - Black	273 (6.3)	2 (5.9)	5 (2.4)	280 (6.1)
Race - Other	96 (2.2)	3 (8.8)	1 (0.5)	100 (2.2)
Race - Asian	38 (0.9)	1 (2.9)	1 (0.5)	40 (0.9)
Ethnicity- Non-Hispanic and Non-Latino	3957 (91.3)	27 (79.4)	199 (96.1)	4183 (91.4)
Ethnicity - Hispanic or Latino	378 (8.7)	7 (20.6)	8 (3.9)	393 (8.6)
Age at 1st dose 11-14 yrs	2518 (58.1)	16 (47.1)	115 (55.6)	2649 (57.9)
Age at 1st dose 15-18 yrs	1732 (40.0)	6 (17.6)	79 (38.2)	1817 (39.7)
Age at 1st dose >18 yrs	85 (2.0)	12 (35.3)	13 (6.3)	110 (2.4)

Source: Integrated Summary of Safety, page 30

Overall, the majority of subjects were white (90.8%), male 56.1%, and 57.9% were 11-14 years old.

8.2 Safety Results

Adverse events

Given that the local reactions and systemic events for subjects receiving rLP2086 were mostly mild or moderate, and given the clinical focus for serious adverse events (SAEs), this review's principal emphasis is on the SAEs, particularly the autoimmune medical conditions occurring among the rLP2086 vaccinees,

regardless of the doses received. The AEs/SAEs include autoimmune and neuroinflamatory disorders, among other medical conditions. The local reactions and systemic events, however, will be presented during the overview of each individual study's safety.

SAEs

Table 36 provides a summary of AEs and SAEs from the pooled 7 studies while Table 37 provides a similar summary for only the 4 controlled core safety studies.

Table 36: Summary of AEs and SAEs, Pooled Safety Data (7 Studies)

AE/SAE and report period	rLP2086 120 µg n/N (%)	rLP2086 60 µg n/N (%)	rLP2086 200 µg n/N (%)	Total n/N (%)	Control[b] n/N (%)
AE during vaccination phase	1723/4335 (39.75)	29/34 (85.29)	103/207 (49.76)	1855/4576 (40.54)	465/1028 (45.23)
AE within 30 days after any dose	1097/4335 (25.31)	25/34 (73.53)	80/207 (38.65)	1202/4576 (26.27)	321/1028 (31.22)
Related AE reported during the vaccination phase	264/4335(6.09)	5/34(14.71)	17/207(8.21)	286/4576(6.25)	36/1028(3.50)
SAE within 30 days after Dose 3	8/3099 (0.26)	0/29 (0.00)	2/192 (1.04)	10/3320 (0.30)	2/926 (0.22)
SAE within 30 days after any dose	27/4335 (0.62)	1/34 (2.94)	4/207 (1.93)	32/4576 (0.70)	5/1028 (0.49)
SAE during follow-up phase	29/4034 (0.72)	1/22 (4.55)	2/186 (1.08)	32/4242 (0.75)	8/934 (0.86)
SAE throughout the study	88/4335 (2.03)	2/34 (5.88)	10/207 (4.83)	100/4576 (2.19)	16/1028 (1.56)
Related SAE throughout the study	2/4335 (0.05)	0/34 (0.00)	1/207 (0.48)	3/4576 (0.07)	0/1028 (0.00)
Newly diagnosed chronic medical conditions throughout the study	30/4335 (0.69)	0/34 (0.00)	2/207 (0.97)	32/4576 (0.70)	10/1028 (0.97)
Neuroinflammatory conditions throughout the study	1/4335 (0.02)	0/34 (0.00)	0/207 (0.00)	1/4576 (0.02)	0/1028 (0.00)
Autoimmune conditions throughout the study	13/4335 (0.30)	0/34 (0.00)	0/207 (0.00)	13/4576 (0.28)	0/1028 (0.00)
Death	1/4335 (0.02)	0/34 (0.00)	0/207 (0.00)	1/4576 (0.02)	0/1028 (0.00)

Note: For B1971003 and B1971004 both life-threatening and severe adverse events were included as 'Severe AE'. Note: For B1971012 group 5 subjects, any AE reported prior to first dose of rLP2086 was not counted.
b. The control arm from B1971004 received Tdap vaccine at month 0, and Saline at month 2,6; the control arm for B1971005 received Saline at month 0,2,6; the control arm from B1971010 received Repevax at month 0, and Saline at month 0,2,6; the control arm from B1971011 received Gardasil and Saline at month 0,2,6.
Source: 2.7.4 Summary of Clinical Safety, page 101-106.

