Saudi Public Assessment Report

TRUMENBA®

Active Pharmaceutical Ingredient(s): Neisseria meningitidis serogroup B fHbp subfamily A, Neisseria meningitidis serogroup B fHbp subfamily B.

ATC code/CAS no.: J07AH09

Pharmaceutical/Dosage Form: Suspension for injection in pre-filled syringe

Dosage Strength: 60, 60 µg

Marketing Authorization Holder: Pfizer Europe MA EEIG, Belgium

Shelf life: 48 months

Storage conditions: Store in a refrigerator (2 ° C-8 ° C).

Registration No.: 0510211105

Decision and Decision Date: Approved on 23/1/1443 H

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1. Terms, Definitions, Abbreviations:

Terms	Definitions
AEs	Adverse events
AlPO4	Aluminum Phosphate
CQAs	Critical Quality Attributes
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EMA	European Medicine Agency
FDA	US Food and Drug Authority
fHBP	factor H binding protein
GCC	Gulf Cooperation Council
GCP	Good Clinical Practice
GMR	Geometric mean ratio
GMT	Geometric mean titers
HAV	Hepatitis A virus
HPV	Human papillomavirus
hSBA	serum bactericidal activity with human complement
ICH	the International Council for Harmonization
IMD	Invasive meningococcal disease
LLOQ	Lower limit of quantitation
LOD	Lower limit of detection
MAEs	Medically attended events
MEASURE	The Meningococcal Antigen Surface Expression
MMR	Measles, Mumps, and Rubella
MnB	Meningococcal serogroup B
MnB bivalent rLP2086	Neisseria meningitides Serogroup B Bivalent Recombinant Lipoprotein
NDCMCs	Newly diagnosed chronic medical conditions
PeRC	Pediatric Review Committee
Ph.Eur.	European Pharmacopoeia
PREA	Pediatric Research Equity Act
PRTC	Plastic rigid tip cap
PSUR	Periodic Safety Update Report
RMM	Risk Minimization Measures
RMP	Risk Management Plan
SAEs	Serious adverse events
SD	Standard deviation
SDI	Saudi Drug Information System
SOC	System organ class
SPC	Summary of Product Characteristics
SUSAR	Sudden unexpected safety adverse reaction
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis

TSE	Transmissible Spongiform Encephalopathy

2. Background

2.1 Submission Details

Type of submission: Regular submission pathway

Pharmacological class: Vaccine

Submitted Indication: Prevention of invasive meningococcal disease caused by Neisseria meningitidis Serogroup B (MenB) in individuals aged 10 years and older

Submitted Dosage form: liquid suspension in a prefilled pen.

2.2 Regulatory Background

This product is considered *(*New Biologic Drug, Vaccine) for Saudi regulatory purposes.

This product qualified for the following regulatory pathway:

☒ Normal submission

☐ Abridged

☐ Verification

☐ Priority

Regulatory status in other countries:

Country	**Product name**	**Dosage form/Strength**	**Approval Authority**	**Date of Approval**
United State	Trumenba	Suspension for injection	FDA	29/10/2014
European Union	Trumenba	Suspension for injection	EMA	24/05/217

2.3 Product Information

The approved Summary of Product Characteristics (SPC) with this submission is described and can be found in Appendix A. For the most recent SPC, please refer to the Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/Home/Result?drugId=11250

3. Scientific discussion about the product:

The drug product contains (MnB rLP2086 subfamily A&B) as an active moiety. Subfamily A protein is composed of 258 amino acids. The subfamily A protein is covalently lipidated at the N-terminus with the four predominant fatty acids. The primary structure of subfamily A, including the sequence of the amino acid polypeptide and the compositions and the structures of the N-terminal lipids, are the critical determinant for the function of the vaccine. The higher-order structure, including the secondary, tertiary and quaternary structures, was analyzed using a variety of biophysical methods. The immunogenicity of the molecule, the specificity of the antibodies induced by the vaccine against the target bacterial strain, as well as the immune-enhancing effects of the N-terminal lipid moiety, were demonstrated using both in vivo and in vitro assays. The results demonstrate that MnB rLP2086 subfamily A has the expected structure and biological activity.

Subfamily B protein is composed of 261 amino acids. The subfamily B protein is covalently lipidated at the N-terminus with the four predominant fatty acids. The primary structure of subfamily B, including the sequence of the amino acid polypeptide and the compositions and the structures of the N-terminal lipids, are the critical determinant for the function of the vaccine. The higher-order structure, including the secondary, tertiary and quaternary structures, was analyzed using a variety of biophysical methods.

3.1 Quality Aspects

Sections related to the product quality submitted as:

Two separate drug substance sections 2 (3.2.S) describe MnB rLP2086 subfamily A protein and a second drug substance section describing MnB rLP2086 subfamily B protein, and one drug product section (3.2.P) which describes how the two drug substance proteins are formulated at 120 mcg/mL/subfamily and filled at Pfizer Grange Castle, Ireland (Pfizer, Ireland).

3.1.1 Introduction

Trumenba® is a sterile liquid suspension vaccine for intramuscular injection, which contains one serogroup B recombinant lipidated factor H binding proteins (fHBP) from subfamilies A and B adsorbed on aluminium phosphate, elicits bactericidal antibodies directed against fHBP found on the surface of Neisseria meningitides group B strains. Available in 0.5 mL single-dose pre-filled syringes with the dosage strength of 60 µg of subfamily A and 60 µg of subfamily B (120 µg total protein) per 0.5 mL dose. Trumenba is indicated for active immunization in individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitides serogroup B.

3.1.2 Drug Substance

General Information:

This vaccine contains two active drug substances Neisseria meningitides B strain subfamily A lipoproteins and Neisseria meningitides B strain subfamily B lipoproteins, which are structural components of bacterial cell wall. The common structure of these bacterial lipoproteins consists of an amino acid polypeptide, a glycerol moiety thioether linked to the N-terminal cysteine, and fatty acids of various structures acyl-linked to two hydroxyl groups of the glycerol (di-O-acylated). In addition, a fatty acid is acyl-linked to the α-amine of the N-terminal cysteine (N-acylated), giving rise to a tri-acylated lipoprotein moiety.

Manufacture, characterization and process controls:

- **Manufacturing process**

  The active substance MnB rLP2086 subfamily A and subfamily B are manufactured in two different locations with the same manufacturing process steps. Only minor process adaptations and adjustments are driven by inherent differences in the facilities and existing equipment. The control strategy has remained unchanged. Both drug substances had been produced with the same commercial scale for each subfamily individually expressed in E-Coli using two main production phases; fermentation phase and recovery phase. The MnB rLP2086 proteins (subfamily A and B) fermentation and recovery phases in both sites are almost identical.

- **Control of materials**

  Information on raw materials used during the manufacturing process had been submitted according to the SFDA requirements. All raw materials used in the drug substances (subfamily A and B) manufacturing process are free from materials originating from animal or human sources, except one component that is/ used in

materials of construction of equipment. This component may come into contact with the DS during the manufacturing process or packaging components. The safety control for that component was properly assessed and concluded that it is safe for its intended use.

- **Control of critical steps and intermediates**

Impurity reduction was successfully demonstrated by the in-process testing and drug substance testing accordingly through the validation studies, the subfamily A and B drug substance manufacturing process has successfully been shown to effectively and consistently remove impurities to acceptable levels as defined within the drug substance specifications.

- **Process validation**

The validation of the subfamily A and B drug substance manufacturing processes was completed for three independent consecutive batches from each subfamily. The in-process pool hold times were validated to demonstrate that the biochemical stability and microbial integrity of subfamily A and B over a defined period under storage conditions and in containers are comparable to those used in manufacturing. Validation results demonstrate that the manufacturing process can consistently produce subfamily A and B drug substances within the expected yields and the process is successfully proven to be effective, and consistently able to remove impurities to the acceptable levels as defined within the drug substance specifications.
Comparability assessment of the N. meningitides serogroup B rLP2086 subfamily A and B proteins produced at both production sites was provided and reviewed. The assessment of the comparability studies shows that the DS manufactured at the initial manufacturing facility is comparable to DS manufactured at the currently licensed site.

- **Control of drug substance:**

The drug substances (both subfamily A and B) are controlled at the time of release and shelf-life condition stability complying with the proposed release and shelf-life specification parameters submitted under section (3.2.S.4), which covers all the potential quality attributes that may impact, the quality, safety and efficacy of the final bulk drug substance or drug product. All parameters tested for every drug substance batch were complying with the compendial requirements, GCC guidelines and ICH guidelines, and were performed by verified analytical methods. The acceptance criteria were established based on the historical data from both clinical and commercial batches complying with the relative guidelines.

- **Reference materials:**

  The drug substance manufacturer established an in-house bivalent reference material selected from representative batches containing 400 µg/mL of each protein (subfamily A and B) and monovalent reference material. Both reference materials met release acceptance criteria used in the testing of MnB rLP2086 subfamily A and subfamily B drug substance and drug product specifications, the reference materials were appropriately characterized concerning identity, purity, concentration. There were two retired reference standard used previously for the clinical batches and PPQ batches before the current primary and secondary reference standard generated and be used for the commercial batches standardization, the protocol of qualification of future reference standard were provided and approved

- **Stability:**

  The proposed shelf-life and storage conditions for the active substance were considered acceptable based on an ongoing stability program designed following the ICH guidelines, GCC guidelines and in compliance with the Ph. Eur. monograph for Product of Recombinant deoxyribonucleic acid (DNA) Technology (0784). Statistical trending analyses of the real-time stability on the latest batches produced by Pfizer were following the proposed commercial specifications moreover a data from one process validation/primary stability batch (Batch no.MnB rLP2086) subfamily A drug substance subjected to ICH photostability conditions; was provided and proved that the purity falls down without light protection.