As seen from Table 36 (2nd row), of the rLP2086 vaccinees, 1202 of 4576 (26.27%) subjects reported AEs within 30 days of any dose, which by and large did not show an excess risk [relative risk (RR)=0.84, 95% CI: (0.76, 0.93) compared to 31.22% in the 1028 control subjects. It appears that dose 120 µg rLP2086 had the lowest AE rate, 25.31% compared to 73.53% at dose 60 µg rLP2086 and 38.65% at dose 200 µg rLP2086. For SAEs within 30 days of any dose, the overall proportion of subjects with SAEs among the rLP2086 vaccinees was 0.70% (32/4576) compared to 0.49% (5/1028) among control subjects. The difference assessed in terms of relative risk was not significant (RR=1.44, 95% CI: (0.59, 4.39)). For SAEs reported throughout the study, the proportion among

the rLP2086 vaccinees was 2.19% (100/4576) compared to 1.56% (16/1028) in control subjects and, again, showed no statistical significance (RR=1.40, 95% CI: (0.85, 2.47)).

A summary of AEs and SAEs reported for the 4 controlled core safety studies is presented in Table 37. The summary in Table 37 is based on the pooled 4 randomized controlled studies with subjects who received at least one dose of the bivalent rLP2086 vaccine final formulation (120 µg dose level) on 0-, 2- ,6-month schedule.

Table 37: Summary of AEs and SAEs, Pooled 4 Randomized Controlled Studies

AE/SAE and report period	rLP2086[a] 120 µg n/N (%)	Control[b] n/N (%)
AE during vaccination phase	1076/2566(41.93)	465/1028 (45.23)
AE within 30 days after any dose	755/2566(29.42)	321/1028 (31.22)
Related AE reported during the vaccination phase	170/2566(6.63)	36/1028(3.50)
SAE within 30 days after Dose 3	6/2272(0.26)	2/926 (0.22)
SAE within 30 days after any dose	15/2566(0.58)	5/1028 (0.49)
SAE during follow-up phase	13/2305(0.56)	8/934 (0.86)
SAE throughout the study	44/2566(1.71)	16/1028 (1.56)
Related SAE throughout the study	0/2566(0.00)	0/1028 (0.00)
Newly diagnosed chronic medical conditions throughout the study	21/2566(0.82)	10/1028 (0.97)
Neuroinflammatory conditions throughout the study	1/2566(0.04)	0/1028 (0.00)
Autoimmune conditions throughout the study	6/2566(0.23)	0/1028 (0.00)
Death	1/2566(0.04)	0/1028 (0.00)

Note: For B1971004 both life-threatening and severe adverse events were included as 'Severe AE'.
a. The rLP2086 arm from B1971010 received Repevax at month 0 in addition to rLP2086 at month 0,2,6, rLP2086 arm from B1971011 combined Group 1 (both Gardasil and rLP2086 at month 0,2,6) and Group 2 (both Saline and rLP2086 at month 0,2,6).
b. The control arm from B1971004 received Tdap vaccine at month 0, and Saline at month 2,6; the control arm for B1971005 received Saline at month 0,2,6; the control arm from B1971010 received Repevax at month 0, and Saline at month 0,2,6; the control arm from B1971011 received Gardasil and Saline at month 0,2,6.
Source: Summary of Clinical Safety, page 101.

From Tables 36 and 37, the rates of AEs or SAEs did not display marked differences between the 4 controlled core safety studies and the pooled 7 studies.

Autoimmune and Neuroinflammatory Conditions

The applicant also reported 13 subjects with autoimmune conditions and 1 subject with neuroinflammatory condition among the 4576 rLP2086 vaccinees. In contrast, no such case was reported among the 1028 subjects who did not receive

rLP2086. The number 1028 here replaces the applicant's previously used number of 1012 for control subjects. In a recent response (08 September 2014), the applicant indicated that 16 subjects (from study B1971012) were not included in the pooled randomized control group of 1012 subjects. The observed autoimmune cases did not provide conclusive evidence favoring clustering in the rLP2086 arm compared to control. By setting the comparison, 14/4576 vs. 0/1028, the 95% CI lower bound (LB) of relative risk (RR) in rLP2086 compared to control was 0.919. The 95% CI lower bounds for RR were calculated for additional comparisons as well and presented in Table 38.

Table 38: 95% CI Lower Bound for Comparing rLP2086 versus Control Based on Subjects as the Units of Analysis, Using Exact Statistical Method

Comparison (rLP2086 vs. Control*)	RR 95% CI lower bound
13/4576 vs. 0/1012	0.840
14/4576 vs. 0/1012	0.905
14/4576 vs. 0/1028	0.919
7/2566 vs. 0/1012	. 0.755
7/2566 vs. 0/1028	0.767

**Due to no cases among the control subjects, the RR point estimate and its 95% CI upper bound are infinity; therefore, the CI lower bounds are shown.*

Source: Table based on the reviewer's analysis.

The RR calculations based on 7/2566 vs. 0/1012 and 7/2566 vs. 0/1028 relate to the comparisons for the core, controlled studies only. The RR lower bound in these core, controlled studies (bottom 2 rows, Table 38) was lower compared to that from the pooled studies. The LB values being less than 1.00 did not support an excess risk of the autoimmune/neuroinflammatory AEs among the rLP2086 vaccinees relative to the control subjects. A listing of the autoimmune/ neuroinflammatory cases is provided below (Table 39). Considering that 11 of the above 14 subjects had either pre-existing autoimmune conditions or known non-vaccine etiology, the observed risk is further diminished by implication.

Table 39: Listing of Autoimmune and Neuroinflammatory Conditions

Study	Subject	Adverse Event MedDRA Term	Adverse Event Verbatim Term	Vaccine Administered	Last Dose	Days Since Last Dose	Related to Study Vaccine[a]	Severity	SAE Flag	Action[b]	Outcome/AE Still Present?
B1971003	001-000006	Psoriasis	Psoriasis - hands and feet	120 mcg rLP2086/120 mcg rLP2086/120 mcg rLP2086	Dose 1	22	No	Mild		CM	Resolved
		Psoriasis	psoriasis flare - left medial Foot	120 mcg rLP2086/120 mcg rLP2086/120 mcg rLP2086	Dose 3	14	Yes	Mild		CM	Persisted
	002-000103	Coeliac disease	Exacerbation of gluten Intolerance	120 mcg rLP2086/120 mcg rLP2086/120 mcg rLP2086	Dose 2		No	Mild		O	Resolved
B1971010	10071013	Autoimmune Thyroiditis	HASHIMOTO'S THYROIDITIS	rLP2086+Repevax/rLP2086	Dose 2	141	No	Moderate	No	Study Vaccine: P.Subject: T,W.	Yes
	10081037	Idiopathic Thrombocytopenic purpura	IDIOPATHIC THROMBOCYTOPENIC PURPURA	rLP2086+Repevax/rLP2086 /rLP2086	Dose 3	31	No	Moderate	Yes	Study Vaccine: N. Subject: T.	Resolved (08MAY2012)
	10201051	Coeliac disease	WORSENING OF COELIAC DISEAS (DIAGNOSED)	rLP2086+Repevax/rLP2086 /rLP2086	Dose 1		No	Moderate	No	Study Vaccine: N. Subject: N.	Resolved (21AUG2012)
	10361013	Arthritis infective	POST INFECTIOUS ARTHRITIS	rLP2086+Repevax	Dose 1	10	No	Severe	Yes	Study Vaccine: P.Subject:O,T, W.	Resolved (25NOV2011)
B1971011	10191031	Sydenham's Chorea	SYDENHAM'S CHOREA	rLP2086+Gardasil/rLP2086 +Gardasil/rLP2086+Gardasil	Dose 2	18	No	Moderate	No	Study Vaccine: N. Subject: O.	Resolved (15JUN2012)
	10931036	IgA nephropathy	IGA NEPHROPATHY	rLP2086+Saline	Dose 1	2	No	Moderate	No	StudyVaccine: P.Subject: O,W.	Resolved(24AUG 2012)
B1971011	10541016	VIIth nerve paralysis[c]	BELL'S PALSY	rLP2086+Sal/ rLP2086+Sal /rLP2086+Sal	Dose 2	33	No	Moderate	No	Study Vaccine: N, Subject: O,T.	Resolved (04JUL2012)
B1971012	10011017	Hypothyroidism	HYPOTHYROIDISM	rLP+Sal+rLP+Sal	Dose 2/FU		No	Mild	No	StudyVaccine: N.Subject: T.	Yes
	10361015	Rheumatoid Arthritis	RHEUMATOIDARTHRITIS	rLP+Sal+rLP	Dose 2	119	No	Mild	No	StudyVaccine: P.Subject: W.	Yes
	10681010	Basedow's disease	GRAVES-BASEDOWDISEASE	rLP+Sal+Sal	Dose 1	84	No	Moderate	No	StudyVaccine: P.Subject: W.	Yes
	10711009	Crohn's disease	CROHNS DISEASE	rLP+rLP+Sal	Dose 2	96	No	Moderate	Yes	StudyVaccine: P.Subject: W.	Yes
	10731005	Hypothyroidism	SUBCLINICAL HYPOTHYROIDISM	rLP+Sal+rLP	Dose 1		No	Mild	No	StudyVaccine: P.Subject: O,W.	Yes