3.1.3 Drug Product

- **Description of the product and Pharmaceutical Development:**
  The drug product is a sterile liquid suspension composed of rLP2086 subfamily A and B proteins formulated with a strength of 120 mcg/mL filled into 1 mL syringes with no overages in the formulation.

- **Manufacture of the product and process controls:**
  Drug product for commercial-scale is manufactured at Pfizer Grange Castle, Ireland. The manufacturing process is summarized as follow: After preparation of Aluminum Phosphate (AlPO4), it will be added aseptically to the formulation vessel then DS proteins previously sterilized by filtration directly added to the formulation vessel that containing the appropriate buffer then the formulated drug product filled into syringes to deliver a nominal dose of 0.5 mL and stoppered appropriately. The filled DP pre-sterile syringes are stored at 2-8°C until ready to be shipped from manufacturing site Pfizer, Ireland to Pfizer, Belgium where the labelling and packaging are performed. The manufacturing process, equipment, fill mechanism, in-process tests and control of

critical steps approach were reviewed and approved by the SFDA quality evaluation team.

Process validation:

Three consecutive process validation runs were performed at the commercial scale to validate the buffer preparation, formulation of bulk vaccine, associated hold times, the filling of the bulk vaccine into syringes with detailed information related to the sterility process and filling validation submitted by the applicant reviewed and accepted with no further data required to prove the validity of the manufacturing process and control.

In the reason of proving the process consistency between the initial production site and the current production site, a total of 9 DP lots from Vetter, Germany and 7 DP lots from Pfizer, Ireland were used in the comparability assessment, based on all the releases, characterization and stability data generated to date on the 9 Vetter lots and the 7 Pfizer lots, the DP manufactured at the two sites is considered comparable.

Excipients:

Water for Injection, Sodium chloride, Histidine and Polysorbate 80 are compendial excipients that were added during the DS manufacturing process. All excipients met compendial requirements as outlined in the European Pharmacopoeia (Ph. Eur.) AlPO4is an in-house excipient that was added during the DP manufacturing process to function as a stabilizer, AlPO4 suspension was manufactured by mixing a solution of aluminum chloride and sodium phosphate and allowing precipitation of the aluminum phosphate suspension. Batch validation results for three batches of AlPO4 suspension manufactured and tested at Pfizer, Ireland were provided. The obtained results met the acceptance criteria demonstrating that the manufacturing process consistently produces AlPO4 suspension with the required quality.

Control of drug product:

Analytical test methods and specifications were chosen to ensure the quality, identity, purity, potency, and safety of the drug product. The analytical test methods and the proposed specifications were derived through the evaluation of (1) development experience with drug product, (2) characterization and process validation data, (3) manufacturing history, (4) release and ongoing stability data for drug product batches, and (5) toxicological and clinical evaluation of drug product manufactured with the drug substance. In addition, compendial requirements for protein-based products were considered to comply with the Ph. Eur. monograph for Vaccines for Human Use (0153) and recombinant DNA proteins (0784). Statistical analysis of the available batch data and evaluation of commercial process variability was used as primary factors to guide the

setting of the proposed commercial specifications. In addition to the Phase 2 and Phase 3 clinical batches at commercial scale, analytical data from clinical batches that were used in Phase 1 and Phase 2 studies, which were manufactured at pilot scale, were considered to reflect the full range of clinical experience. Assessment of the provided commercial batch analysis data comply with the specifications of the DP at the time of release.

Container closure system:
The container closure system for the drug product is a 1 mL glass syringe with a latex-free rubber tip cap, sealed with a latex-free rubber stopper. The syringe presentation includes the following non-product contact components: plunger rod, backstop, and plastic rigid tip cap (PRTC) overseal. The container closure system is controlled mainly by microbial ingress, leak testing, light protection, extractables/leachables. Safety and compatibility studies have been completed.

Stability
Stability information for drug product stored under the long-term condition of 5 ± 3˚C, the accelerated condition of 25 ± 2˚C/60 ± 5% relative humidity, as well as thermal stress, thermal cycling. The testing of the drug product complies with Ph. Eur. monograph for Vaccines for Human Use (0153). Photo-stability conditions are completed from primary and supportive stability studies on drug product produced using the commercial-scale process at Pfizer, Ireland. Data generated from the stability program at phase 2/3 clinical batches that were manufactured at the Vetter, Germany manufacturing facility was submitted. Assessment of the submitted data confirmed the proposed shelf life of 48 months at the proposed storage condition. The product should be stored in a refrigerator (2°C - 8°C) and should not be frozen. Syringes should be stored in the refrigerator horizontally to minimize the re-dispersion time, Shake well before use.

Adventitious agents safety evaluation
MnB bivalent rLP2086 vaccine is composed of components derived from bacterial fermentation and not a viral product. Although ingredients of animal origin are used in the preparation of the vaccine component, the main theoretical risk associated with these ingredients is a contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents. The animal-derived ingredients used in MnB bivalent rLP2086 vaccine production are excluded from the scope of the 2011 revision to the TSE guideline.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

Therapeutic area: Meningitis, Meningococcal

Trumenba is a vaccine composed of two recombinant lipidated fHbp variants. fHbp is found on the surface of meningococcal bacteria and is essential for bacteria to avoid host immune defenses. fHbp variants segregate into two immunologically distinct subfamilies, A and B, and over 96% of meningococcal serogroup B isolates in Europe express fHbp variants from either subfamily on the bacterial surface. Immunisation with Trumenba, which contains one fHbp variant each from subfamily A and B, is intended to stimulate the production of bactericidal antibodies that recognize fHbP expressed by meningococci. The Meningococcal Antigen Surface Expression (MEASURE) assay was developed to relate the level of fHbp surface expression to the killing of meningococcal serogroup B strains in serum bactericidal assays with human complement (hSBAs).

3.2.1.1 Pharmacokinetic studies

Not applicable.

3.2.1.2 Pharmacodynamic studies

Not applicable.

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical studies

Study ID*	No. of study center / location	Design	Study Objective	Subjs by arm	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
B1971003	3 sites in Australia	Phase 1/2, open-label safety and assay development study	Assay development, safety and tolerability assessment & immunogenicity of bivalent rLP2086	rLP2086 120 µg (0,1,6 m) [n=60]	27/10/2008 to 28/05/2010	26.7/73.3 26.0 years	Healthy adults between 18 and 40 years of age	hSBA titres for MnB test strains expressing fHbp variants A05 and B02.
B1971003	3 sites in Australia	Phase 1/2, open-label safety and assay development study	Assay development, safety and tolerability assessment & immunogenicity of bivalent rLP2086	rLP2086 120 µg (0,1,6 m) [n=60]	27/10/2008 to 28/05/2010	26.7/73.3 26.0 years	Healthy adults between 18 and 40 years of age	hSBA titres for MnB test strains expressing fHbp variants A05 and B02.
B1971005	25 sites in Australia, Spain, and Poland	Phase 2, randomized, single-blind, placebo-controlled study	Stage 1 Safety & immunogenicity of bivalent rLP2086 Stage 2 (4 primary test strains) Antibody persistence up to 48 months after last dose given in Stage 1	60 µg, 120 µg, 200 µg (0,2,6 m) Group 1 : 22 Group 2:198 Group 3:198 Group 4: 121(Control)	9/02/2009 to 8/12/ 2010	46.6 / 53.4 14.0 years	Healthy adolescents aged 11 to 18 years	Proportions of subjects with ≥4 fold-rise in hSBA for strains PMB1745 (A05) and PMB17 (B02) (Stage 1) after 2 and 3 doses (Note: the 4-fold definition is not the same as the Phase 3 definition used in Studies B1971010, B1971011, and B1971012).
B1971009 [PIVOTAL]	USA, Global.	Phase 3, randomized,	**Primary (Immunogenicity):**	**Bivalent rLP2086:** 120	18/04/2013 to 14/04/ 2015	51.5/48.5 13.9 years	Healthy adolescents aged	Primary Immunogenicity: • hSBA titer fold rise ≥4 from baseline

	82 sites in Canada, the United States, Czech Republic, Finland, Germany, Italy, Poland, and the United Kingdom	active-controlled, observer-blinded, multi-center study Bivalent rLP2086 (120 mcg) versus HAV/ saline	-To assess the immune response, as measured by hSBA performed with 4 primary MnB test strains, measured 1 month after the third vaccination with bivalent rLP2086. -To demonstrate that the immune responses induced by 3 lots of bivalent rLP2086 are equivalent, as measured by hSBA performed with 2 primary MnB test strains, 1 month after the third vaccination with bivalent rLP2086. **Primary (Safety):** -To evaluate the safety profile of bivalent rLP2086 compared to a control (HAV/saline) as measured by local reactions, systemic events, AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended events (MAEs), and immediate AEs.	mcg; 0, 2, and 6-month. Group 1-Lot 1 (n=1509) Group 2-Lot 2 (n=600) Group 3-Lot 3 (n=589) **Control:** HAV: 0, 6 month Saline: 2-month to maintain blinding as appropriate Group 4-HAV /saline (n=898)			>=10 to <19 years	• Composite hSBA response (hSBA titer ≥ LLOQ for all 4 primary strains) Primary Lot consistency: • hSBA geometric mean titers (GMTs) for each of the 2 primary MnB test strains PMB80 (A22) and PMB2948 (B24), at 1 month after the third vaccination with bivalent rLP2086 for subjects in Groups 1, 2, and 3. Primary Safety: • Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity after each vaccination visit. • Percentage of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain [other than muscle pain at any injection site], and joint pain) and by severity after each vaccination visit. • Percentage of subjects reporting the use of antipyretic medication after each vaccination visit. • Percentage of subjects with at least 1 SAE during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 MAE occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 NDCMC occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects who develop at least 1 AE occurring during the following periods: [30 days after

								each vaccination, 30 days after any vaccination, during the vaccination phase]. • Percentage of subjects reporting at least 1 immediate AE after each vaccination. Subject missing days of school or work due to AEs during the vaccination phase.
B1971010	34 sites in Finland, Germany and Poland.	Phase 2, randomized, placebo-controlled, single-blind multicenter study	Safety & immunogenicity of bivalent rLP2086 when used concomitantly with Repevax (dTaP/IPV)	120µg (0,2,6 m) Group 1 (rLP2086/dTaP-IPV): 373 Group 2 (dTaP/IPV): 376	18/03/2011 to 30/08/ 2013	51.1 / 48.9 13.0 years	Healthy Subjects Aged ≥11 to <19 Years	% subjects achieving the pre-specified level of antibody to Repevax antigens 1-month after Dose 1 (Visit 2) was computed along with the difference in proportions (Group 1- Group 2) and 2-sided 95% exact CI for the difference.
B1971011	63 sites in the USA	Phase 2, randomized, active-controlled, observer-blinded, multicenter study	Immunogenicity of Gardasil® (HPV) when given concomitantly with bivalent rLP2086. To assess the safety, tolerability & immunogenicity of bivalent rLP2086.	120 µg (0,2,6 m) Group 1 (rLP2086/ HPV): 999 Group 2 (rLP2086/ saline): 998 Group 3 (HPV/ saline): 502	28/09/ 2011 to 18/12/ 2013	66.5 / 33.5 13.0 years	Healthy Subjects Aged ≥11 to <18 Years	The co-primary immunologic endpoints are a) GMTs for each of the 4 HPV antigens in subjects receiving HPV alone compared to GMTs for each of the 4 HPV antigens in subjects receiving HPV + rLP2086, and b) hSBA titres to primary MnB test strains expressing fHBP A22 and B24 variants in subjects receiving rLP2086 alone compared to the response in subjects receiving HPV + rLP2086.
B1971012	60 sites in Czech Republic, Denmark, Finland, Germany, Poland, Spain, and Sweden	Phase 2, randomized, placebo-controlled, single-blind, multicenter study in which subjects were randomly	Safety & immunogenicity of bivalent rLP2086	120 µg Group 1 (0,1,6 m): 427 Group 2 (0,2,6 m): 430 Group 3 (0,6 m): 427 Group 4 (0,2 m): 286	03/03/ 2011 to 30/08/ 2013	49.2/50.8 14.4 years	Healthy Subjects Aged ≥11 to <19 Years	The proportion of subjects achieving an hSBA titre ≥ LLOQ for each of the 4 primary MnB test strains measured 1 month after Dose 3 in Groups 1 and 2.

		assigned to 5 groups in a 3:3:3:2:1 ratio		Group 5 (0,4 m): 143				
B1971014 (safety study, no immunogenicity analysis)	USA, Global. 78 sites in Australia, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Lithuania, Poland, Spain, Sweden, and the USA	Phase 3, randomized, active-controlled, observer-blinded multicenter study randomized in a 2:1 ratio Bivalent rLP2086 (120 mcg) versus HAV/ saline	To evaluate the safety of bivalent rLP2086 compared to a control (HAV/saline), as assessed by SAE and MAEs.	Group 1 Bivalent rLP2086; 120 µg; 0, 2, and 6 months (n = 3804) Group 2 HAV at 0 and 6 months; saline at 2 months (n = 1908)	07/11/ 2012 to 29/09/2014	48.2 / 51.8 17.0 years	Healthy adolescents/ adults 10 to <26 years old	Adverse events and serious adverse events.
B1971015	80 sites in the USA	Phase 2, randomized, active-controlled, observer-blinded Multicenter study. 1:1:1 ratio	Safety, tolerability & immunogenicity of bivalent rLP2086 when used concomitantly with MCV4 and Tdap vaccines	120 µg (0,2,6 m) Group 1 (rLP2086 /MCV4/Tdap): 888 Group 2 (MCV4/Tdap /Saline): 878 Group 3 (rLP2086/ Saline followed by	28/09/2011 to 20/10/2014	51.0 / 49.0 10.0 years	Healthy subjects aged ≥10 to <13 years	Co-primary endpoints for the first co-primary objective were the GMTs or GMCs for each of the antibodies reactive with each of the 10 antigenic components in the marketed vaccines at Visit 2 (Month 1), among subjects in Groups 1 and 2. Co-primary endpoints for the second co-primary objective were the hSBA GMTs for each of the 2 primary strains (PMB80 [A22] and PMB2948 [B24]) at Visit 6 (Month 7), among subjects in Groups 1 and 3.

				MCV4/Tdap: 882				
B1971016 [PIVOTAL]	USA, Global. 53 sites in Canada, Denmark, Finland, Poland, Spain, and the USA	Phase 3, randomized, placebo-controlled, observer-blinded, multicenter study Bivalent rLP2086 (120 mcg) versus saline	**Primary (Immunogenicity):** -To assess the immune response, as measured by hSBA performed with 4 primary MnB test strains, measured 1 month after the third vaccination with bivalent rLP2086. **Primary (Safety):** -To evaluate the safety profile of bivalent rLP2086 compared to a control (saline), as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs.	**Group 1** Bivalent rLP2086;120 µg 0, 2, and 6 months (n = 2480) **Group 2** Saline; 0, 2, and 6 months (n = 824)		41.3/58.7 21.5 years	Young adults 18 to <26 years old	% of subjects ≥4-fold increase in hSBA titre from baseline to 1-month after 3rd vaccination with bivalent rLP2086 for each of the 4 primary test strains and % achieving the composite response
B1971033	17 sites in the Czech Republic, Denmark, Germany, Sweden during Stage 1 with 14 of these 17 sites	Phase 3 antibody persistence up to 48 months after last dose of a 2dose or 3-dose primary series with bivalent rLP2086 and	**Primary (Immunogenicity):** -To describe the immunogenicity of bivalent rLP2086 as determined by hSBA titers to 4 primary test strains at approximately 6, 12, 18, 24, 36, and 48 months after the last dose (second or third dose) of bivalent rLP2086 or saline in the	**Stage 1**: NA immunopersistence enrolled from primary Studies B1971010, B1971012, B1971015 (n=698) -**Group 1** (0, 1, 6	07 /09/ 2012 to 01/08/ 2016	**Stage 1**: Sex (%) Male: 48.3 Female: 51.7 Age (Years) Mean: 14.8 Range: 11, 20	Healthy adolescents and young adults who had completed primary vaccination studies B1971010, B1971012, or B1971015	**Primary Immunogenicity Endpoints:** Stage 1 • Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary strains at each blood draw visit in Stage 1 (Visits 1 through 6). Booster Stage • Proportions of subjects with hSBA titers ≥ LLOQ for each of the 4 primary strains at 1 month following the last vaccination received in the primary study, before the booster vaccination (Visit 6), and 1 month following booster vaccination (Visit 8).

	in the Czech Republic, Denmark, and Sweden for the booster stage	the safety, tolerability, & immunogenicity of a booster dose of bivalent rLP2086; and the persistence of hSBA response up to 26 months after the booster dose	primary study (ie, a previously conducted Pfizer study using the final formulation and dose of bivalent rLP2086). -To describe the immune response as measured by hSBA titers to 4 primary test strains 1 month after the last dose (second or third dose) of bivalent rLP2086 in the primary study, before the booster vaccination, and 1 month, 12 months, and 26 months after a single booster vaccination of bivalent rLP2086. **Primary (safety):** -To evaluate the safety profile of bivalent rLP2086 as measured by the incidence of local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs following a booster vaccination of bivalent rLP2086.	months primary): 103 -**Group 2** (0, 2, 6 month primary): 277 -**Group 3** (0, 6 month primary): 116 -**Group 4** (0, 2 month primary): 86 -**Group 5** (0, 4 month primary): 46 -**Group 6** (control): 70 **Stage 2:** Bivalent rLP2086; 120 µg, single dose given 4 years after completion of primary series in the primary study Booster Stage (n=300) -**Group 1** (0, 1, 6 months primary): 59 -**Group 2** (0, 2, 6-month primary): 91		**Stage 2:** Sex (%) Male: 45.2 Female: 54.8 Age (Years) Mean: 19 Range: 15, 23	(enrolled in primary study at 10 to 18 years of age)	**Primary Safety Endpoints:** • Percentages of subjects reporting local reactions via the e-diary by type (pain at the injection site, redness, and swelling) and by severity after a booster vaccination of bivalent rLP2086. • Percentages of subjects reporting systemic events via the e-diary by type (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain) and by severity after a booster vaccination of bivalent rLP2086. • Percentage of subjects reporting the use of antipyretic medication via the e-diary after a booster vaccination of bivalent rLP2086. • Percentages of subjects with at least 1 AE [From Visit 7 to Visit 8] • Percentages of subjects with at least 1 SAE [From Visit 7 to Visit 8] • Percentages of subjects with at least 1 NDCMC [6-month safety telephone call in the primary study to Visit 6 (Stage 1)] [From Visit 7 to Visit 8] • Percentages of subjects with at least 1 MAE [From Visit 7 to Visit 8] • Percentage of subjects reporting at least 1 immediate AE after receiving the booster dose of bivalent rLP2086. Numbers of day's subjects missed school or work because of AEs from Visit 7 through Visit 8.

				-**Group 3** (0, 6 month primary): 64 -**Group 4** (0, 2 month primary): 54 -**Group 5** (0, 4 month primary): 32				
B1971042	1 site in the USA	Phase 2, single-arm, open-label study	Safety, tolerability, & immunogenicity of bivalent rLP2086 in laboratory workers	120 µg (0,2,6 m) N=13	11/02/ 2013 to 25/03/2014	30.8 / 69.2 50.0 years	Laboratory workers ≥18 to ≤65 years of age.	Proportion of subjects with an hSBA titre ≥LLOQ for each of the 4 primary MnB test strains at 1 month after Dose 3 with bivalent rLP2086.