Abbreviations: AE=Adverse Event, MedDRA=Medical Dictionary for Regulatory Activities; SAE=Serious Adverse Eventa.

a. Based on investigator assessment.

b. Action Taken: CM=Concomitant medication; D=Discontinued test article permanently; H= Hospitalized; I=Increased; N=No action taken; O=Other; T=Treatment Given

c. The adverse event was a consequence of Lyme's disease (ref. Sponsor's Response dated 08 September 2014 to CBER's IR Request, page 28)

P = Permanently discontinued; R=Reduced; S=Stopped temporarily; T=Treatment given; W=Withdrawn from study.

Source. Integrated Summary of Safety, pages 555, 557.

There was one death among the rLP2086 recipients and there were none among controls. The death, a traffic accident case, was considered not related to the vaccine by the investigator.

8.3 Safety Conclusions

With the submitted data from Phase 1 and Phase 2 clinical trials, targeted comparisons were not always straightforward due to differing control regimens, despite common saline. Nevertheless, the submitted results by and large did not establish excess risk in safety among subjects receiving the investigational rLP2086 vaccine compared to subjects considered as controls in the study.

9. Additional Statistical Issues

None.

10. Conclusions

Immunogenicity conclusion

Analyses of data generated by B1971011, B1971012, and B1971010 clinical trials for 5 or 4 co-primary endpoints and limited to 4 primary MnB test strains showed that the lower limits of the 95% CIs for these co-primary endpoints were above acceptable levels after the third dose of the bivalent rLP20806 vaccine. Results were consistent across these three studies. Additionally, results were comparable across studies for the other immunogenicity parameters such as hSBA geometric mean titers (GMTs) for each of the 4 primary MnB test strains.

Overall, based on 4 clinical trials, which generated immunogenicity data in the indicated age range, three doses of the bivalent rLP2086 vaccine administered on the 0-, 2-, and 6-month schedule elicited immune responses expressed for four primary MnB test strains in healthy adolescents aged ≥ 11 to < 19 years. Immunogenicity data submitted by the applicant from three studies for subjects older than 18 years provided some additional information (about 72 subjects evaluated) supporting a similar conclusion for this older age group as well.

However, it is worth noting that results of analyses on data generated by the clinical trials for four primary MnB test strains do not provide apparent information on the breath of protection against MnB meningococcal disease the bivalent rLP2086 vaccine might confer, since there are many MnB strains that cause meningococcal disease.

Concomitant administration of bivalent rLP2086 with Gardasil resulted in non-inferior responses when compared with administration of Gardasil alone for 3 of 4 HPV antigens.

The response for HPV-18 missed the 1.5-fold non-inferiority criterion by a very small margin. On the other hand, given that the seroconversion rates for other 3 HPV antigens were greater than 99% in the bivalent rLP2086 + Gardasil group, it appears that Gardasil can be co-administered with bivalent rLP2086 without concerns regarding the effectiveness of the Gardasil vaccine. The statistical reviewer defers to the medical reviewers regarding the clinical relevance of these findings.

Safety conclusion

The majority of the local and systemic reactogenicity events, collected on electronic diaries, were reported as mild to moderate in severity and of short median duration (< 5 days). These rates among the rLP2086 vaccinees were higher compared to the saline control.

Based on the overall safety data of the pooled 7 studies, the overall rates of AEs among the rLP2086 vaccinees were by and large similar or lower compared to control.

A death occurred in the 120 μg rLP2086 group but was determined to be due to a traffic accident and as such not related to the study vaccine.

Thirteen (13) subjects with autoimmune conditions and 1 subject with neuroinflammatory condition were reported among 4576 rLP2086 vaccinees, compared to none among 1028 subjects who did not receive rLP2086, in the pooled 7 studies. Statistical analysis, however, did not detect excess risk of the autoimmune/neuroinflammatory conditions in the vaccine arm. The 95% CI lower bound for relative risk (rLP2086 vs. Control) was 0.92 (Table 38, Section 8.1). Due to the fact that 11 of the above 14 subjects had either pre-existing autoimmune conditions prior to vaccination, or known non-vaccine etiology, the observed risk in the rLP2086 arm is further diminished by implication.

Overall, an excess risk in safety among the rLP2086 vaccinees compared to controls was not established based on the available data.