3.2.2.2 List of submitted clinical studies in Children 1 to 9 Years of Age

Study ID*	**No. of study centers / locations**	**Design**	**Study Objective**	**Subjs by arm entered/ compl.**	**Duration**	**Gender M/F Median Age**	**Diagnosis Incl. criteria**	**Primary Endpoint**
B1971017	14 sites were included in this study. Six sites were in Finland, 8 sites were in Poland	Phase 2 Randomized, active-controlled, observer-blinded study to assess the Safety & immunogenicity	**Primary 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,	120 µg rLP2086 at 0, 2, and 6 months [n=294] -HAV at 0 and 6 months; saline at 2 months [n=106] Almost 400 subjects were planned to be	August 2015 and May 2017	47.2/52.8 4.3 years	Healthy subjects aged ≥24 months to <10 years	<u>The primary immunogenicity endpoints were:</u> • Proportion of subjects aged ≥24 months to <4 years (at study entry) with hSBA titre ≥ lower limit of quantitation (LLOQ)1 for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086. • Proportion of subjects aged ≥4 years to <10 years (at study entry) with hSBA titre ≥LLOQ for each of the 4 primary MnB test strains 1 month after the third vaccination with bivalent rLP2086.

			measured 1 month after the third vaccination with bivalent rLP2086, in healthy subjects aged ≥24 months to <4 years at study entry. • To describe the immune response as measured by hSBA performed with 4 primary MnB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy subjects aged ≥4 years to <10 years at study entry. **Primary Safety:** To evaluate the safety profile of bivalent rLP2086 compared to a control (hepatitis A virus [HAV] vaccine).	randomly assigned to one of the two groups in a 3:1 ratio.				
B1971035	26 centers in four countries (Australia, Czech Republic,	Phase 2 Randomized, active-controlled, observer-blinded, sponsor-un-	**Primary Immunogenicity:** • To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2	60 or 120 µg rLP2086 at 0, 2, and 6 months -HAV at 0 and 6 months;	August 2015 and August 2017	47.2/52.8 17.3 months	Healthy subjects aged 12 to <24 months of age	<u>The primary immunogenicity endpoints were:</u> • Proportions of subjects achieving an hSBA titre ≥ lower limit of quantitation (LLOQ) 1 month after the third vaccination, for each of the 4 primary MnB tests strains in healthy toddlers 12 to <18 months of age at study entry.

	Finland and Poland)	blinded study to assess the Safety & immune-genicity This study contains two stages: stage 1, which evaluates the primary vaccination and stage 2, which assesses the duration of the immune response and the response to a booster dose	expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 12 to <18 months at study entry. • To describe the immune response as measured by hSBA performed with 4 primary MnB strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the third vaccination with bivalent rLP2086, in healthy toddlers aged 18 to <24 months at study entry. **Primary Safety Objective** • To evaluate the safety profile of bivalent rLP2086 compared to a control (hepatitis A virus [HAV] vaccine), as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and	saline at 2 months In Stage 2, subjects who received rLP2086 will continue to be followed for antibody persistence through 48 months after the last study dose. 396 healthy toddlers stratified by age, 12 to <18 months or 18 to <24 months old, were randomly assigned in a 2:1 ratio A total of 44 subjects received 60 µg of bivalent rLP2086, 220 subjects received 120 µg of bivalent rLP2086, and				• Proportions of subjects achieving an hSBA titre ≥LLOQ 1 month after the third vaccination, for each of the 4 primary MnB tests strains in healthy toddlers 18 to <24 months of age at study entry.

			immediate AEs in healthy toddlers 12 to <18 months and 18 to <24 months of age at study entry, and in both age strata combined.	132 subjects received HAV vaccine/saline .				

* Includes clinical trials registry identifier or sponsor protocol number

3.2.2.3 Data integrity and GCP

The submitted studies were conducted following the Good Clinical Practice (GCP) as required by the International Council for Harmonization (ICH) guidelines as claimed by the applicant.

3.2.2.4 Inter-changeability studies

Not applicable.

Assessors' comments on the submitted clinical studies

The current submission included data from almost 21,282 subjects 10 years of age and older who received at least one dose of bivalent rLP2086, administered either as a single agent or given concomitantly with either; saline alone, licensed vaccine alone, or saline and a licensed vaccine. These participants were enrolled in one of the following 12 studies included in the submission package supporting the indication in individuals 10 years of age and older:

- Two pivotal phase 3 immunogenicity and safety studies using 4 primary and 10 secondary MnB test strains (B1971009 and B1971016).
- One phase 3 study assessing only safety (B1971014).
- Five phase 2 immunogenicity and safety studies:
    - One phase 2 study that examines various 2 and 3 doses schedules and supports the 2 doses (0, 6-month) posology for routine vaccination (B1971012).
    - Three phase 2 concomitant vaccine studies (B1971010 [Repevax], B1971011 [Gardasil], and B1971015 [Menactra and Adacel]).
    - One phase 2 study in laboratory workers (B1971042).

Three early studies (B1971003, B1971004, and B1971005-Stage 1 and Stage 2 [Stage 2 tested persistence of immune response up to 48 months after the last vaccination using the 4 primary test strains. During Stage 2 testing, response for Stage 1 time points was also measured using the 4 primary test strains]).

One study (Study B1971033) evaluated the persistence of the immune response up to 4 years after the primary vaccination in studies B1971010, B1971012, and B1971015. At 4 years after primary vaccination, some of the subjects also received a booster vaccination of bivalent rLP2086, with the evaluation of persistence through 26 months after the booster dose.

Two additional studies, conducted in 1,277 subjects from 1 to <10 years of age, were also included in this submission to support information included in the product label concerning the safety and immunogenicity of bivalent rLP2086 in individuals 1 to <10 years of age.

One phase 2 study evaluating the immunogenicity and safety of a 3-dose regimen of bivalent rLP2086 (0, 2, 6 months) in subjects ≥24 months to <10 years of age (B1971017).

One phase 2 study evaluating the immunogenicity and safety of a 3-dose regimen (0, 2, 6 months) of bivalent rLP2086 at doses of 60 µg and 120 µg in subjects 12 to <24 months of age (B1971035).

For the immunogenicity assessment of bivalent rLP2086 for the phase 3 program, Pfizer and the regulatory authorities (FDA/EMA) agreed on the use of 5 co-primary endpoints, which were pre-specified primary immunogenicity endpoints for the phase3 studies and pre-specified as exploratory endpoints in phase 2 studies -B1971010 (4 endpoints), B1971011 (5 endpoints), B1971012 (5 endpoints), and B1971015 (2 endpoints). All of which used the meningococcal correlate of protection hSBA (human complement serum bactericidal assay) that measures functional antibodies in human sera resulting in the complement-dependent killing of the respective MnB test strain.

In regard to the two pivotal phase 3 studies (B1971009, B1971016), subject randomization was stratified according to the geographic region to ensure sufficient geographic representation and was generally well-balanced with an acceptable blinding method. HSBA titer fold rise ≥4 from baseline, the composite hSBA response (hSBA titer ≥ LLOQ for all 4 primary strains) and lot consistency were chosen as primary endpoints, which were considered appropriate to evaluate the clinical efficacy of the candidate vaccine. As hSBA serves' as the surrogate marker of vaccine efficacy and is the current validated meningococcal correlate of protection against invasive meningococcal disease (IMD).

Study 1

Title: Phase 3, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Lot Consistency, Safety, Tolerability, and Immunogenicity of a Meningococcal Serogroup B Bivalent rLP2086 Vaccine in Healthy Subjects Aged ≥10 to <19 Years.	
Study identifier	Protocol B1971009 (6108A1-3001)
Design	Phase 3, randomized, active-controlled, observer-blinded multicentre trial that assessed the safety, tolerability, and immunogenicity of 3 lots of bivalent rLP2086 and compared the immune response to each of the lots in subjects aged ≥10 to <19 years. Bivalent rLP2086 was administered at Months 0, 2, and 6. Approximately 3600 subjects were to participate in this study at approximately 120 sites (approximately 30 subjects at each site). *The disposition of all randomized subjects are displayed in (Table A.1, Appendix B).*
	Duration of the main phase: 03 May 2013 to 09 July 2015
Hypothesis	The aim of the study was to test bivalent rLP2086 vaccine efficacy followed by lot consistency using the following hypothesis: **Primary Immunogenicity Objective** Null Hypothesis (H0): $p_{A22} \leq 75\%$, or $p_{A56} \leq 85\%$, or $p_{B24} \leq 65\%$ or $p_{B44} \leq 60\%$ or $p_{comp} \leq 75\%$ Alternative Hypothesis (HA): $p_{A22} > 75\%$ and $p_{A56} > 85\%$ and $p_{B24} > 65\%$ and $p_{B44} > 60\%$ and $p_{comp} > 75\%$ p_{A22}, p_{A56}, p_{B24}, p_{B44} and p_{comp} are the response rates for each of the 5 co-primary endpoints. **Lot Consistency Objective** The 2 primary strains (variants) to be tested for lot consistency objectives are PMB80 (A22) and PMB2948 (B24). Null Hypothesis (H0): The 6 comparisons among the 3 rLP2086 lots for the 2 primary strains PMB80 (A22) and PMB2948 (B24) are not equivalent. Alternative Hypothesis (HA): The 6 comparisons among the 3 rLP2086 lots for the 2 primary strains PMB80 (A22) and PMB2948 (B24) are equivalent.
Treatments arms	Bivalent rLP2086: 120 mcg, IM; 0, 2, and 6-month. [Group 1-Lot 1 (n=1509)]
	Bivalent rLP2086: 120 mcg, IM; 0, 2, and 6-month. [Group 2-Lot 2 (n=600)]
	Bivalent rLP2086: 120 mcg, IM; 0, 2, and 6-month. [Group 3-Lot 3 (n=589)]
	Control: HAV, IM; 0, 6 month Saline: 2-month to maintain blinding as appropriate [Group 4- HAV /saline (n=898)]

Randomization	Subjects were randomly assigned to receive 1 of 3 lots of bivalent rLP2086 or the active control/saline. Subjects were randomized into 1 of 4 groups in a 5:2:2:3 ratio (Lot 1: Lot 2: Lot 3: HAV vaccine/saline) and stratified by geographic region. Approximately 1800 subjects from US investigative sites, 1440 subjects from European investigative sites, and 360 subjects from additional regions were to be enrolled. Regional stratification ensured sufficient population representation. The randomization number and the date on which the randomization number was assigned were recorded on a case report form (CRF). Through the use of an interactive voice response system (IVRS), interactive web-based response system (IWRS), or an equivalent system that was accessible 24 hours a day, 365 days a year. Were they confirmed the randomization number and kit randomization number assignment to the site personnel by confirmation reports.		
Blinding	The study staff dispensing and administering the vaccine were un-blinded, but all other study personnel, including the principal investigator and the sponsor, were blinded. In particular, the individuals who evaluated subject safety, as well as the subject, were blinded.		
Endpoints and definitions	Co-primary endpoint	Composite hSBA response	Defined as the proportion of subjects achieving an hSBA titer ≥ lower limit of quantitation (LLOQ) for all 4 primary MnB test strains combined [PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).], 1 month after the third vaccination with bivalent rLP2086.
	Co-primary endpoint	4-fold increase	Defined as the proportion of subjects achieving at least a 4-fold increase in hSBA titer from baseline to 1 month after the third vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains [PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)]. The 4-fold increase for the first 4 co-primary endpoints was defined as below using a 3-tiered approach: • For subjects with a baseline hSBA titer below the limit of detection ([LOD] or an hSBA titer of <1:4), a 4-fold response was defined as an hSBA titer of ≥1:16 or the LLOQ (whichever titer was higher). • For subjects with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response was defined as an hSBA titer ≥4 times the LLOQ. For subjects with a baseline hSBA titer of ≥ LLOQ, a 4-fold response was defined as an hSBA titer of ≥4 times the baseline titer.
	Primary endpoint	lot consistency	hSBA geometric mean titers (GMTs) for each of the 2 primary MnB test strains PMB80 (A22) and PMB2948 (B24), at 1 month after the third vaccination with bivalent rLP2086 for subjects in Groups 1, 2, and 3.

	Primary endpoint	Safety	• Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity after each vaccination visit. • Percentage of subjects reporting systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, muscle pain [other than muscle pain at any injection site], and joint pain) and by severity after each vaccination visit. • Percentage of subjects reporting the use of antipyretic medication after each vaccination visit. • Percentage of subjects with at least 1 SAE during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 MAE occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 NDCMC occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects who develop at least 1 AE occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase]. • Percentage of subjects reporting at least 1 immediate AE after each vaccination. Subject missing days of school or work due to AEs during the vaccination phase.
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Results and Analysis

Sample size determination:

The study had a 5% type I error, which was controlled with a hierarchical order by testing the primary immunogenicity objective first, followed by the lot consistency objective once the immunogenicity objective was achieved. Based on power for both the primary and lot consistency objectives, in consideration of appropriate randomization ratio and block size;

- The primary immunogenicity objective was estimated with the number of evaluable subjects, and appropriate study success criteria (threshold of the lower bound of the 95% confidence interval [CI]) based on exploratory data from a phase 2 study. *(Refer to Table A2 in Appendix B)*. The lower bound of 95% CI rounding to the next lower 5th

percentile from phase 2 data was used as study success criteria and the actual response rate from phase 2 data was used as a point estimate.
- 2-fold equivalence criterion with type I error of 5% (2-sided) for the lot consistency objective.

Overall, assuming a total of 880 evaluable subjects globally and 440 evaluable subjects from the US, the sample size in group 1 provides approximately 100% power on the primary immunogenicity objective for the global population and the US population. Using a 3:1 randomization ratio for rlp2086: control, a total of **3600 subjects** needed to be enrolled in the study, with a randomization ratio of 5:2:2:3 (Lot 1: Lot 2: Lot 3: HAV vaccine/saline).

Immunogenicity Data

GMTs

- hSBA titers logarithmically transformed for analysis and geometric mean hSBA titers (GMTs) for each applicable primary strain.
- 2-sided, 95% confidence intervals.
- Student t distribution.

GMT Ratios (GMRs)

- For the lot consistency objective, the mean difference of the logarithmically transformed results is equivalent to the mean of the ratio on the logarithmic scale: log (Lot1/Lot2) = (log (lot1)) – (log (lot2)). The proper exponential transformation is used to calculate the GMR.
- 2-sided, 95% confidence intervals.
- Student t distribution.
- Statistical inference is based on the 2-sided 95% CIs of the hSBA GMRs between any 2 of the 3 lots at 1-month after the third vaccination with the bivalent rLP2086 vaccine, for both primary strains [PMB80 (A22) and PMB2948 (B24)].

Safety Data

The safety population was used for all safety analyses. All of the safety endpoints will be summarized as descriptive statistics (including p-values), and no multiplicity adjustment will be made.

Results:

A. Demographic Characteristics

A total of 3,596 subjects were randomized in this study, of which, 3,272 (91.0%) subjects completed the vaccination phase of the study. A summary of subject demographic characteristics for the safety population is presented in ***Table 1***. Overall, 51.5% of subjects were male while 48.5% were female, 87.3% were white and 94.2% non-Hispanic/non-Latino. The mean age and standard deviation (SD) at first vaccination were 13.9 (2.6) years (range of 10 to 19 years). Generally, the demographic characteristics were similar between groups in all three vaccinations. The characteristics of the modified intent-to-treat (mITT) population and evaluable immunogenicity population were similar to the characteristics of the safety population.

B. Immunogenicity Results

A total of 3,590 (99.8% of 3,596 subjects randomized) subjects were included in the mITT population.

B.1. Four (4) Primary MnB Test Strains: Primary Immunogenicity Endpoints

B.1.1. Five (5) Co-primary Endpoints: hSBA Titer 4-Fold Rise and Composite Response

The first primary objective was to assess the immune response as measured by hSBA performed with four primary MnB test strains measured 1 month after the third vaccination with bivalent rLP2086 through the following five co-primary endpoints: The proportion of subjects in Group 1 achieved at least 4-fold increase in hSBA titer for each of the four primary MnB test strains and the proportion of subjects achieving a composite response at 1 month after the third vaccination with bivalent rLP2086. Which was achieved if the lower bounds of the 95% CIs at visit 5 were greater than the threshold specified below for each of the five co-primary endpoints among subjects in Group 1.

For the evaluable immunogenicity population, the proportion of subjects achieving a ≥ 4-fold rise in hSBA titer in Group 1 displayed in table 1 was 83.2% for PMB80 (A22) (95% CI: 81.0, 85.2), 90.2% for PMB2001 (A56) (95% CI: 88.4, 91.9), 79.8% for PMB2948 (B24) (95% CI: 77.4, 82.0), 85.9% for PMB2707 (B44) (95% CI: 83.8, 87.8), and 83.5% for composite hSBA (95% CI: 81.3, 85.6). The lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the four primary MnB strains and the composite response; therefore, the first primary objective

(immunogenicity) was met using subjects from all sites globally. The mITT population displayed similar findings.

Table 1. Primary Immunogenicity Analysis – Subjects Achieving ≥4-Fold Rise in hSBA Titer and Composite Response at 1 Month After Vaccination 3 for Primary Strains – Evaluable Immunogenicity Population

Endpoint Strain (Variant)	Vaccine Group (as Randomized) Group 1 rLP2086 Lot 1 N[a]	n[b] (%)	(95% CI)[c]	Lower Bound Threshold[d]
hSBA titer fold rise ≥4 from baseline[e]				
PMB80 (A22)	1225	1019 (83.2)	(81.0, 85.2)	75%
PMB2001 (A56)	1128	1018 (90.2)	(88.4, 91.9)	85%
PMB2948 (B24)	1235	985 (79.8)	(77.4, 82.0)	65%
PMB2707 (B44)	1203	1033 (85.9)	(83.8, 87.8)	60%
Composite hSBA response (hSBA titer ≥ LLOQ for all 4 primary strains)	1170	977 (83.5)	(81.3, 85.6)	75%

B.1.2. Lot Consistency

Lot consistency was the second primary objective, where the purpose was to demonstrate that the immune responses induced by three lots of bivalent rLP2086 were equivalent as measured by hSBA performed with two primary MnB test strains, 1 expressing an LP2086 subfamily A protein and 1 expressing an LP2086 subfamily B protein, 1 month after the third vaccination with bivalent rLP2086. Through the following primary endpoints: hSBA GMTs for each of the 2 primary MnB test strains PMB80 (A22) and PMB2948 (B24), at 1 month after the third vaccination with bivalent rLP2086 for subjects in Groups 1, 2, and 3. Which was achieved if the 2-sided 95% CIs on the hSBA GMTs ratios between any two of the three lots for both PMB80 (A22) and PMB2948 (B24) were within the interval (0.5, 2.0) 1 month after Vaccination 3 (Visit 5) after the primary immunogenicity objective was achieved.
As displayed in table 2, the 95% CI for all pairwise GMRs between lots were within the interval (0.5, 2.0), for both test strains PMB80 (A22) and PMB2948 (B24). Therefore, the lot consistency objective was met for the evaluable immunogenicity population. The mITT population displayed similar findings.

Table 2. Primary Lot Consistency Analysis – Comparison of hSBA GMTs 1 Month after Vaccination 3 for Primary Strains – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)											
	Group 1 rLP2086 Lot 1			Group 2 rLP2086 Lot 2			Group 3 rLP2086 Lot 3			GMR[d] (95% CI)[e]		
Strain (Variant)	n[a]	GMT[b]	(95% CI)[c]	n[a]	GMT[b]	(95% CI)[c]	n[a]	GMT[b]	(95% CI)[c]	Lot 1 to Lot 2	Lot 1 to Lot 3	Lot 2 to Lot 3
PMB80 (A22)	1266	86.8	(82.29, 91.50)	518	84.3	(77.54, 91.68)	492	85.1	(78.26, 92.47)	1.03 (0.93, 1.14)	1.02 (0.92, 1.13)	0.99 (0.88, 1.12)
PMB2948 (B24)	1250	24.1	(22.70, 25.48)	516	25.3	(23.08, 27.72)	479	25.2	(23.03, 27.58)	0.95 (0.85, 1.06)	0.95 (0.86, 1.06)	1.00 (0.88, 1.14)

Study 2

Title: A Phase 3, Randomized, Placebo-Controlled, Observer-Blinded, Trial to Assess the Safety, Tolerability, and Immunogenicity of Bivalent rLP2086 Vaccine When Administered as a 3-Dose Regimen in Healthy Young Adults Aged ≥18 to <26 Years	
Study identifier	Protocol B1971016 (6108A1-2004)
Design	Phase 3, randomized, placebo-controlled, observer-blinded, multicentre trial designed to assess the safety, tolerability, and immunogenicity of bivalent rLP2086 when administered as a 3-dose regimen in healthy young adults aged. 18 to <26 years. *The disposition of all randomized subjects are displayed in (Table B.1, Appendix B).*
	Duration of the main phase: 03 May 2013 to 09 July 2015
Hypothesis	**The study aimed to test bivalent rLP2086 vaccine efficacy using the following hypothesis:** Null Hypothesis (H_0): $p_{A22} \leq 55\%$, or $p_{A56} \leq 85\%$, or $p_{B24} \leq 50\%$ or $p_{B44} \leq 60\%$ or $p_{comp} \leq 60\%$ Alternative Hypothesis (H_A): $p_{A22} > 55\%$ and $p_{A56} > 85\%$ and $p_{B24} > 50\%$ and $p_{B44} > 60\%$ and $p_{comp} > 60\%$ PA_{56}, PA_{22}, PB_{24}, PB_{44} , P_{comp} are the response rates for each of the 5 co-primary endpoints.
Treatments arms	Bivalent rLP2086: 60 mcg, IM; 0, 2, and 6-month. (n= 2480) [Lot number: 12-005668]
	Placebo: Sterile normal saline solution (0.9% sodium chloride) for injection: IM; 0, 2, 6 month. (n= 824) [Lot number: 11-008411]
Randomization	Subject randomization was stratified according to the geographic region. Approximately 1668 subjects from US investigational sites, 1336 subjects from European investigational sites, and 296 subjects from additional regions (Canada) were to be enrolled. Regional stratification ensured sufficient geographic representation to satisfy region-specific success criteria. Almost a total of 3300 subjects were to be randomly assigned to 1 of 2 groups in a 3:1 ratio (Group 1: Group 2). Through the use of an interactive voice response system (IVRS), interactive web-based response system (IWRS), or an equivalent system that was accessible 24 hours a day, 365 days a year. The IVRS, IWRS, or an equivalent system confirmed the randomization number and kit randomization number assignment to the site personnel by confirmation reports.
Blinding	In this observer-blind study, the study staff dispensing and administering the vaccine were un-blinded, but all other study personnel, including the principal investigator and the sponsor, were blinded. In particular, the individuals who evaluated subject safety were also blinded. Because the investigational products were different in physical appearance, the syringes were labelled in a manner that prevented the study subject from identifying the vaccine type based on its appearance.

Endpoints and definitions	Co-primary endpoint	Composite hSBA response	Defined as the proportion of subjects achieving an hSBA titer ≥ lower limit of quantitation (LLOQ) for all 4 primary MnB test strains combined [PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44).], 1 month after the third vaccination with bivalent rLP2086.
	Co-primary endpoint	4-fold increase	Defined as the proportion of subjects achieving at least a 4-fold increase in hSBA titre from baseline to 1 month after the third vaccination with bivalent rLP2086 for each of the 4 primary MnB test strains [PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44)]. The 4-fold increase for the first 4 co-primary endpoints was defined as below using a 3-tiered approach: • For subjects with a baseline hSBA titre below the limit of detection ([LOD] or an hSBA titre of <1:4), a 4-fold response was defined as an hSBA titre of ≥1:16 or the LLOQ (whichever titer was higher). • For subjects with a baseline hSBA titre of ≥ LOD (i.e., hSBA titre of ≥1:4) and < LLOQ, a 4-fold response was defined as an hSBA titre ≥4 times the LLOQ. • For subjects with a baseline hSBA titre of ≥ LLOQ, a 4-fold response was defined as an hSBA titre of ≥4 times the baseline titre.
	Primary endpoint	Safety	• Percentage of subjects reporting local reactions (pain, redness, and swelling) and by severity after each vaccination visit. • Percentage of subjects reporting systemic events (fever, vomiting, diarrhoea, headache, fatigue, chills, muscle pain [other than muscle pain at any injection site], and joint pain) and by severity after each vaccination visit. • Percentage of subjects reporting the use of antipyretic medication after each vaccination visit. • Percentage of subjects with at least 1 SAE during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 MAE occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects with at least 1 NDCMC occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase, during the follow-up phase, throughout the study period.] • Percentage of subjects who develop at least 1 AE occurring during the following periods: [30 days after each vaccination, 30 days after any vaccination, during the vaccination phase]. • Percentage of subjects reporting at least 1 immediate AE after each vaccination. • Subject missing days of school or work due to AEs during the vaccination phase.
Database lock	*N.A*		

Results and Analysis

Sample size determination:

The study had a 5% type I error, which was controlled for the primary objective. Study power for the primary immunogenicity objective was estimated with the number of evaluable subjects and appropriate study success criteria (threshold of the lower bound of the 95% CI) based on exploratory phase 2 data. *(Refer to Table B2 in Appendix B)*. The lower bound of 95% CI rounding to the next lower 5th percentile from phase 2 data was used as study success criteria and the actual response rate from phase 2 data was used as a point estimate.

Overall, assuming 880 evaluable subjects from the US and a total of 1,700 evaluable subjects globally, the sample size in group 1 provides approximately 100% power for the US population and the global population. With a randomization ratio of 3:1, assuming approximately a 30% non-evaluable rate (insufficient sera, protocol violation, subject dropouts, and indeterminate assay results), 3,300 subjects will be enrolled.

Immunogenicity Data

GMTs

- hSBA titers logarithmically transformed for analysis and geometric mean hSBA titers (GMTs) for each of the 4 primary strains PMB80 (A22), PMB2001(A56), PMB2948(B24), PMB2707(B44).
- 2-sided, 95% confidence intervals.
- Student t distribution.

Safety Data

- All of the safety endpoints (including reactogenicity data recorded from e-Diary and (S) AE recorded from the CRF will be summarized with percentages and 95% exact CI for each group.
- Due to the large sample size for this study, other safety data recorded from CRF [included each preferred term of the (S) AE] will be compared with Fisher's Exact test.

Results:

A. Demographic Characteristics

A total of 3,304 subjects were randomized in this study, of which, 2,474 subjects (74.88%) completed the vaccination phase: 3,293 subjects (99.67%) received vaccination 1; 2,902 subjects (87.83%) received vaccination 2; and 2,538 subjects (76.82%) received vaccination 3. A summary of the subject demographic characteristics for the safety population is presented in table 5. Overall, characteristics were similar between groups 1 and 2, where 41.27% of subjects were male and 58.73% female, 76.13% white and 82.84% non-Hispanic/non-Latino. The mean age (SD) at first vaccination was 21.48 (2.15) years (range of 18 to 26 years). The demographic characteristics of the mITT population and evaluable immunogenicity population were generally similar to the characteristics of the safety population.

B. Immunogenicity Results

Of the 3,304 subjects randomized, 2,305 subjects (69.8%; 69.5% in Group 1 and 70.6% in Group 2) were included in the primary analysis population (evaluable immunogenicity population).

B.1. Four (4) Primary MnB Test Strains: Primary Immunogenicity Endpoints

B.1.1. Five (5) Co-primary Endpoints: hSBA Titer 4-Fold Rise and Composite Response

The first primary objective was to assess the immune response as measured by hSBA performed with four primary MnB test strains measured 1 month after the third vaccination with bivalent rLP2086.

The five co-primary endpoints are achieved if the lower bounds of the 95% CIs at 1 month post third dose were greater than the pre-specified thresholds among subjects in Group 1.

For the evaluable immunogenicity population, the proportion of subjects achieving a ≥4-fold rise in hSBA titer in Group 1 as displayed in Table 3 was 80.5% for PMB80 (A22) (95% CI: 78.6, 82.4), 90.0% for PMB2001 (A56) (95% CI: 88.4, 91.4), 79.3% for PMB2948 (B24) (95% CI: 77.3, 81.2), 79.6% for PMB2707 (B44) (95% CI: 77.6, 81.5), and 84.9% for composite hSBA (95% CI: 83.1, 86.6).

The lower limit of the 2-sided 95% CIs was greater than the corresponding pre-specified lower bound threshold for each of the four primary MnB strains and the composite response; therefore, the first primary immunogenicity objective was met using subjects from all sites globally. The mITT population displayed similar findings.

Table 3. Primary Immunogenicity Analysis – Subjects Achieving ≥4-Fold Rise in hSBA Titer and Composite Response at 1 Month After Vaccination 3 for Primary Strains – Evaluable Immunogenicity Population

Endpoint Strain (Variant)	Vaccine Group (as Randomized) Group 1 rLP2086 N[a]	n[b] (%)	(95% CI)[c]	Lower Bound Threshold[d]
hSBA titer fold rise ≥4 from baseline[e]				
PMB80 (A22)	1695	1365 (80.5)	(78.6, 82.4)	55%
PMB2001 (A56)	1642	1477 (90.0)	(88.4, 91.4)	85%
PMB2948 (B24)	1675	1328 (79.3)	(77.3, 81.2)	50%
PMB2707 (B44)	1696	1350 (79.6)	(77.6, 81.5)	60%
Composite hSBA response (hSBA titer ≥ LLOQ for all 4 primary strains)	1664	1413 (84.9)	(83.1, 86.6)	60%

Overall conclusion of clinical immunogenicity:

The clinical development program assessing the vaccines immunogenicity profile consisted of three phase 3 studies, of which two were pivotal studies (B1971009 and B1971016) where bivalent rLP2086 was administered on a 0, 2, 6-month schedule, and 11 supportive studies (B1971003, B1971004, B1971005, B1971010, B1971011, B1971012, B1971015, B1971017, B1971033, B1971035, B1971042) assessing the vaccine candidate on various age groups.

The clinical development program utilized immunogenicity data of bivalent rLP2086 through the current accepted Meningococcal correlate of protection [hSBA titer ≥1:4] instead of efficacy outcome. It was measured using the human complement serum bactericidal assay (hSBA) in 4 primary MnB test strain variants, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), and 10 secondary MnB test strain variants, PMB3175 (A29), PMB3010 (A06), PMB1989 (A19), PMB3040 (A07), PMB824(A12), PMB1672 (A15), PMB1256 (B03); PMB866 (B09); PMB431 (B15), and PMB648(B16).

Summary of Pivotal studies:

In summary, the lower limit of the 2-sided 95% CI for the proportion of subjects aged 10 to <19 years achieved a 4-fold rise in hSBA titer for each of the 4 primary MnB test strains at 1 month after Vaccination 3 and for the composite response was greater than the corresponding pre-specified lower bound thresholds. The first primary immunogenicity objective was therefore achieved, demonstrating a robust immune response after 2 and 3 doses of bivalent rLP2086. Which was also achieved in adults (aged 18 to <26 years) from Study B1971016. In addition, the 95% CI for all pairwise GMRs between the 3 lots of bivalent rLP2086 in study b1971009 were within the pre-specified interval (0.5, 2.0) for

both primary test strains, PMB80 (A22) and PMB2948 (B24); hence, the primary lot consistency objective was also achieved.

Summary of supportive studies:

Three early studies, B1971003, B1971004, and B1971005-Stage 1 and Stage 2. Stage 2 tested the persistence of hSBA responses up to 48 months after the last vaccination using the 4 primary test strains. During Stage 2 testing, hSBA response at Stage 1 time points (baseline and 1-month post-dose 3, using validated hSBA) was also tested using the 4 primary test strains. In addition, three Phase 2 studies that evaluated the concomitant administration of bivalent rLP2086 using a schedule of 0, 2, 6 months with licensed vaccines commonly used in adolescents; human papilloma virus (HPV) vaccine (Gardasil) (Study B1971011, ages 11 to <18 years), quadrivalent meningococcal vaccine (Menactra) and a Tdap vaccine (Adacel) (Study B1971015, ages 10 to <13 years), and a combined low-dose diphtheria, tetanus, acellular pertussis, and inactivated poliomyelitis virus vaccine (Repevax) (Study B1971010, ages 11 to <19 years). The persistence of hSBA response was assessed in 2 studies. In Study B1971005, subjects who had received 3 doses of vaccine were followed for 4 years for antibody persistence. In Study B1971033, subjects who had received 2 or 3 doses of bivalent rLP2086 in primary Studies B1971010, B1971012, or B1971015 were followed for antibody persistence up to 48 months after their last primary study dose, after which time some of these subjects received a booster dose of bivalent rLP20086 and antibody persistence was evaluated for up to 26 months thereafter. Moreover, US microbiology laboratory workers (aged ≥18 to ≤65) were assessed in study B1971042, which was an uncontrolled Phase 2 safety and immunogenicity study after receiving 120 µg of bivalent rLP2086 using a 0, 2, 6-month schedule. Lastly, two additional phase 2 studies evaluating the immunogenicity and safety of a 3-dose regimen of bivalent rLP2086 (0, 2, 6 months), conducted in subjects ≥24 months to <10 years of age (B1971017), and 12 to <24 months of age (B1971035) were also included in this submission.

Overall, the data provided from these supportive studies demonstrated the consistency of vaccine-induced immune response to diverse disease-causing MnB strains across various age groups.

3.2.3 Clinical Safety

The safety endpoints included the proportion of subjects reporting local reactions, systemic events, the use of antipyretic medication associated with vaccine administration, AEs, SAEs, NDCMCs, MAEs, immediate AEs, and days of missed school or work due to an AE. The safety evaluation includes all data through 6 months after the last study vaccination.

Study b1971009:

Across all vaccinations, the proportions of subjects that reported any local reaction at the injection site within 7 days after any vaccination was higher in the combined rLP2086 (Lots 1-3) groups (93.0%) than in HAV/Saline control group (58.8%). Most of the events were mild to moderate in severity. A higher proportion of subjects reported pain at the injection site, redness, and swelling of any severity in the combined bivalent rLP2086 group when compared to the HAV/saline group (92.6% vs 58.8%, 24.1% vs 2.4%, and 27.4% vs 2.9%, respectively). Severe pain, redness and swelling were reported by 11.7%, 3.5% and 1.3% of subjects in the combined bivalent rLP2086 group and 0.9%, 0% and 0% of subjects in the HAV/saline group. The reported local reaction lasted mostly a median of approximately 1 to 2 days.

Across all vaccinations, the proportions of subjects that reported any systemic events within 7 days after any vaccination were generally higher in the combined rLP2086 (Lots 1-3) groups (84.2%) than in HAV/Saline control group (73.3%). Headache and fatigue (67.1% vs 53.4%, and 65.5% vs 50.8%, respectively) were the most frequently reported systemic events in the combined bivalent rLP2086 group when compared to the HAV/saline. Severe events were relatively low as the reported systemic events were generally mild to moderate in severity. The use of antipyretic medications was higher in the combined bivalent rLP2086 group than in the control (32.1% vs 20.2%, respectively), which was consistent with the higher proportion of systemic events observed. The reported events lasted a median of approximately 1.2 to 3.5 days. Twenty-two subjects reported 24 moderate or severe systemic events with a duration >14 days; 17 subjects who received bivalent rLP2086 (Lots 1-3) reported 19 events and five subjects receiving HAV vaccine/saline reported five events. The events were chills, fatigue, headache, and joint pain. A low proportion of subjects in the combined bivalent rLP2086 group and the HAV/saline group reported AEs that led to discontinuation from the study (0.82% and 0.33%, respectively).

Overall, the percentage of AEs reported during the vaccination phase was numerically lower in the combined bivalent rLP2086 group compared to the HAV/saline group (40.74% and 43.70%, respectively). In severity, most of the events were reported as mild or moderate and moderate or severe. A total of 89 (3.30%) subjects in the combined bivalent rLP2086 group and 35 (3.90%) subjects in the HAV/saline group reported AEs that were categorized as severe. In addition, no clinically meaningful differences were noted in the AEs, SAEs, MAEs, NDCMCs and days of missed school or work because of adverse Events reported throughout the study. No reported death cases during the study.

Study B1971016:

Across all vaccinations, the proportions of subjects that reported any local reaction at the injection site within 7 days after any vaccination was higher in Group 1 (90.0%) than in Group 2 (19.2%). Generally, the proportion of subjects who reported pain at the injection site, redness, and swelling of any severity was higher in Group 1 when compared to Group 2 (88.0% vs 15.7%, 17.8% vs 0.9%, and 21.0% vs 0.9%, respectively). Most of the reported local reactions were mild or moderate in severity. Pain at the injection site was the most documented local reaction and was reported higher in Group 1 compared to Group 2 after Vaccination 1 (84.2% and 11.8%, respectively). Severe pain was reported by 7.7% of subjects in Group 1 vs none in Group 2. Severe redness and swelling were reported in 1.5% and 0.5% of the subjects, respectively, in Group 1 and 0.2% and 0.1% of subjects, respectively, in Group 2. The reported reactions lasted a median of approximately 3 to 4 days for redness and approximately 2 to 3 days for swelling.

A higher proportion of subjects in Group 1 reported any systemic events within 7 days compared to Group 2 after Vaccination 1 (71.6% vs 60.5%, respectively), Vaccination 2 (56.8% vs 43.6%, respectively) and Vaccination 3 (56.9% vs 36.7%, respectively). Fatigue and headache (64.6% vs 50.9%, and 59.1% vs 48.4% respectively) were the most frequently reported systemic events in Group 1 and Group 2; systemic events were generally mild and moderate in severity. Severe events were relatively infrequent. The reported events lasted a median of approximately 2 to 3 days. Thirty-nine systemic events (30 in Group 1 and 9 in Group 2) with a duration of >14 days were reported by 26 subjects. The events were fatigue, headache, muscle pain, chills, joint pain, diarrhea, and fever. However, none led to withdrawal.

Overall, the percentages of AEs reported during the vaccination phase were similar in Group 1 compared to Group 2 (31.20% and 31.14%, respectively). The most frequently observed AEs were in the system organ class (SOC) of infections and infestations (17.28% in Group 1 and 17.64% in Group 2). Percentages of AEs reported in all SOCs were similar between groups. Most of the events were mild or moderate in severity. A total of 71 (2.87%) subjects in Group 1 and 16 (1.95%) subjects in Group 2 reported AEs that were categorized as severe. The use of antipyretic medications was higher in the group that received bivalent rLP2086, which was consistent with the higher rate of systemic events observed.

MAEs within 30 days after each vaccination were reported by similar proportions of subjects in Group 1 compared to Group 2. Most MAEs reported by subjects in both groups were mild or moderate in severity. A similar number of subjects in both groups reported “days of missed school or work” because of an AE. Additionally, no notable differences in the proportions of subjects with NDCMCs were observed between Group 1 and Group 2.

Three (3) subjects in Group 1 died during the study, however, none of the deaths was considered by the investigator as related to the candidate vaccine.

Study B1971014:

Overall, the proportion of subjects reporting at least one SAE within 30 days of each vaccination was <3.0% for both groups and similar between bivalent rLP2086 and HAV vaccine/saline control. In which a numerically greater proportion of SAEs was reported by subjects in Group 2 (HAV vaccine/saline) than Group 1 (bivalent rLP2086) (2.52% and 1.55%, respectively) in both the vaccination and follow-up phases. The most common type of SAE belonged to the SOC of infections and infestations. Similar proportions of subjects in Group 1 and Group 2 reported medically attended AEs for each analysis interval, of which, were mostly mild to moderate in severity. One subject died during the study, however, was not related to the candidate vaccine.

3.2.3.3 Overall conclusion on clinical safety:

In summary, bivalent rLP2086 was safe and generally well tolerated across various age groups as supported by the global phase 3 randomized safety study (B1971014) that assessed the safety of bivalent rLP2086 compared to active control (HAV/saline) in 5712 healthy subjects (10 to <26 years of age) via the occurrence of adverse events and serious adverse events.

In both pivotal studies (B1971009 and B1971016), pain at the injection site was the most reported local reaction. Headache and fatigue were the most common systemic events in both groups. Overall, the percentage of AEs reported during the vaccination phase was numerically lower in the combined bivalent rLP2086 (Lots 1–3) group compared to the HAV/saline group; AEs and SAEs were most frequently observed in the SOC of infections and infestations. Most local reactions and systemic events were mild or moderate in severity. Additionally, no related SAEs were reported during study B1971009, in contrast, to study B1971016, which reported 3 subjects experiencing related SAEs (i.e. severe Pyrexia, Dystonia, and Multiple Sclerosis) all of which led to study discontinuation. No related deaths were reported in both studies.

These findings were in line with the global phase 3 safety study B1971014, which also reported two related SAEs (i.e., Neutropenia, and Anaphylactic reaction).

3.2.4 Discussion on Clinical efficacy and safety aspects

Based on the Benefit and Risk department review of the submitted safety and efficacy data, TRUMENBA ® demonstrated a consistent vaccine-induced immune response to diverse disease-causing MnB strains, in addition, displaying a good safety and tolerability profile in adolescents and adults 10 years of age and older. Thus, the clinical study section recommends the approval of TRUMENBA ® for the active immunization of individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B

4. Risk Management Plan (RMP)

Every new drug approved in Saudi Arabia has an RMP in place to ensure that the drug or vaccine is used as safe as possible. The RMP is a comprehensive document describing current knowledge about the safety and efficacy of a drug. The SFDA has revised the RMP version 4.1, and concluded the following:

- Use in pregnancy and lactation were considered as Missing information.
- Use in co-administration with MMR and pneumococcal vaccines were considered as Missing information.
- Use in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia) were considered as Missing information.
- Vaccine effectiveness was considered as missing information.

4.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond reporting adverse drug reactions and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concern.
- Other forms of routine pharmacovigilance activities for safety concerns.

4.2 Additional Pharmacovigilance Activities

The following 3 studies are additional pharmacovigilance activities.

Table of on-going, planned and completed additional pharmacovigilance activities:

Activity title/type	Objectives	Safety concerns addressed	Status

Study B1971052 Pregnancy and Birth Outcome Assessment in a Population-based Cohort after Exposure to Trumenba®.	Obtain safety data regarding pregnancy exposure and birth outcomes	Use in pregnancy and lactation.	Planned
Study C3511006 A phase 3, randomized, controlled, open-label trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy participants ≥12 to 24 months of age, and when administered concomitantly with MMR and pneumococcal vaccine in healthy participants ≥12 to 16 months of age.	Assess the safety, tolerability and immunogenicity of MenABCWY when administered concomitantly with MMR and 13vPnC	Use in co-administration of bivalent rLP2086 / bivalent rLP2086-containing vaccine with MMR and pneumococcal vaccines.	Planned
Study B1971060 Phase 4, open-label, single-arm trial to describe the safety, tolerability, and immunogenicity of Trumenba when administered to immunocompromised participants ≥10 years of age.	the safety and immunogenicity of 2 doses of bivalent rLP2086 administered on a 0- and 6-month schedule in immunocompromised participants ≥10 years of age.	Use in immunocompromised individuals (eg, individuals with terminal complement deficiency or asplenia).	Planned

4.3 Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Routine risk minimization measures include:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SPC, addressed to patients and healthcare professionals
- Important advice on the medicine's packaging.
- The authorized pack size
- The medicine's legal status.

In addition to these measures, information about adverse events is collected continuously and regularly analyses, including PSUR assessment so that immediate action can be taken as necessary.

No additional risk minimization measures are proposed.

4.4Artwork and Trade Name assessment (Artwork available in appendix)

Proposed trade Name	Dosage Form
Trumenba	Suspension for Injection in Pre-filled Syringe

Lookalike/Sound-alike (LA/SA) Error Risk Potential:

Trumenba name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN and USAN STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Trumenba	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Trumenba is accepted.

Trumenba ®

Outer and Inner Package:

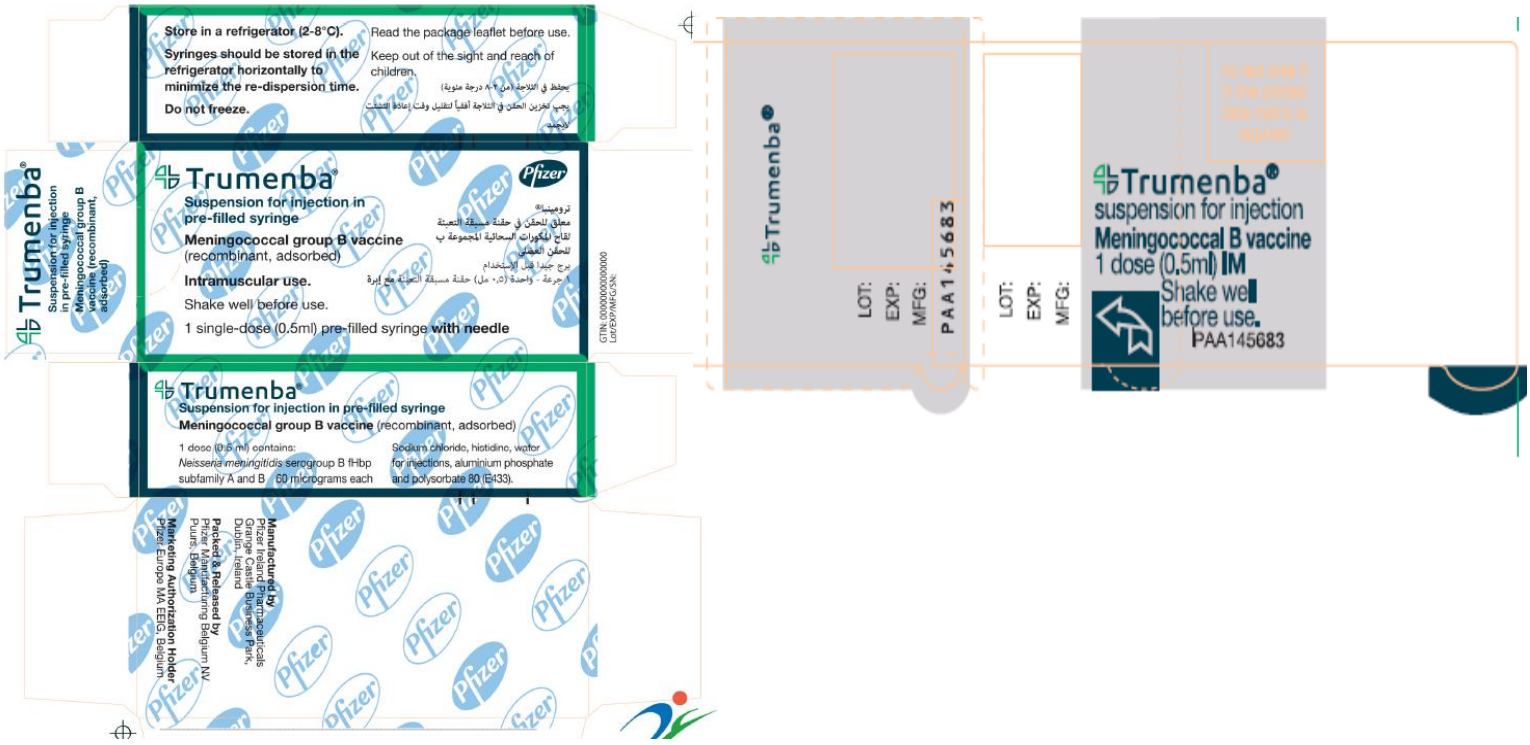
Based on the submitted data, the proposed artwork is accepted.

5. Overall Conclusion

Based on a review of data on quality, safety and efficacy, SFDA considered that the benefit/risk profile of Trumenba was favorable and decided to grant the marketing authorization of Trumenba for the treatment of Prevention of invasive meningococcal disease caused by Neisseria meningitidis Serogroup B (MnB) in individuals aged 10 years and older.

6. Appendixes

A. Artwork



The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published in (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa